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I manoscritti devono essere preparati seguendo rigorosamente le norme per gli Autori, che sono conformi agli Uniform Requirements for Manuscripts Submitted to Biomedical Editors editi a cura dell’International Committee of Medical Journal Editors (www.icmje.org). Non saranno presi in considerazione gli articoli che non si uniformano agli standard internazionali.

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TIPI DI ARTICOLI SCIENTIFICI

Istruzioni per i più frequenti tipi di lavori inviati alla rivista.

Editoriale. Su invito (del Redattore Capo, del Direttore Responsabile), deve riguardare un argomento di grande rilevanza in cui l’Autore espri- me la sua opinione personale. Sono ammesse non più di 100 parole (3 pagine dattiloscritte con spaziatura doppia) e fino a 15 citazioni bibliografiche.

Articolo originale. Deve portare un contributo originale all’argomento trattato. Il testo deve essere di 3000-5500 parole (8-16 pagine dattiloscritte con spaziatura doppia) escluse bibliografia, tabelle e figure. Sono ammesse fino a 50 citazioni bibliografiche. L’articolo deve essere suddiviso nelle sezioni: introduzione, materiali e metodi, risultati, discussione, conclusioni. Nell’introduzione sintetizzare chiaramente lo scopo del lavoro. Nella sezione dei materiali e metodi descrivere in sequenza logica come è stato impostato e portato avanti lo studio, come sono stati analizzati i dati (quali ipotesi è stata testata, come è stata fatta la randomizzazione, come sono stati reclusi i dati e gli eventualierrori, fornire dettagli accurati sulle caratteristiche essenziali del trattamento, sui materiali utilizzati, sui dosaggi di farmaci, sulle apparecchiature non comuni, sul metodo statistico ...). Nella sezione dei risultati dare le risposte alle domande poste nell’introduzione. I risultati devono essere presentati in modo completo, chiaro, conciso eventualmente correlati di figure, grafici e tabelle. Nella sezione discussione riassumere i risultati e confrontare i risultati ottenuti con gli altri dati della letteratura, discutere le implicazioni dei risultati. Nelle conclusioni riassumere brevemente il significato dello studio e le sue implicazioni future.

Review. Preferibilmente su invito (del Redattore Capo, del Direttore Responsabile), deve trattare un argomento di attualità ed interesse, presente lo stato delle conoscenze sull’argomento, analizzare le differenti opinioni sul problema trattato, essere aggiornata con gli ultimi dati della letteratura. Il testo deve essere di 6000-12000 parole (17-34 pagine dattiloscritte con spaziatura doppia) escluse bibliografia, tabelle e figure. Son"
L’articolo dovrà essere dattiloscritto con spaziatura doppia e con margini di almeno 2,5 cm su cartelle del formato 212×297 mm (SO4A). I formati accettati sono Word e RTF. Il file del manoscritto deve contenere il titolo, i dati autori, le note, il riassunto, le parole chiave, il testo, la bibliografia, le didascalie delle tabelle e delle figure. Tabelle e figure devono essere inviate in file separati.

**Titolo e dati autori**
- Titolo (in inglese e in italiano) conciso, senza abbreviazioni.
- Nome e Cognome degli Autori.
- Affiliazione (sezione, dipartimento e istituzione) di ciascun autore.

**Note**
- Dati di eventuali Congressi ai quali il lavoro sia già stato presentato.
- Menzione di eventuali finanziamenti o contratti di ricerca o conflitti di interesse.
- Ringraziamenti.
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**Riassunto e parole chiave**
Il riassunto (in inglese e in italiano) non deve superare né essere inferiore alle 200-250 parole e, in caso di articolo originale e nota di terapia, deve essere strutturato nelle sezioni: obiettivo (scopo dello studio), metodi (disegno sperimentale, pazienti e interventi), risultati (cosa è stato messo in atto), conclusioni (significato dello studio). Per le parole chiave (in inglese e in italiano) usare i termini del Medical Subjects Heading (MeSH) di MEDLINE/PubMed. Gli editoriali e le lettere alla direzione non necessitano di riassunto.

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Identificare metodologie, apparecchiature (nome e indirizzo del costruttore) e procedure con dettaglio sufficiente a permettere ad altri studiosi di riprodurre i risultati. Menzionare le metodologie già definite, incluse quelle statistiche; menzionare e fornire brevi descrizioni circa metodologie che sono state pubblicate ma non sono ben conosciute; descrivere metodologie nuove o modificate nel modo sostanziale; giustificare il loro utilizzo e valutarne i limiti. Di tutti i farmaci si deve cita-
re nome generico, dosaggio e vie di somministrazione. I nomi commerciali dei farmaci vanno citati tra parentesi. Unità di misura, simboli, abbreviazioni devono essere conformi agli standard internazionali. Le misure di lunghezza, altezza, peso e volume dovrebbero essere espressi in unità del sistema metrico (metro, chilogrammo, litro) o in loro multipli decimali. Le temperature dovrebbero essere espressi in gradi Celsius. Le pressioni esprimere in millimetri di mercurio. Tutte le misura-

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È sottolineato che gli articoli citati in bibliografia siano stati letti dagli Autori. La bibliografia, che deve comprendere i soli Autori citati nel testo, va numerata con numeri arabi in ordine consecutivo. Menzionare le metodologie già definite, incluse quelle statistiche; menzionare e fornire brevi descrizioni circa metodologie che sono state pubblicate ma non sono ben conosciute; descrivere metodologie nuove o modificate in modo sostanziale; giustificare il loro utilizzo e valutarne i limiti. Di tutti i farmaci si deve citare nome generico, dosaggio e vie di somministrazione. I nomi commerciali dei farmaci vanno citati tra parentesi. Unità di misura, simboli, abbreviazioni devono essere conformi agli standard internazionali. Le misure di lunghezza, altezza, peso e volume dovrebbero essere espressi in unità del sistema metrico (metro, chilogrammo, litro) o in loro multipli decimali. Le temperature dovrebbero essere espressi in gradi Celsius. Le pressioni esprimere in millimetri di mercurio. Tutte le misurazioni di chimica clinica dovrebbero essere espressi in unità del sistema metrico nei termini dell’International System of Units (SI). Si sconsiglia l’uso di simboli e sigle poco comuni. Essi vanno comunque spiegati alla prima apparizione nel testo.

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Per ogni voce si devono riportare il cognome e l’iniziale del nome degli Autori (elencare tutti gli Autori fino a sei; se sette o più elencare solo i primi sei nomi seguiti da: et al.), il titolo originale dell’articolo, il titolo della rivista (attenendosi alle abbreviazioni usate di MEDLINE/PubMed), l’anno di pubblicazione, il numero del volume, il numero di pagina iniziale e finale. Nelle citazioni bibliografiche seguire attentamente la punteggiatura standard internazionale.

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  - Atti congressuali.
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  - Per la redazione della bibliografia non utilizzare le note a pie’ de pagina.
    Per le voci bibliografiche citate per la prima volta in una tabella o nella didascalia di una figura devono essere numerate in sequenza con le voci bibliografiche citate nel testo tenendo conto del punto in cui la tabella o la figura è richiamata per la prima volta. Di conseguenza tali voci bibliografiche devono essere elencate in fondo alla bibliografia ma secon-
do l’ordine di citazione nel testo.
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  Le didascalie di tabelle e figure devono essere inserite sia nel file di testo sia nel file delle tabelle e delle figure.

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Le tabelle devono essere inviate come file separati. I formati accettati sono Word e RTF. Ogni tavola deve essere correttamente dattiloscritta, preparata graficamente secondo lo schema di impaginazione della rivi-
sta, numerata in cifre romane, corredata dal rispettivo titolo. Eventuali annotazioni devono essere inserite al piede della tavola e non nel titolo. Le tabelle devono essere richiamate nel testo in ordine consecutivo.

**File delle figure**
Le figure devono essere inviate come file separati. I formati accettati sono JPEG, TIFF, PNG, PDF (alta qualità) e Word (per i grafici). Le figure devono essere numerate in cifre arabe e corredate dalla rispettiva didascalia. Le figure devono essere richiamate nel testo in ordine consecutivo. La riproduzione deve essere limitata alla parte essenziale ai fini del lavoro. Le foto istologiche devono essere accompagnate dal rapporto di ingrandimento e dal metodo di colorazione.

Per le Figure a colori specificare sempre se si desidera la riproduzione a colori o in bianco e nero. Il costo della riproduzione delle figure a colori sarà addebitato agli Autori.

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Instructions for the most frequent types of articles submitted to the journal.

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Original articles. These should be original contributions to the subject. The text should be 3000-3500 words (8 to 16 typed, double-spaced pages) not including references, tables, figures. No more than 50 references will be accepted. The article must be subdivided into the following sections: introduction, materials and methods, results, discussion, conclusions. In the introduction the aim of the study should be clearly summed up. The materials and methods section should describe in a logical sequence how the study was designed and carried out, how the data were analyzed (what hypothesis was tested, what type of study was carried out, how randomization was done, how the subjects were recruited and chosen, provide accurate details of the main features of treatment, of the materials used, of drug dosages, of unusual equipments, of the statistical method...). In the results section the answers to the questions posed in the introduction should be given. The results should be reported fully, clearly and concisely supported, if necessary, by figures, graphs and tables. The discussion section should sum up the main results, critically analyze the methods used, compare the results obtained with other published data and discuss the implications of the results. The conclusions should briefly sum up the significance of the study and its future implications.

Review articles. Generally commissioned by the Editor in Chief or the Managing Editor, review articles should discuss a topic of current interest, outline current knowledge of the subject, analyze different opinions regarding the problem discussed, be up-to-date on the latest data in the literature. The text should be 6000-12000 words (17 to 34 typed, double-spaced pages) not including references, tables, figures. No more than 100 references will be accepted.

Case reports. These give a description of particularly interesting cases. The text should be 2000-3000 words (6 to 8 typed, double-spaced pages) not including references, tables, figures. No more than 30 references will be accepted. The article must be subdivided into the following sections: introduction, case report or clinical series, discussion, conclusions.

Therapeutical notes. These are intended for the presentation and assessment of new medical and surgical treatments. The text should be 3000-5500 words (8 to 16 typed, double-spaced pages) not including references, tables, figures. No more than 30 references will be accepted. The article must be subdivided into the following sections: introduction, materials and methods, results, discussion, conclusions.

Special articles. These are articles on the history of medicine, health care delivery, ethics, economic policy and law concerning dermatology. The text should be 3000-7000 words (8 to 20 typed, double-spaced pages) not including references, tables, figures. No more than 50 references will be accepted.

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Guidelines. These are documents drawn up by special committees or authoritative sources.

The number of figures and tables should be appropriate for the type and length of the paper.

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Manuscripts must be drafted according to the template for each type of paper (editorial, original article, review, case report, therapeutic note, special article, letter to the Editor).
The paper should be typed written double spaced with margins of at least 2.5 cm on 212×297 mm format sheets (ISOA4). The formats accepted are Word and RTF. The text file must contain title, authors’ details, notes, abstract, key words, text, references and titles of tables and figures. Tables and figures should be submitted as separate files.

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- **Short title**, with no abbreviations.
- First name and surname of the authors.
- Affiliation (section, department and institution) of each author.

**Notes**

- Dates of any congress where the paper has already been presented.
- Mention of any funding or research contracts or conflict of interest.
- Acknowledgements.
- Name, address, e-mail of the corresponding author.

**Abstract and key words**

Articles should include an abstract of between 200 and 250 words. For original articles and therapeutic notes, the abstract should be structured as follows: **aim** (of the study), **methods** (experimental design, patients and interventions), **results** (what was found), **conclusion** (meaning of the study). Key words should refer to the terms from Medical Subject Headings (MeSH) of MEDLINE/PubMed. No abstracts are required for editorials or letters to the Editor.

**Text**

Identify methodologies, equipment (give name and address of manufacturer in brackets) and procedures in sufficient detail to allow other researchers to reproduce results. Specify well-known methods including statistical procedures; mention and provide a brief description of published methods which are not yet well known; describe new or modified methods at length; justify their use and evaluate their limits. For each drug generic name, dosage and administration routes should be given. Brand names for drugs should be given in brackets. Units of measurement, symbols and abbreviations must conform to international standards. Measurements of length, height, weight and volume should be given in metric units (meter, kilogram, liter) or their decimal multiples. Temperatures must be expressed in degrees Celsius. Blood pressure must be expressed in millimeters of mercury. All clinical chemistry measurements should be expressed in metric units using the International System of Units (SI). The use of unusual symbols or abbreviations is strongly discouraged. The first time an abbreviation appears in the text, it should be preceded by the words for which it stands.

**References**

It is expected that all cited references will have been read by the authors. The references must contain only the authors cited in the text, be numbered in Arabic numerals and consecutively as they are cited. Bibliographical entries in the text should be quoted using superscripted Arabic numerals. References must be set out in the standard format approved by the International Committee of Medical Journal Editors (www.icmje.org).

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Each entry must specify the author’s surname and initials (list all authors when there are six or fewer; when there are seven or more, list only the first six and then “et al.”), the article’s original title, the name of the Journal (according to the abbreviations used by MEDLINE/PubMed), the year of publication, the volume number and the number of the first and last pages. When citing references, please follow the rules for international standard punctuation carefully.

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- **Standard article.**
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For occasional publications, the names of authors, title, edition, place, publisher and year of publication must be given. Examples:

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- **Chapter from book.**
- **Congress proceedings.**

**Electronic material**

- **Standard journal article on the Internet.**
- **Standard citation to a book on CD-ROM or DVD.**
- **Standard citation to a homepage.**

Footnotes and endnotes of Word must not be used in the preparation of references. References first cited in a table or figure legend should be numbered so that they will be in sequence with references cited in the text taking into consideration the point where the table or figure is first mentioned. Therefore, those references should not be listed at the end of the reference section but consecutively as they are cited.

**Titles of tables and figures**

Titles of tables and figures should be included both in the text file and in the file of tables and figures.

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Each table should be submitted as a separate file. Formats accepted are Word and RTF. Each table must be typed correctly and prepared graphically in keeping with the page layout of the journal, numbered in Roman numerals and accompanied by the relevant title. Notes should be inserted at the foot of the table and not in the title. Tables should be referenced in the text sequentially.

**File of figures**

Each figure should be submitted as a separate file. Formats accepted: JPEG set at 300 dpi resolution preferred; other formats accepted are TIFF, PNG, PDF (high quality) and Word (for graphs). Figures should be numbered in Arabic numerals and accompanied by the relevant title. Figures should be referenced in the text sequentially. Reproductions should be limited to the part that is essential to the paper. Histological photographs should always be accompanied by the magnification ratio and the staining method. If figures are in color, it should always be specified whether color or black and white reproduction is required. The cost of color figures will be charged to the Authors.

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- 8.6 cm (basis) × 4.8 cm (height)
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Website: http://verona2012.eadv.org

June 13-16, 2012
Malmo (Sweden)
11th Congress of the European Society of Contact Dermatitis (ESCD)
Contact:
Website: www.escd2012.com

June 27-July 1, 2012
Stockholm (Sweden)
3rd World Psoriasis and Psoriatic Arthritis Conference
Contact:
Website: www.ifpaworldconference.com

September 6-9, 2012
Riga (Latvia)
21st EADV Congress
Contact:
E-mail: info@eadvriga2012.com

September 10-12, 2012
Cardiff (UK)
Stratum Corneum VII
Contact:
Website: www.stratumcorneum2012.com

September 11-14, 2012
Geneva (Switzerland)
17th Meeting of the European Society for Pigment Cell Research (ESPCR)
Contact:
Website: www.espcr.org

September 19-22, 2012
Venice (Italy)
European Society for Dermatological Research 42nd Annual ESDR Meeting
Contact:
Website: www.esdr.org

October 4-7, 2012
Mumbai (India)
European Society of Cosmetic and Aesthetic Dermatology
COSMODERM - 2012
Contact:
Website: www.escad.org

May 8-11, 2013
Edinburgh (Scotland, UK)
International Investigative Dermatology 2013
Contact:
Website: www.iid2013.org

July 18-20, 2013
Hamburg (Germany)
8th World Congress of Melanoma
Contact:
Website: www.worldmelanoma2013.com

September 25-27, 2013
Madrid (Spain)
WCDP 2013
12th World Congress of Pediatric Dermatology
Contact:
Website: www.wcpd2013.com
Comparable to other cancers melanoma susceptibility results from interactions between environmental exposures and inherited genetic factors. Therefore, recognizing these environmental and genetic/personal risk factors will allow for the identification of a subgroup of high-risk patients that will benefit most from skin cancer surveillance strategies and from approaches aimed at minimizing exposure to ultraviolet radiation. Herein, we will review the melanoma risk factors, melanoma prognostic factors and discuss management of melanoma patients, focusing on prevention and early detection strategies.

Melanoma risk factors

Recognizing risk factors for melanoma (Table I) allows for the identification of high-risk individuals that will benefit most from strategies aimed at preventing melanoma and detecting it while the tumor is confined to the skin. Preventive strategies, such as educational campaigns (primary prevention) and early-detection programs (secondary prevention) may help in curtailing melanoma-related mortality. As mentioned above, cancer susceptibility results from interactions between environmental and inherited factors. Risk factors for melanoma can be broad-
risk of being diagnosed with a melanoma by age 85 is 1 in 15 males and 1 in 24 females.3

Genes

It is well known that having a family history of melanoma increases the personal risk for melanoma (RR=1.74, 95% CI 1.41, 2.14),11 (RR=2.06; 95% CI: 1.72, 2.45).12 In particular, first-degree relatives of patients with melanoma are at increased risk for melanoma, especially if their relatives were diagnosed at a younger age. Begg et al. reported that the cumulative risk for melanoma in a male relative ranges from 0.8% by age 50 to 6% by age 80, and for a female relative it ranges from 1.3% by age 50 to 7% by age 80.13 Similarly, Olsen et al. found that approximately 7% of melanoma cases are attributable to having an affected family relative.12 The aforementioned information suggests that germline mutations or somatic mutations arising in families presumably from shared environmental carcinogens may predispose one to melanoma.

Several pathways and genes have been associated with susceptibility to melanoma (Figure 1). Particularly, there are two recognized high-penetration gene mutations (CDKN2A and CDK4), which are often found in familial cases and rarely in sporadic melanomas.14 Conversely, the low-penetrance gene MC1R has been more commonly associated with sporadic melanomas.15 Although germline mutations are the

### TABLE I.—Risk factors for cutaneous melanoma.1-9

<table>
<thead>
<tr>
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<th>High-risk (RR &gt;=2.1)</th>
<th>Moderate-risk (RR=1.1-2.0)</th>
<th>Low-risk (RR &lt;=1.0)</th>
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<tr>
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<td>Many atypical nevi</td>
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<td>&gt;100 Common nevi</td>
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<td>NMSC</td>
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<td>Actinic damage</td>
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<td>Tanning bed</td>
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*RHC: red hair color; NMSC: non-melanoma skin cancer.

Age and gender

From 2004 to 2008 the median age at diagnosis for melanoma in the USA was 60 years, with 81% of the cases diagnosed after age of 45.8 Melanoma often affects persons at younger age as compared to other major cancers and the risk increases with advancing age. Studies have shown that melanomas in the elderly are thicker, predominantly of the nodular type and often occur on the head and neck of males.9 Males appear to be at increased risk for developing melanoma and they tend to present with thicker tumors as compared to females.10 The probability of developing an invasive cutaneous melanoma during the life-time of an individual in the USA is 1 in 32 for males and 1 in 55 for females.5 In Australia the
ones that are responsible for familial melanoma, we will briefly highlight both germline and somatic mutations, since any one of these mutations can increase the risk of melanoma in the affected individual. Furthermore, with the emergence of targeted therapies for melanoma, this may be an appropriate time for physicians managing melanoma patients to become acquainted with the molecular pathways driving melanoma development and progression. This knowledge will in turn assist ones understanding of the mechanism of action of many of the emerging targeted therapies directed against melanoma such as therapy targeting Braf and Kit mutations.

**Signaling pathways altered in melanoma**

1. **Mitogen-activated protein (MAP)-kinase pathway** (Figure 1A).—The MAP-kinase pathway regulates cell proliferation in response to extracellular mitogenic signals (i.e., growth factors) through their respective receptor tyrosine kinase (i.e., c-kit, VEGFR, etc.). The RAS-RAF-MEK-ERK-MAP-kinase pathway mediates cellular responses to growth signals and the majority of melanomas harbor somatic mutations in this pathway. These mutations are usually mutually exclusive, meaning that two different mutations are not present in the same cell, for example both RAS and Braf mutations do not normally occur in the same cell.

   - **v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT), 4q11-12.**—KIT receptor is a trans-membrane receptor of the tyrosine kinase family and it is normally activated by stem cell factor or kit ligand in the extracellular domain. Activation of Kit receptor results in downstream signal transduction through different pathways, including the MAP-Kinase pathway and the PI3K pathway (Figure 1A). Kit is important for the development of melanocytes, hematopoietic cells, mast cells, and primordial germ cells. Melanomas with Kit mutations are most commonly located on acral regions with 9% to 36% of acral melanomas manifesting Kit mutations. This mutation can also occur in 15% to 39% of mucosal melanomas. Lastly, this mutation has also been shown to occur in 2% to 28% of melanomas located on chronically sun-damaged skin (Table II).

   - **Neuroblastoma RAS viral (v-ras) oncogene homolog (N-RAS), 1p13.**—N-RAS activates the MAPK pathway resulting in cellular proliferation, and it also activates the phosphatidylinositol 3’ kinase pathway, which in turn inhibits apoptosis (Figure 1A). Most mutations in N-RAS have been found in melanocytes on sun-damaged skin and in melanomas lacking Braf mutations. In addition, NRas mutations have been found in mucosal melanoma (Table II).

   - **v-raf murine sarcoma viral oncogene homologue B1 (BRAF) gene, 7q34.—**Somatic mutations in the BRAF oncogene have been reported in up to 70% of melanomas and melanocytic nevi. The most common mutation corresponds to a single substitution of glutamic acid for valine at position 600 (V600E). This mutation is common in melanomas arising on intermittently sun-exposed skin and are rare in acral, mucosal or chronically sun-exposed skin sites. Melanomas with BRAF mutations tend to occur on the trunk, are usually of the superficial spreading or nodular type, and occur at younger ages, in individuals with high nevus counts and few freckles (Figure 1A, Table II).

   - **Cyclin-dependent kinase 4 (CDK4), 12q14; and Cyclin D1 (CCND1), 11q13.—**The CDK4 gene binds to CCND1 and is considered a high-risk melanoma susceptibility gene [24]. Both CDK4 and CCND1 genes have been suggested to be independent oncogenes in melanoma and are frequently mutated in acral and mucosal melanomas (Figure 1A, B, Table II).

   - **Cyclin-dependent kinase inhibitor 2A (CDKN2A) gene, 9p21.—**The CDKN2A gene codes for tumor suppressors p16 and p14. Inactivating mutations in p16 (also known as INK4a) promotes the uncontrolled transition from G1 to S phase of the cell cycle. Thus CDKN2A mutations lead to alteration of the cell cycle with uncontrolled proliferation (Figure 1B). On the other hand, p14 (also known as ARF), regulates the p53 tumor suppressor gene, which controls the transcription of numerous genes that ultimately lead to DNA repair and cell-cycle arrest, or leads to apoptosis. Hence, p53 dysfunction can result in melanoma progression (Figure 1B).

CDKN2A is the most well known high-risk melanoma susceptibility gene in the setting of familial melanoma. Goldstein et al. described 466 melanoma-prone families, of which 38% had CDKN2A mutations that involved the p16 protein. Germline mutations have been observed in different
Figure 1A.—Pathways and genes in melanoma. Left: α-melanocyte stimulating hormone (α-MSH)/Melanocortin-1 Receptor (MC1R) or Microphthalmia-associated transcription factor (MITF) pathway. UVR stimulates keratinocytes to release α-MSH, which is a cleavage product of pro-opiocortin (POMC). α-MSH binds to MC1R on the surface of melanocytes. MC1R activates cyclic AMP (cAMP), which activates the camp response-element binding protein (CREB), which in turn increases expression of MITF. MITF can also be regulated by ERK phosphorylation. Right: Mitogen-activated protein kinase and phosphatidylinositol 3′ kinase pathway (PI3K) pathways. Binding of ligands (i.e. growth factors, stem cell factor, etc) to their respective receptor tyrosine kinase (RTK) leads to activation of RAS. RAS can activate BRAF, which activates MEK, and MEK then activates the extracellular-related kinase (ERK). Phosphorylated ERK (ERK-p) kinases translocates to the nucleus to activate transcription factors, which promote proliferation. ERK can also interact with the PI3K-AKT pathway. Activated PI3K converts the plasma membrane lipid phosphatidylinositol 4,5-bisphosphonate to phosphatidylinositol triphosphate (PIP3). PIP3 leads to the phosphorylation of AKT and subsequent up-regulation of cell cycle, growth, and survival proteins. Phosphatase and tensin homolog (PTEN) inhibits the generated PIP3 by PI3K.
mon in mucosal and acral melanomas \(^\text{16}\) (Table II). Furthermore, functional CDKN2A mutations are more common in individuals with multiple primary melanomas than in persons with single primary melanomas \((2.9\% \text{ vs. } 1.3\%)\). These individuals are often younger, with more nevi and are more likely to have a family history of melanoma.\(^\text{27}\) Regarding sun exposure, there is no evidence to suggest that sun exposure increases the risk for melanoma in CDKN2A mutation carriers above and beyond non-carriers.\(^\text{28}\)

Mutations of the p16 gene have also been linked with pancreatic cancer and this will be discussed in more detail below within the context of the atypical mole syndrome.\(^\text{29}\)

2. Phosphatidylinositol 3’ kinase (PI3K) pathway (Figure 1A).—The PI3K pathway mediates cell survival in response to extracellular signals (i.e., growth factors, stem cell factor, etc.), through their respective receptor tyrosine kinase (i.e., VEGFR, c-kit, etc.).\(^\text{16}\)

**Phosphatase and tensin homolog (PTEN), 10q23.**—PTEN is a negative regulator of AKT in the PI3K pathway. It inhibits growth factor signaling by inactivating phosphatidylinositol triphosphate (PIP3) generated by PI3K. Loss of PTEN decreases apoptosis. Mutations or deletions of PTEN have been demonstrated in up to 37% of cutaneous melanomas and tend to occur together with BRAF mutations but not with N-RAS \(^\text{30}\) (Figure 1A).

3. a-melanocyte stimulating hormone (\(\alpha\)-MSH)/Melanocortin-1 Receptor (MC1R) or Microphthalmia-associated transcription factor (MITF) pathway.—Mutations of these receptors and factors may increase the risk of developing melanoma (Figure 1A).

**Melanocortin-1 Receptor (MC1R) gene, 16q24.**—MC1R is a transmembrane receptor for the \(\alpha\)-MSH gene.
that is expressed in melanocytes of the skin and hair follicles. It contributes to skin pigmentation by regulating the concentrations of eumelanin and pheomelanin. Its activation by ultraviolet radiation results in increased synthesis of eumelanin and increased melanocyte dendricity, proliferation, cell survival and DNA repair capability. On the other hand, loss of function of MC1R results in increased synthesis of pheomelanin pigment, as seen in 80% of individuals with red hair color, fair skin and poor tanning ability (also known as red hair phenotype).31, 32.

MC1R mutations associated with red phenotype increases the risk of developing melanoma, independent of pigmentation phenotype.32, 33 Indeed, results from meta-analyses have shown that MC1R variants linked with red hair color are associated with an increased relative risk for melanoma (RR=2.4, 95% 1.72, 3.46).34 In addition, melanomas in these patients tend not to be overtly conspicuous due to the fact that they often lack significant color variegation and often display few dermoscopic structures.35

MITF, 3p14.1-p12.3.—In normal melanocytes MITF stimulates melanin production and cell cycle arrest (anti-proliferative) by activating p16. Mutations in MITF have been shown in melanoma, which result in the inhibition of apoptosis (Figure 1). MITF gene has been found to be amplified in up to 20% of metastatic melanomas.36

4. Other genes.—Melanoma has been reported to occur more often in carriers with breast cancer 2 (BRCA2), or a combination of gene mutations.

BRCA2, 13q12.—Melanoma has been reported to occur more often in families with BRCA2. The Breast Cancer Linkage Consortium reported a relative risk of 2.6 (95% CI: 1.3, 2.5) for melanoma among BRCA2 carriers.37

Combination of genes.—Combination of gene mutations may increase the risk of melanoma by acting synergistically or by enhancing penetrance of one or the other gene. For example, MC1R variants in melanoma-prone families can double the risk of melanoma in CDKN2A mutation carriers. In addition, MC1R variants alleles can increase the penetrance of CDKN2A mutations in melanoma-prone families.38

Phenotypic characteristics

Individual phenotypic characteristics such as hair color, eye color, skin color and freckling are strongly related to ultraviolet radiation (UVR) sensitivity, which is an important risk factor for melanoma (Table III). Two independent phenotypic traits that place individuals at higher risk for melanoma are fair skin (see phototype below) and the presence of a large number of melanocytic nevi (see nevi 5 below).11

Phototype

The Fitzpatrick scale is most commonly used to determine the skin’s response to UVR and the skin’s ability to tan. Individuals with fair skin and poor ability to tan are classified having skin type I or II. Persons with darker skin are classified as skin types III-VI. Based on this scale, fairer skin types have an increased risk for melanoma. In fact, photo-types I and II have a significant higher risk for developing melanoma (RR=2.99; 95% CI: 1.75, 5.12) compared with persons with darker photo-types who rarely or never burn and tan easily.11

Nevi

There is a recognized association between nevi and melanoma. On the one hand, there is the observation that high nevus counts (common and atypical) are a risk marker for melanoma.39 On the other hand, any nevus may be a potential precursor to melanoma. In one study the lifetime risk of a nevus transforming into a melanoma was estimated to be approximately 0.03% for male and 0.009% for females.40 With that said it is important to note that only 26% of melanomas arise in association with a pre-existent nevus.
(Figure 2), while the remaining 74% of melanomas arise de novo (Figure 3).^{23,41}

**Number of common melanocytic nevi**

Nevus counts are correlated with pigmentary traits, sun-exposure and history of sunburns.\(^{39}\) Studies in twins have demonstrated that genetics play an important role in predicting total nevus counts. However, the ultimate nevus count can be influenced by sun exposure.\(^{42}\) Numerous studies from different parts of the world have shown that the relative risk for developing melanoma increases as the number of common melanocytic nevi increases.\(^{39,43}\) People with more than 100 nevi are at significant high risk for melanoma (RR=6.89; 95% CI: 4.63, 10.25) as compared with people with less than 15 nevi.\(^{39}\) In addition, 27% of melanoma cases are found in patients with more than 50 nevi, while individuals with less than ten nevi account for only 4% of melanoma cases.\(^{12}\) The number of nevi has been reported to be one of the strongest risk determinants for superficial spreading melanoma (OR 23.22, P<0.001).\(^{44}\)

**Number of atypical or dysplastic melanocytic nevi**

Clinically, an atypical nevus is considered to be at least 5 mm in diameter with a macular component and with at least two of the following three characteristics: variable pigmentation, irregular asymmetric outline and indistinct borders.\(^{45}\) Numerous studies have documented that the relative risk for developing melanoma increases as the number of atypical nevi increase,\(^{39,43}\) ranging from 1.60 (95% CI: 1.38, 1.85) for the presence of one atypical nevus up to 10.49 (95% CI: 5.05, 21.76) for five atypical nevi.\(^{39,45,49}\) In another study, Olsen et al. reported that 25% of melanoma cases occurred in individuals with one of more atypical nevi.\(^{12}\)

Atypical or dysplastic nevi were first recognized in rare melanoma-prone families. These families have one or more first- or second degree relatives with melanoma, multiple nevi and dysplastic nevi.\(^{46}\) Affected individuals in these families are said to have the familial atypical multiple-mole melanoma (FAMMM) syndrome or atypical mole syndrome. FAMMM syndrome is also linked to the development of other cancers including breast cancer and pancreatic cancer.\(^{29,46}\) The FAMMM syndrome may be considered as a spectrum of phenotypic expressions, in which there is an associated p16 mutation.\(^{29,47}\) The lifetime risk of melanoma in an affected family member has been reported to approach 100%.\(^{47,48}\) Clues to help identify FAMMM syndrome, include families with multiple cases of melanoma, multiple primary cancers in the same person and the diagnosis of melanoma at younger age (before 40 years of age).\(^{45}\)

Atypical or dysplastic nevi can also occur in the non-familial setting. The estimated prevalence in the general Caucasian population may range from 7% up to 18%, depending on the type of study or geographical location.\(^{49,50}\) These individuals have a lifetime risk for melanoma of approximately 10%. In addition, atypical nevi have been associated with higher risk of developing multiple primary melanomas (OR=3.28).\(^{51}\) One study showed that up to 38% of patients with multiple primary melanomas presented with atypical nevi as compared with 18% of patients with only one primary melanoma.\(^{52}\)

It is important to highlight that dysplastic nevi are stronger risk markers for melanoma than they are precursors to melanoma.\(^{53}\) Since most melanomas develop de novo, the prophylactic whole scale removal of dysplastic nevi will not eliminate the risk for developing melanoma. Hence, these patients will benefit more from meticulous surveillance than they will from indiscriminate removal of their nevi.
DERMOSCOPY OF MELANOCYTIC NEVI

Dermoscopic patterns further define individuals at higher risk for developing melanoma.54, 55 Scope et al. suggested that children with complex pattern nevi, which includes the presence of both network and globules in the same lesion, may be individuals at increased risk for developing atypical nevi or melanoma in the future [55]. Furthermore, Lipoff et al. demonstrated that nevi manifesting a complex dermoscopic pattern in adults were more frequent in melanoma patients than in controls (OR 2.9, P=0.003).54

CONGENITAL MELANOCYTIC NEVI (CMN)

The presence of a CMN is determined in utero and while they can be visible at birth, some may not become apparent until sometime after birth (“tardive” CMN).56 Melanoma can develop within any CMN;57 however, the risk for developing melanoma appears to correlate with the size of the nevus.58 Essentially, the risk for melanoma developing in a small CMN (≤1.5 cm) or medium CMN (1.6-19.9 cm) is low, with a lifetime risk reported to be between 0% and 5%; with a relative risk of approximately 10. In contrast, the lifetime risk for melanoma developing in a large (20-39.9 cm) or giant CMN (≥40 cm) is between 4.5% and 10%; with a relative risk that ranges from 52 to 1046.45

History of previous melanoma

A personal history of melanoma is considered an important risk factor for developing subsequent melanomas.31 Most second primary melanomas tend to be diagnosed within the first two years after the diagnosis of the first primary melanoma.11 Ferrone et al. reviewed a prospective database of 4484 melanoma patients to determine the incidence of multiple primary melanomas (MPM). They found that the estimated cumulative five-year risk to develop a second primary melanoma was 11.4%, with more than half of the risk occurring within the first year. After the second primary melanoma was diagnosed, the cumulative five-year risk to develop a third primary melanoma was estimated to be 31%, with half of that risk occurring during the first year after the diagnosis of the second melanoma.59 Subsequent melanoma, whether synchronous (60%) or metachronous, tend to be thinner; probably a result of increased detection pressure resulting in heightened surveillance, scrutiny and vigilance.60

Actinic damage and non-melanoma skin cancer (NMSC)

A positive association between actinic damage and melanoma has been demonstrated with a reported relative risk of 2.96.11 Chronic actinic damage is correlated with the number of solar lentigines, elastosis, actinic keratoses and lentigo maligna melanoma (LMM).44, 61, 62 The number of solar lentigines is considered one of the strongest predictors for LMM (OR 15.93, P<0.001).44 Intermittent actinic damage is correlated with number of nevi, sunburns and superficial spreading melanoma.44, 62 In addition, having a history of a basal cell carcinoma or SCC increases the risk for melanoma between 4 to 17-fold11, 63 (RR=4.28, 95% CI 2.80, 6.55).11

Immunosuppression

Immunosuppression secondary to cancer or acquired immune deficiency syndrome has been shown to be associated with melanoma. Likewise, organ transplant recipients have a 3- to 5-fold increased risk for melanoma and these melanomas tend to be diagnosed at a mean of 5 years post-transplant.64 In addition, patients with diagnosis of non-Hodgkin’s lymphoma or chronic lymphatic leukemia are also at increased risk for developing melanoma.65

Other medical conditions

XERODERMA PIGMENTOSUM (XP)

XP is an autosomal recessive pigmentary skin disorder characterized by photosensitivity and a high predisposition for developing skin cancers.15 XP gene mutations result in an inability to repair DNA damage sustained from UVR. This inability to repair the damaged DNA is due to defective nucleotide excision enzymes. These patients are at higher risk for developing melanoma. One study showed that the frequency of skin, eye and tongue cancers was increased 1000-fold or more in patients with XP who were younger than 20 years. Of the skin cancers diagnosed in these patients 22% were melanomas and 57% were basal cell or squamous
cell carcinomas. Although XP is a rare disease, this condition highlights the carcinogenic effect of UVR and its direct role in induction of mutations that result in the formation of skin cancer.

**PARKINSON DISEASE**

Recent studies have shown a moderate association of Parkinson disease with melanoma, independent of levodopa treatment.

**Environmental risk factors**

Epidemiological, basic science, molecular and animal studies have demonstrated that UVR plays a major role in the development of melanoma and is currently considered the only preventable environmental cause for this malignancy. Both UVB (290-320 nm) and UVA (320-400 nm) have been implicated in the development of melanoma by causing either direct (UVB) or indirect (UVA) DNA damage. Specifically, UVB produces direct pyrimidine dimer lesions, while UVA triggers damage through reactive oxygen species intermediates.

Exposure to UVR can be obtained from natural sunlight and artificial sources including indoor tanning beds. Both UVR sources have been classified as “carcinogenic to humans” by the working group of the International Agency for Research on Cancer (IARC). Recently, Pleasance et al. performed a comprehensive sequencing of the entire genome of a melanoma, demonstrating for the first time that most somatic substitutions in this melanoma were attributable to UVR-induced DNA damage.

**Natural UVR (sunlight)**

The amount of UVR an individual receives is often classified as chronic or intermittent. Although not all melanomas are related to sun exposure, most melanomas appear to be related to UVR exposure. Intermittent sun exposure confers a high risk for melanoma (RR = 1.61 with 95% CI: 1.31, 1.99) of the superficial spreading type. In contrast, chronic sun exposure has been linked to the formation of lentigo maligna melanoma (Table II).

Intermittent intense exposure resulting in sunburns has been associated with melanoma (RR=2.03 with 95% CI: 1.73, 2.37). This association is higher if the sunburn occurs during childhood (RR=2.24) or at higher latitudes (RR=2.54) as compared with sunburns during adulthood (RR=1.92) or at lower latitudes (RR=1.91). Moreover, it has been shown that the number of lifetime sunburns is more strongly associated with superficial spreading melanoma than it is with LMM.

**Artificial UVR**

**TANNING BEDS**

The amount of UVR obtained from indoor UV often exceeds that received during normal outdoor activities and has been associated with melanoma (OR 2.06 95% CI 1.30-3.26). A meta-analysis of epidemiological studies on indoor tanning and risk for melanoma concluded that the risk of cutaneous melanoma was higher (RR=1.75) when tanning beds were used for the first time before the age of 30 years.

**PHOTOTHERAPY**

Photochemotherapy and UVA radiation (PUVA) has been associated with an increased risk for melanoma. The latency period from the time of the PUVA to the time of the melanoma diagnosis was reported to be as long as 15 years.

**Melanoma prognostic factors**

The most significant prognostic factors for melanoma are included in the seventh edition of the American Joint Committee on Cancer (AJCC) for melanoma staging and classification (Table IV). The most important prognostic factors for localized melanoma (Stage I and II) are tumor thickness, mitotic rate and ulceration. Thus, the initial biopsy is critically important for diagnostic staging and prognosis. If feasible, an excisional biopsy with a narrow 1 to 2 mm margin is preferred to a shave or punch biopsy since this provides the necessary prognostic information and prevents histopathologic misdiagnosis. The most important predictor of disease-specific survival is the status of the sentinel lymph node. The number of regional lymph nodes harboring metastatic disease and the regional node tumor burden are also considered independent predictors of survival. Other prognostic factors in regional metastatic melanoma...
Management of melanoma patients

The cornerstone of melanoma management remains surgical removal of resectable primary and metastatic tumors. For the primary tumor, studies and meta-analyses have shown that there is no significant difference in overall survival between narrow versus wide local excision. Recently, Gillgren et al. evaluated the overall survival of 936 patients with primary tumors thicker than 2 mm (median thickness of 3.1 mm). Patients were randomly assigned to undergo excision with a 2 cm margin (N.=465) or 4 cm margin (N.=471) and were followed for up to 11.8 years. The authors found that the outcome in both groups was the same, with a five-year overall survival of 65% for both groups. Thus, it was concluded that 2-cm margins are sufficient for patients with melanomas thicker than 2 mm.

Sentinel lymph node biopsy is a procedure performed in patients with localized disease to identify those with nodal metastases with a high degree of accuracy. Candidates for sentinel lymph node biopsy include patients with melanomas that are 1.0 mm or more in thickness or patients with melanomas that have other factors not included in the AJCC for melanoma staging that have been shown to impact the prognosis are listed in Table V. Older age has been reported to be an independent adverse prognostic factor among patients with melanoma. Conversely, studies in children have demonstrated that children with melanoma have a higher survival probability as compared to adults, particularly when diagnosed before puberty. Scalp melanomas have more than a three-fold increased risk for mortality and a higher rate of recurrence as compared with other sites. Tseng and Martinez reported a series of 27097 patients with cutaneous melanoma on the head and neck. They found that scalp/neck and lip melanomas had a 64% and 55% increased risk of disease-related death, respectively and were associated with poorer melanoma-specific survival.

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<tr>
<th>Table IV.—Prognostic factors for melanoma according to the AJCC staging.12, 13</th>
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<td><strong>Localized melanoma (Stage I and II)</strong></td>
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<td>Tumor thickness (mm)</td>
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<td>Mitotic rate</td>
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<td><strong>Regional metastatic melanoma (Stage III)</strong></td>
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<td>Number of regional lymph nodes harboring metastatic disease</td>
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<td>Regional node tumor burden (micro- vs. macroscopic)</td>
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<td>Satellites/in-transit metastases</td>
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<td><strong>Prognostic factor</strong></td>
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<td><strong>Comment</strong></td>
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<tr>
<td>Age</td>
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<tr>
<td>Older age has been associated with poor prognosis</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Male gender has been associated with poor prognosis</td>
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<tr>
<td>Anatomic location of the primary melanoma</td>
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<tr>
<td>Scalp, neck and lip melanomas have been associated with poor prognosis</td>
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<tr>
<td>Other histological features</td>
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<td>Lympho-vascular invasion in the primary tumor</td>
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<tr>
<td>Presence vertical growth-phase</td>
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<td>Tumor-infiltrating lymphocytes</td>
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<td>Dermal regression</td>
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(Stage III) include the presence or absence of satellite/in-transit metastases. In distant metastatic melanoma (Stage IV), an elevated serum lactate dehydrogenase (LDH) is an independent and significant predictor of survival. Additionally, the number and location of metastases at distant sites is also an important prognostic factor.

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The cornerstone of melanoma management remains surgical removal of resectable primary and metastatic tumors. For the primary tumor, studies and meta-analyses have shown that there is no significant difference in overall survival between narrow versus wide local excision. Recently, Gillgren et al. evaluated the overall survival of 936 patients with primary tumors thicker than 2 mm (median thickness of 3.1 mm). Patients were randomly assigned to undergo excision with a 2 cm margin (N.=465) or 4 cm margin (N.=471) and were followed for up to 11.8 years. The authors found that the outcome in both groups was the same, with a five-year overall survival of 65% for both groups. Thus, it was concluded that 2-cm margins are sufficient for patients with melanomas thicker than 2 mm (Table VI).

Sentinel lymph node biopsy is a procedure performed in patients with localized disease to identify those with nodal metastases with a high degree of accuracy. Candidates for sentinel lymph node biopsy include patients with melanomas that are 1.0 mm or more in thickness or patients with melanomas that
are less than 1.0 mm in thickness with other adverse prognostic features such as thickness greater than 0.75 mm, positive deep margins, ulceration, high mitotic rate, lymphovascular invasion and younger age.79, 89

In the event of unresectable disease, treatments with systemic therapy utilizing chemotherapy, biotherapy, and/or immunotherapy need consideration; the most well known of these include Dacarbazin, interleukin-2, and interferon. Recent advances in our understanding of the immune system and the molecular “drivers” of melanoma cell proliferation have lead to the development of targeted therapies for melanoma. These new therapies include Vemurafenib, which is a selective BRAF inhibitor, and Ipilimumab, which is an IgG1 monoclonal antibody that blocks cytotoxic T-lymphocyte associated antigen-4, which in turn increases T-cell activation and proliferation.90, 91 It is beyond the scope of this review to discuss the myriad of management choices available for each stage of melanoma. However, it is clear that patients with a previous melanoma are at increased risk for developing subsequent new primary melanomas and thus, these patients are likely to benefit from the implementation of prevention strategies. Prevention strategies have been categorized into primary and secondary prevention. Primary prevention entails the prevention of the disease via modifying melanoma risk factors. Secondary prevention involves early detection and treatment of melanoma (or melanoma precursor lesions) while the tumor is thin and easily curable by simple surgical excision.92

**Primary prevention**

Avoiding excessive and unnecessary UV exposure from natural or artificial sources and protecting the skin from harmful UV radiation constitutes the mainstay of primary prevention.

### Ultraviolet Protection

Physical barriers such as clothing, sun glasses, hats and seeking shade are important elements for sun protection.93 Factors that limit the amount of UV passing through clothing include tightly woven fibers, thicker and dark-color fabrics, unbleached fabrics, lax and dry materials.93 The UV protection factor (UPF) is the rating placed on sun protective textiles/clothing and it is a measure of the fabric’s ability to block both UVA and UVB. A UPF rating of at least 40 blocks more than 96% of the UV radiation and is the current recommended UPF rating that will provide sufficient protection irrespective of geographical location.94

The eyelids and the skin surrounding the eyes also need to be protected from UV rays. One method to accomplish this task is the wearing of UV-blocking glasses or sunglasses. An added benefit of wearing UV protective eyewear is the lowering of the risk for cataract development. The wearing of a broad brimmed hat can also decrease the amount of UV reaching the eyes. Such hats have the added advantage of also protecting the scalp, ears, face and neck from UVR.95

Topical sunscreens are broadly categorized into inorganic (also known as physical) and organic (also known as chemical). The inorganic sunscreens, such as zinc oxide and titanium dioxide, reflect and scatter UVR and visible light. In contrast, organic sunscreens absorb UVR, and are further categorized into UVA filters, UVB filters or broad-band filters, which absorb both UVA and UVB.93 The sunscreen’s ability to protect the skin from UV radiation can be measured. The Sun Protection Factor (SPF) is used as the worldwide standard gauge for UVB protection and it is reported as a number, which is a proportion derived from measurements of the minimal erythema dose of sunscreen protected skin versus unprotected skin. Regarding UVA protection measurements, there is no one worldwide standard. Current labeling regulations of the European Commission (2006), accepts two methods for measuring UVA protection (i.e., persistent-pigment darkening method and the critical wavelength) divided into four “levels of protection” categories (i.e., “low”, “medium”, “high”, “very high”).96 In contrast, the FDA, in June 2011, recommended one pass/fail test using the *in vitro* critical wavelength (CW) as the method for measuring UVA or broad-spectrum protection.97 The CW is an *in vitro*
demonstrated that the regular use of sunscreen with an SPF of at least 15 reduces the incidence of new primary melanomas.98

Primary prevention can also be achieved through educational campaigns, which can help change behavior and result in reduced UV exposure in the population. Some of these campaigns and educational resources include the Euromelanoma,99 National Council in Skin Cancer Prevention (http://www.skincancerprevention.org/), Skin Cancer Foundation (www.skincancer.org), Sunwise (www.epa.gov/sunwise/), SunSmart (http://www.sunsmart.com.au/) and the Slip! Slop! Slap! Campaign. Some of these educational programs have demonstrated a general improvement in sun-protective behaviors of individuals over time, highlighting that population’s sun-protective behavior is amenable to change.100, 101

Chemoprevention of melanoma

Chemoprevention aims to prevent the development of melanoma. However, chemopreventive agents for melanoma remain under investigation and, to date, there are no drugs approved for this purpose. Although chemoprevention agents such as nonsteroidal anti-inflammatory drugs (NSAIDs, COX-inhibitors), statins and antioxidants (i.e., resveratrol, betacarotene) have been studied, results have been conflicting.102-104 For example, Curiel et al. performed a case-control study to assess the association between melanoma and NSAIDs and found that the con-

Figure 3.—Melanoma de novo in a patient with the atypical mole syndrome. A) A new lesion on the face was observed on comparison with baseline images; B) dermoscopy evaluation demonstrates a melanoma with a multicomponent pattern. Lesion was biopsied revealing a melanoma without any associated nevus.
A recent study on melanoma detection patterns in high-risk individuals under surveillance demonstrated that physician detected melanomas were thinner as compared to self-detected melanomas (0.30 mm vs. 0.5 mm).108 The efficiency and effectiveness of physician based total body skin examination can be enhanced by the use of imaging technologies. Two of the most commonly used techniques are dermoscopy and total body photography (TBP). TBP consists of a set of clinical images of the entire skin surface. These images serve as a baseline to which subsequent skin examinations are compared. Comparing the skin to previ-
The combined use of TBP and dermoscopy is likely to translate into a much improved sensitivity and specificity for the detection of melanoma, which in turn results in the appropriate removal of skin cancers while at the same time minimizing the unnecessary removal of benign and biologically indolent lesions. Some physicians have started advocating total body dermoscopy, which entails obtaining baseline dermoscopic imaging of all or almost all nevi in a given individual. These lesions can then be reimaged with dermoscopy in the future and compared to the baseline dermoscopic images. Changes noted on dermoscopic follow-up of lesions is necessary. The combined use of TBP and dermoscopy is likely to translate into a much improved sensitivity and specificity for the detection of melanoma, which in turn results in the appropriate removal of skin cancers while at the same time minimizing the unnecessary removal of benign and biologically indolent lesions. Some physicians have started advocating total body dermoscopy, which entails obtaining baseline dermoscopic imaging of all or almost all nevi in a given individual. These lesions can then be reimaged with dermoscopy in the future and compared to the baseline dermoscopic images. Changes noted on dermoscopic follow-up of lesions.
may further improve upon the sensitivity of finding early melanoma.\textsuperscript{112, 113} (Figure 8).

Patient detection.—Patients also play an important role in melanoma detection. It has been reported that more than 68\% of melanomas are detected by patients or their relatives.\textsuperscript{114} Although physicians are more likely to detect thinner melanomas than patients,\textsuperscript{114, 115} patients who perform SSE detect thinner melanomas as compared to patients that do not perform SSE.\textsuperscript{116} One study showed a reduction in the incidence of melanoma, less advanced disease and decreased melanoma mortality by up to 63\% in patients performing SSE.\textsuperscript{117} Kovalyshyn \textit{et al.} demonstrated that high-risk patients that are under active surveillance detect a greater percentage of their own melanomas while the melanomas are in situ (70\% vs. 57\%) and thin (0.45 mm vs. 0.82 mm) as compared to patients who are not under active surveillance.\textsuperscript{108} In other words, SSE and physician based surveillance examinations should be viewed as complementary methods that together enhance the discovery of thin curable melanomas. To assist patients in their SSE some have advocated provided them with their own set of baseline TBP and perhaps even their own dermatoscope.\textsuperscript{108, 118}
Secondary prevention by removing precursor lesions

It is important to point out that there are no known obligate precursor lesions to melanoma. Although melanoma can arise in association with dysplastic nevi, congenital nevi and lentigines, these lesions are all considered potential non-obligate precursors to melanoma.\textsuperscript{40, 41, 57} Furthermore, the absolute risk of any one of the aforementioned lesions transforming into melanoma is very small and thus, the prophylactic removal of all these benign lesions would be unwarranted, impractical and cost prohibitive. Unfortunately, there is currently no method available at our disposal that can reliably identify which of the benign lesions is destined to transform into melanoma. However, it is intriguing to speculate that while biologically indolent (non-changing or senescent) lesions are likely benign, some of the biologically dynamic (changing, breaking out of senescence) lesions that are found to be histologically benign may in fact be lesions that are on the road to melanoma. In other words, albeit histologically “benign,” a higher percentage of these changing lesions, matched with their histologically equivalent, clinically static counterparts, are biologically destined towards melanoma (i.e., the true melanoma precursor lesion). What this implies is that some lesions that are histologically diagnosed as benign lesions may in fact be malignant when viewed on the molecular level.\textsuperscript{119}

Entire textbooks have been written on risk factors, prognosis and management of melanoma. With that said, the aim of this brief review was to provide a concise overview and to highlight some of the new and/or novel research published on this topic over the past few years. Attempts were made to focus on issues that are likely to be pertinent to busy practicing dermatologists such as awareness of variables that predispose an individual to skin cancer, strategies for UVR protection, and the importance of screening and surveillance of high-risk patients for the development of new primary melanomas. An emphasis on the molecular /genetic pathways in melanoma was deemed important due to the exciting emergence of targeted therapies for melanoma. In the future it is highly likely that management of melanoma patients will be individualized based on identifying a given patient’s immune system and molecular “drivers” for their specific melanoma.

Riassunto

Un aggiornamento su fattori di rischio, prognosi e gestione dei pazienti con melanoma

Il melanoma cutaneo continua a essere un problema di salute pubblica mondiale, con un’incidenza in crescita in tutto il mondo. Il riconoscimento dei fattori di rischio per l’insorgenza del melanoma permette di identificare un sottogruppo di pazienti ad alto rischio, i quali hanno un’elevata probabilità di beneficiare da approcci volti a ridurre l’esposizione alle radiazioni ultraviolette e da strategie di controllo orientate alla rilevazione dei melanomi quando
sono sottili e facilmente curabili. In questa review forniamo una panoramica sui fattori prognostici e di rischio più pertinenti, nuovi e recenti. Esamineremo quindi i potenziali benefici delle strategie di controllo dei tumori cutanei, inclusi l’esame cutaneo completo da parte del medico, la valutazione fotografica dell’intera superficie cutanea, la dermoscopia e l’autovalutazione cutanea da parte del paziente. Oltre a ciò, discuteremo della gestione dei pazienti con melanoma, con un accento particolare sulla prevenzione e sulle strategie di rilevazione in fase iniziale.

Parole chiave: Melanoma - Rischio, fattori - Nevo - Raggi ne e sulle strategie di rilevazione in fase iniziale.

References


Lentigo maligna melanoma (LMM) is a malignancy with increasing incidence, accounting for about 4% to 15% of all melanomas. Lentigo maligna (LM) is LMM in situ, usually presenting an irregular tan colored or brownish pigmented macular lesion persisting for years on chronically sun-exposed skin. Left untreated, LM may evolve into invasive form of LMM. Histologic evaluation of LM/LMM can be difficult due to widespread atypical melanocytes that are present in the area chronically sun damaged skin. It has been shown that chronically sun-damaged non-lesional skin can display some atypical features even in the absence of a melanocytic neoplasm. It is important for dermatopathologists to be aware of these findings so that such features are interpreted appropriately when making a histological assessment that may ultimately influence therapy and outcome. LMM is characterized by significant subclinical lesion extension which makes the treatment another challenge. Nowadays, a variety of therapeutic options are available in the treatment of LMM. Surgery remains the mainstay of LMM therapy, however the treatment of LM remains controversial subject in the literature. Non-surgical treatment modalities for LM include: destructive procedures such as radiotherapy, cryotherapy, curettage, laser, electro-destruction and immunotherapy with the topical application of 5% imiquimod cream. These treatment options should be considered for a subset of patients with LM, especially in elderly patients with extensive or unresectable disease in difficult areas on the face or, as a second-line therapy if surgery is contraindicated. Surgical options include simple excision and margin-control techniques such as staged excision and Mohs micrographic surgery. In this article, authors are reviewing the latest diagnostic and therapeutic advances in the management of LMM.

**Key words:** Hutchison’s melanotic freckle - Melanoma - Diagnosis - Histology - Therapeutics - Surgical procedures, minimally invasive.

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breuilh, represents LMM in situ. This lesion was first described by Hutchinson in 1892 as the presence and overgrowth of atypical melanocytes at the dermal-epidermal junction in chronically sun-damaged skin. Clinically, LM presents as an irregular tan colored or brownish pigmented macular lesion persisting for years on chronically sun-damaged skin. Lesions can vary in location, size, and color, ranging from tan to black. Left untreated, LM may continue to grow and evolve into invasive form of LMM with dermal invasion. The estimated lifetime risk of LM progressing to invasive LMM is estimated to be around 5%. In fact, some authors report that approximately 16% of LM harbor areas of early invasive LMM. Clinical diagnosis of LM and LMM, especially in early stage may be very difficult. Early diagnosis of LM requires a high index of suspicion for the often subtle atypical signs of pigmented lesions on sun-damaged skin. Clinical margins of these melanocytic lesions can be better visualized by Wood’s light examination. Dermatoscopy and confocal laser microscopy are imaging methods that can be useful tool and aid in diagnosing LM/LMM.

The progression from LM into LMM is clinically usually noticeable by the development of darker areas or elevated parts or dark nodules within the previously uniformly pigmented long-lasting macule. Since the complete LM or LMM lesion is often an extensive lesion on cosmetically sensitive parts of the body, such as face and neck area, in specific situations the prominent parts of the lesion are biopsied (with full-thickness incisional or punch biopsy) to confirm the diagnosis.

Differential diagnoses of LM/LMM include a wide spectrum of pigmented skin lesions such as: solar lentigo (early lesions of seborrheic keratoses), lentigo simplex, lichen planus-like keratosis, pigmented actinic keratosis, pigmented basal cell carcinoma, squamous cell carcinoma and dysplastic nevus. A specific problem in clinical recognition and diagnostics is amelanotic LM which presents as a pink macule with little to no pigmentation and often resembles an inflammatory lesion rather than a melanocytic neoplasm.

Dermatoscopy, a non-invasive clinical technique which has become a part of an every-day dermatological practice over the last decade, has been shown to have higher diagnostic accuracy, especially in the diagnosis of pigmented skin lesions. Major dermatoscopical features of LM/LMM include: asymmetrical pigmented follicular openings, rhomboidal structures, annular-granular structures and gray pseudo-network. LM, at first, seems to occur as asymmetrical pigmented follicular openings and/or annular-granular structures, then expand and develop into the rhomboidal structures. However, annular-granular structures and gray pseudo-network can also be found (but usually more homogeneous) in regressive areas of solar lentigo (early stage of seborrheic keratosis), as well as in lichen planus-like keratosis and pigmented actinic keratosis.

One should also keep in mind that previous treatments may alter clinical presentation of LM/LMM. For example, it has been reported that topical imiquimod may remove visible pigment while having no effect on the histological findings.

**Histology**

The histologic hallmark of LM is the presence of an increased number of atypical melanocytes in the basal layer of the epidermis in small nests or single cells, usually extending into periadnexal structures. Other histologic features of LM/LMM are: an atrophic epidermis, solar elastosis, predominance of spindle-shaped melanocytes, poor circumscription, and melanocytic nuclear atypia, as well as the presence of an inflammatory dermal infiltrate. However, the diagnosis of cutaneous melanocytic lesion requires special expertise and experience of the pathologist. Establishing the histological diagnosis of LM/LMM can be challenging due to several reasons. Since LM/LMM are often large lesions commonly located on the head and neck area, usually small (subtotal) biopsy samples are taken to confirm the diagnosis before the definitive treatment. For dermatopathologists, it can be very difficult to interpret such small lesion samples. Also, LM is a type of lesion in which a marked heterogeneity in the histological features in different portions of the same lesion can be found. In certain areas, the lesion of malignant skin tumour such as LM/LMM, may display features of a benign skin lesion such as solar lentigo or dysplastic nevus. Therefore, interpreting just a small part of an extensive melanocytic lesion like LM may be misleading. Another problem in diagnosing LM/LMM is the fact that these lesions typically develop in areas of chronically sun-exposed skin. These transition areas between the lesion itself and the surrounding solar
damaged skin can lead to inadequate excisions and recurrent disease depending on the choice of surgical procedure and how the histology is processed and analyzed.\textsuperscript{8} The differentiation of melanoma in situ, including LM from melanocytic hyperplasia (so-called solar melanocytosis) in sun-damaged skin can sometimes be difficult. In a study conducted by Weyers et al., several criteria have been proposed after examining the epidermis adjacent to 50 consecutive basal cell carcinomas and 50 melanomas in situ (MIS) in the area of the skin with significant solar elastosis.\textsuperscript{28} In this study, the most valuable criteria for the diagnosis of melanoma in situ (MIS), as opposed to melanocytic hyperplasia, were: presence of nests of melanocytes, irregular distribution of melanocytes, descent of melanocytes far down adnexal epithelial structures, irregular distribution of pigment, presence of melanocytes above the junction, a high number of melanocytes, pleomorphism of melanocytes, and atypical nuclei of melanocytes.\textsuperscript{28}

Furthermore, atypical lentiginous melanocytic lesions, especially when encountered in older patients, often pose a diagnostic difficulty.\textsuperscript{29} LM is histologically characterized by a broad atypical lentiginous growth pattern of moderately atypical melanocytes showing focal nesting and pagetoid spread without significant dermal fibroplasia or alteration of the rete ridges.\textsuperscript{29} It may show significant overlap in clinical and histologic features with atypical lentiginous nevus (of the elderly), but the relationship between these entities has not yet been explained.\textsuperscript{29}

In order to improve diagnosing lesions of LM/LMM, several immunohistochemical staining methods have been employed and the most commonly used stains are HMB-45 and MART-1. Hendi et al. analyzed the density and distribution of melanocytes using Melan-A and H&E stains on nonlesional sun-exposed skin of the face and neck in 100 patients, and quantified the presence and extent of features considered characteristic of melanoma in noncancerous specimens of sun-damaged skin. They reported that relatively high melanocyte density, mild to moderate confluence of melanocytes, focal pagetosis, superficial follicular extension (<1.0 mm), and mild or moderate cytologic atypia may be observed in the absence of a melanocytic neoplasm.\textsuperscript{30} It is important for dermatopathologists to be aware of these findings to potentially prevent the overdiagnosis of melanoma.\textsuperscript{30}

Bowen \textit{et al.}, in their study with Melan-A immuno histochemical staining found that uninvolved sun-damaged skin shows features characteristic of LM.\textsuperscript{31} In order to identify the immunohistochemical similarities and differences in melanocyte distribution between LM and LMM and chronically sun-exposed skin, they retrospectively analyzed Melan-A-stained original biopsy specimens of LM and LMM and uninvolved sun-damaged skin (negative controls), from 70 LM and LMM cases.\textsuperscript{31} Their research showed that histologic features commonly associated with LM were common in negative controls from chronically sun-exposed skin. Melanocyte confluence (27/70, 39%), stacking (34/70, 49%), theque formation (9/70, 13%), adnexal extension (59/68, 87%), and suprabasilar scatter (23/70, 33%) were observed in the negative controls from sun-damaged skin. Such features were present nearly uniformly in the LM and LMM specimens. Epidermal melanocyte density in LM and LMM differed significantly from that in negative controls.\textsuperscript{31} Therefore, greater density and unusual patterning of melanocytes in chronically sun-exposed skin may be difficult and, on occasion, complicate interpretation of intraoperative Melan-A immunohistochemical stained margins during margin-controlled surgery for LM and LMM.\textsuperscript{31}

Another possible problem in diagnosing LM/LMM lesions may result from the classification of LM as MIS. This is because some pathologists make differentiation between LM as melanoma precursor and a true MIS according to the number of atypical melanocytes and the pattern of their arrangement in the basal epidermis.\textsuperscript{8} However, today’s nomenclature uses the term LM for malignant melanoma in situ occurring in the head and neck sun-damaged skin area in elderly people.\textsuperscript{8}

\textbf{Treatment}

Nowadays, a variety of therapeutic options are available in the treatment of LMM. Surgery remains the mainstay of melanoma treatment at all sites.\textsuperscript{15, 32} However, the treatment of MIS, particularly the LM subtype, has been a controversial subject in the literature for many years.\textsuperscript{33} In cases of LM, treatment modalities other than surgical excision may be used in certain situations.\textsuperscript{14, 16} Non-surgical treatment modalities for LM include: destructive procedures such as radiotherapy, cryotherapy, curettage, laser and electro-destruction.\textsuperscript{14} These treatment options should be
considered for a subset of patients with LM, especially in elderly patients with extensive or unresectable disease in difficult areas on the face or, as a second-line therapy if surgery is contraindicated. Immuno-therapy with the topical application of 5% imiquimod cream has also been more recently proposed as a possible therapy for LM. Initial studies of the LM treatment with imiquimod 5% cream have shown promising results with good cosmetic outcome, but the follow-up duration in most studies was short. In a recently published study with a long-term follow-up after the treatment of LM with imiquimod cream, complete clinical clearance was achieved in nine out of 10 patients, and five out of 10 patients sustained clinical remission. According to these results, imiquimod appears to be an effective treatment for a subset of patients with LM. However, long-term follow-up and multiple post-treatment biopsies are strongly recommended, even in the absence of a clinical recurrence. On contrary, some authors reported low cure rates with local imiquimod cream, emphasizing the importance of caution because some of these lesions contain an unrecognized invasive component. Generally, non-surgical treatment modalities carry a significantly increased risk of local recurrence.

As it was already mentioned, surgical excision remains the treatment of choice for LM and LMM. Surgical methods that have been used for years in the treatment of LM/LMM include simple excision and margin-control techniques such as staged excision and Mohs micrographic surgery, as well as certain new modifications of the aforementioned techniques.

The current recommendation is local resection with a 0.5 to 1.0 cm margin of normal skin. Traditional excisional surgery refers to excision of tumour with surgical margins defined beyond the clinically determined borders of the lesion. The excised tissue is then analyzed by the pathologist. However, the standard bread-loafing technique enables analysis of only around 1% of the margins. Simple excision seems to be an appropriate therapy for clinically well-defined tumours however; LM and LMM are often large and clinically ill defined lesions. Moreover, subclinical extension of tumour together with the poikilodermatous aspect of the solar damaged skin, make the border distinction difficult. Because of these characteristics, the margins of LM/LMM lesions may be underestimated which carries a risk of insufficient resection with simple excision surgery. Therefore, margins of at least 10 mm are usually recommended for complete excision of LMM, in some cases even for in situ lesions. Since most LMM lesions occur on the skin of the face and neck area, the narrowest possible margin is desired in order to minimize the scarring. Hence, the surgical challenge is to spare tissue while still achieving clear margins.

Margin-control surgery offers the highest cure rate while minimizing loss of normal tissue. Mohs micrographic surgery (MMS) is still considered a valuable option for the treatment of melanoma in situ, especially for LM subtype which is usually clinically ill defined. The technique of MMS refers to the removal of lesions in stages, with serial examination of histologic margins by the Mohs surgeon using horizontally oriented frozen sections. On contrary, some authors reported low cure rates with local imiquimod cream, emphasizing the importance of caution because some of these lesions contain an unrecognized invasive component. Generally, non-surgical treatment modalities carry a significantly increased risk of local recurrence.

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As it was already mentioned, surgical excision remains the treatment of choice for LM and LMM. Surgical methods that have been used for years in the treatment of LM/LMM include simple excision and margin-control techniques such as staged excision and Mohs micrographic surgery, as well as certain new modifications of the aforementioned techniques.

The current recommendation is local resection with a 0.5 to 1.0 cm margin of normal skin. Traditional excisional surgery refers to excision of tumour with surgical margins defined beyond the clinically determined borders of the lesion. The excised tissue is then analyzed by the pathologist. However, the standard bread-loafing technique enables analysis of only around 1% of the margins. Simple excision seems to be an appropriate therapy for clinically well-defined tumours however; LM and LMM are often large and clinically ill defined lesions. Moreover, subclinical extension of tumour together with the poikilodermatous aspect of the solar damaged skin, make the border distinction difficult. Because of these characteristics, the margins of LM/LMM lesions may be underestimated which carries a risk of insufficient resection with simple excision surgery. Therefore, margins of at least 10 mm are usually recommended for complete excision of LMM, in some cases even for in situ lesions. Since most LMM lesions occur on the skin of the face and neck area, the narrowest possible margin is desired in order to minimize the scarring. Hence, the surgical challenge is to spare tissue while still achieving clear margins.

Margin-control surgery offers the highest cure rate while minimizing loss of normal tissue. Mohs micrographic surgery (MMS) is still considered a valuable option for the treatment of melanoma in situ, especially for LM subtype which is usually clinically ill defined. The technique of MMS refers to the removal of lesions in stages, with serial examination of histologic margins by the Mohs surgeon using horizontally oriented frozen sections. On contrary, some authors reported low cure rates with local imiquimod cream, emphasizing the importance of caution because some of these lesions contain an unrecognized invasive component. Generally, non-surgical treatment modalities carry a significantly increased risk of local recurrence.
of resection for LM.\(^{39}\) In their study, a Wood’s light was used to delineate the clinical margin in 16 cases of LM that were resected with serial excisions 0.3, 0.6, 1.0, and 1.3 cm from the clinical border of the tumor. Frozen sections were confirmed by fixed histopathologic specimens. Subsequently these tissue blocks were examined with HMB-45 monoclonal antibodies. Patients were observed 5 to 9 years. Only one of the 16 patients had a recurrence 8 years after surgery.\(^{39}\) In general, traditional Mohs surgery represents a reliable treatment option for LM/LMM, however this method became less popular over the last years, due to development of improved alternative techniques such as staged excision procedures.

Staged excision procedures are specialized surgical techniques that focus on meticulous assessment of peripheral margins prior to closure (staged margin control) conducted with analysis of either frozen or permanent histologic sections.\(^{13, 43}\) These techniques include different excisional patterns and histologic processing methods. Depending on the technique, primary tumor is excised with the initial margin specimens or left in place until margins are cleared.\(^8\) Techniques utilizing permanent sections include variations like the “square”, “perimeter”, and “contoured” excisions, and recurrence rates with these techniques are reportedly low, however mostly based on short-term follow-up.\(^{43, 45-46}\) Mahoney et al. describe the perimeter technique as a simple method of margin-controlled excision of LM. According to them, the main advantage of perimeter technique is that all margins are examined with permanent sections, whereas the main drawback is that multiple operative sessions are required to complete the procedure. However, this technique does not require specific Mohs training and is therefore applicable to non-Mohs surgeons.\(^{45}\) Bosbous et al. report their 10-year experience using staged excision for the treatment of LMM and LMM of the head and neck.\(^{11}\) In this study, staged excision was performed on 59 patients. Using staged excision, 62.7% of patients required a 10-mm or greater margin to achieve clearance of tumor. Two or more stages of excision were required in 50.9% of patients. Invasive LMM was identified in 10.2% of patients initially diagnosed with LM. There was one documented recurrence during a median 2.25-year follow-up period.\(^{11}\) Agarwal-Antal et al. found that 58% of 92 LM lesions required margins greater than 5 mm.\(^{13}\) They performed polygonal perimeter excisions with serial histopathologic permanent sections in a staged fashion with each stage of resection used a 5-mm margin.\(^{13}\) Specimens were color-coded and mapped. Any sites of tumor at resected margins were identified by a dermatopathologist and noted on the map of the excised specimen. Positive margins and areas with markedly atypical melanocytes were further resected, color-coded, mapped, and evaluated as previously described until margins free of tumor were attained. This study demonstrated that the standard recommendation of 5-mm margins is adequate in less than 50% of cases.\(^{13}\)

Recently, the “spaghetti technique”, as an alternative to Mohs surgery or staged surgery has been described.\(^{38}\) It is a two-phase surgical technique which can be applied for lentiginous melanomas (LM, LMM and acral lentiginous melanomas) that are not suitable for en bloc resection. In the first phase, a narrow band of skin, “the spaghetti”, is resected just beyond the clinical outline of the melanoma, immediately sutured, and sent for pathological examination without removing the tumour. The same procedure is repeated beyond the segments which are shown not to be tumour free and so forth until the minimal tumour-free perimeter is outlined. No operative wound is left between operative sessions. In the second phase, the melanoma resection and reconstruction are performed at the same time. In the study performed by Gaudy-Marqueste et al. on 21 patients with LM (N.=16) or ALM (N.=5), the mean operative defect size was 27.5 cm\(^2\). The mean number of steps in the procedure was 1.55. Grafts were used for reconstruction in all cases. The relevance of the “spaghetti”-defined outline was confirmed in 19 of 21 patients. After a median follow-up period of 25.36 months (range, 0-72 months), the local control rate was 95.24% with one case (4.76%) of in-transit invasive recurrence after 48 months. Unlike Mohs surgery, “spaghetti technique” does not require specific training of surgeons or pathologists. Unlike staged surgery, it does not leave patients with an open wound before the final reconstruction. However, this study was performed at a single centre and included a limited number of patients, with a relatively short follow-up period.\(^{38}\) Further studies are required to fully explore the advantages and disadvantages of this technique.

However, the treatment of LM, remains controversial subject in the literature for over a decade. Multiple studies of excisional surgery have shown that 5 mm standard margins are often insufficient to clear
the LM lesion due to unseen subclinical extension, accounting for this treatment’s reported 8-20% recurrence rate.\textsuperscript{12, 33, 37} Mohs surgery and staged excision may offer better margin control and lower recurrence rates (4-5%).\textsuperscript{47, 48} Estimates of recurrence rates following nonsurgical therapies such as cryosurgery, radiotherapy, electrodessication and curettage, laser surgery, and topical medications range from 20% to 100% at 5 years.\textsuperscript{12, 33}

Conclusions

LM/LMM are skin tumours with specific clinical and histologic features characterized by significant subclinical lesion extension and predilection for sun-exposed areas of the skin. When analyzing a lentiginous lesion in the area of chronically damaged skin, dermatopathologists should be aware of numerous pitfalls in the histologic and immunohistochemical analysis.

Since the borders of LM/LMM are often clinically and histologically ill-defined, treatment of these lesions, including surgical and non-surgical methods, is another challenge. Margin-control surgical techniques offer the highest cure rate while minimizing loss of normal tissue. Nowadays, classical Mohs micrographic surgery is modified with the use of rapid intraoperative immunohistochemistry to identify melanocytes in frozen sections. Also, staged excision procedures represent an effective treatment for LM and LMM.

Even though surgery is the treatment of choice, alternative options should also be considered, especially for the elderly for whom the need for efficiency and acceptability plays a significant role.

Riassunto

Pitfall chirurgici e istologici nella gestione del melanoma lentigo maligna

Il melanoma lentigo maligna (MLM) è un tumore maligno con crescente incidenza, che rappresenta dal 4% al 15% circa di tutti i melanomi. La lentigo maligna (LM) è un MLM \textit{in situ}, che solitamente presenta una lesione maculare pigmentata irregolare di color marrone chiaro o bruno persistente per anni su una pelle cronicamente esposta al sole. Se non trattata, la LM può evolvere in una forma invasiva di MLM. La valutazione istologica di LM/MLM può risultare complessa a causa di diffusi melanociti atipici presenti nell’area della pelle cronicamente danneggiata dal sole. È stato dimostrato che una cute non-lesionale cronicamente danneggiata dal sole può presentare alcune caratteristiche atipiche anche in assenza di neoplasia melanocitica. È importante che i dermatologi siano a conoscenza di questi risultati in modo che tali caratteristiche siano interpretate appropriatamente nel momento della valutazione istologica che è in grado di influenzare, in ultima analisi, la terapia e l’esito. Il MLM è caratterizzato da significativa lesione subclinica che rende il trattamento difficile. Oggi, sono disponibili una varietà di opzioni terapeutiche nel trattamento del MLM. La chimio chiusa della LM può essere controindicata. Le opzioni di trattamento possono includere terapia di seconda linea nel caso in cui la chirurgia fosse controindicata. Le opzioni chirurgiche includono escissione semplice e tecniche margin-cruise controindicato qualunque escissione a strati e chirurgia micrografica di Mohs. Nel presente articolo gli autori esaminano gli ultimi progressi diagnostici e terapeutici nella gestione del MLM.

Parole chiave: Macchia melanotica di Hutchinson - Melanoma - Diagnosi - Esame istologico - Trattamenti - Procedure chirurgiche mininvasive.

References

A variety of non-invasive techniques have been utilized for the enhancement of cutaneous changes seen with photoaging. Such methods include chemical peels, microdermabrasion, ablative and nonablative lasers, and various rejuvenating light sources. However, the most widely used minimally invasive cosmetic procedures for the correction of undesired rhytides and enhance facial features through contouring and volumization are injections with botulinum toxin and soft tissue fillers. Their extensive long term safety and relative ease of procedural techniques have led to high satisfaction levels worldwide. Nonetheless, proper training of the fundamentals in injection technique, the choice of the appropriate candidate, and knowledge of potential adverse events are imperative to ensure an excellent and safe outcome.

**KEY WORDS:** Botulinum toxins - Rejuvenation - Skin aging.

### Fillers

Injectable fillers have become the mainstay treatments for nonsurgical treatment of wrinkles and facial contouring. A plethora of fillers are currently available and even more so internationally. Because of unique characteristics for each kind of filler, there are different indications for each filler type as well as advantages and disadvantages. How these fillers are distinguished from one another depends on the active ingredient used, the degree of viscosity, the source of the material, and the indications for use. Proper selection type of the filler for the appropriate areas to be injected is paramount to avoid potential complications and to achieve the desired outcome. Using the wrong filler class can lead to disastrous consequences. For example, injecting calcium hydroxyapatite or poly-L-lactic acid into the fine rhytides of the upper lip or the infraorbital area for tear trough deformity (nasaljugal groove) may lead to unevenness and unwanted papules of significant duration that ultimately results in a highly dissatisfied patient.

### Types of fillers

Fillers are divided into three classes: non-permanent, semipermanent, and permanent. Nonpermanent fillers are the most commonly used. Some common materials that make up nonpermanent fillers include hyaluronic acid and collagen. These are of short duration with typical lengths of several months to 1 year and are eventually reabsorbed through macrophage activation. Semipermanent fillers have a longer duration of placement with time periods of years and typically result in a foreign body reaction that elicits fibroblast activation and collagenesis at the site of the material placed in the dermis. Calcium hydroxyapatite and poly-L-lactic are examples of semipermanent fillers. Permanent fillers are the
longest acting and also involve fibrogenesis and collagen production. Such fillers include materials composed of silicon and polymethylmethacrylate.

**Collagen-based fillers**

There are several types of collagen-based fillers depending on the source of origin. These include bovine collagen (Zyplast, Zyderm) and recombinant human collagen derived from neonatal human foreskin fibroblasts (Cosmoplast, Cosmoderm). The bovine-based collagen requires intradermal skin testing prior to usage but the human derived collagen does not. Zyderm and Cosmoderm are injected into the papillary dermis whereas Zyplast and Cosmoplast are injected into the reticular dermis due to the collagen fibers crosslinked with glutaraldehyde. These collagen fillers already contain 0.3% lidocaine making injections easier to tolerate. Collagen based fillers are nonpermanent. Another collagen-based product called Evolence which was derived from porcine was previously available in the United States but was voluntarily withdrawn from the market by the supplier.

**Hyaluronic acid**

The hyaluronic acid derivatives are the most popular filler agents for rejuvenation. Like collagen, they are also nonpermanent. Hyaluronic acid is a naturally occurring glycosaminoglycan polysaccharide polymer that is important in the matrix of the skin, subcutaneous tissue, connective tissue, and synovial tissue. With age, less hyaluronic acid is produced intrinsically and the molecular weight decreases. Hyaluronic acid has properties of being elastic and hydrating and therefore temporary water retention occurs at the site of injection. There are several hyaluronic acid agents available commercially. Restylane, Perlane, and Juvederm are nonanimal stabilized hyaluronic acid (NASHA) derivatives. The properties of NASHA derivatives are they are slowly biodegradable and undergo isovolumic degradation. When such materials are injected into the dermis, the NASHA products bind water more water and the volume of correction is maintained during degradation due to retention of water. The differences between the NASHA derivatives depend on the concentration of hyaluronic acid, the gel particle size, and the degree of viscosity. Such differences dictate the level of placement of the within the dermis as well as the gauge of the needle.

**Calcium hydroxyapatite**

Calcium hydroxyapatite fillers are composed of spherical particles blended in an aqueous cellulose based carrier. They are considered semipermanent fillers. The gel carrier is resorbed by macrophages and the calcium hydroxyapatite particles are left behind and become encapsulated by the fibroblastic stroma. Radiesse is filler agent that is composed of calcium hydroxyapatite and is used for volume restoration and for deep and prominent folds. The level of injection is accomplished with a 27-gauge needle at the lower dermis to subdermal junction or just above the periosteum.

**Poly-L-lactic acid**

Sculptra is a volumizing agent that is composed synthetic polymer of poly-L-lactic acid microspheres that are immunologically inert and no skin testing is required. Sculptra is considered a semipermanent, long acting filler in which the poly-L-lactic acid stimulates dermal and subcutaneous macrophages, fibroblasts, and neovascularized fibroplasia with subsequent collagen formation. Sculptra requires a series of injections by cross-hatching and fanning over a period of several weeks to months. The initial correction attained disappears within a few days but gradual volumization occurs over the next several weeks through collagenesis. Sculptra is supplied in vials and requires reconstitution with sterile water prior to injection with a 26 gauge needle.

**Polymethylmethacrylate**

Artefill is a filling agent that is comprised of a suspension of microspheres composed of 20% polymethylmethacrylate and 80% bovine collagen. Artefill is considered a permanent filler and has dual action. Immediate correction is achieved with the bovine collagen component of the filler. The polymethylmethacrylate spheres are permanent and collagenesis and fibrogenesis occur on the spheres which leads to volumetric enhancement. Implantation is performed with a 27-gauge needle into the deep reticular dermis and skin testing is required due to the collagen derived from bovine.
Injection techniques

Various injection techniques are performed when injecting different fillers. The method used most often depends on the injector’s preference and experience but in some situations, it may be necessary to employ a specific placement technique to attain the desired outcome. These procedural methods are used to deliver the filler material into the different levels of the skin ranging from upper-, mid, and lower-dermis and deeper into the dermal-subcutaneous junction and immediately above the periosteum. One must take into account the properties of the filler material such as the material, viscosity, and degree of cross-linking as well the area to be injected.

Linear threading

This is the most commonly employed technique for injecting a filler, particularly in the nasolabial folds and lips and other rhytides and furrows. Typically, the filler is injected in a linear manner, either in a retrograde or anterograde direction. For the retrograde method, the body of the needle (typically 30- or 27-gauge) is inserted entirely into the tissue (e.g., mid-dermis) at a 30 degree angle and the filler is injected with gentle pressure while slowly withdrawing the needle. Care is taken to stop injecting just as the bevel of the needle reaches the point of total withdrawal to avoid formation of an unwanted papule. Gentle molding can be performed afterwards with the gloved injectors’ fingers to evenly distribute the filler along the rhytide. The use of a lubricant such as ultrasound gel facilitates molding.

Serial puncture

This is another common technique for injecting a filler. Typically the filler is of low to medium viscosity to minimize formation of unwanted papules and is injected more superficially into the upper and mid dermis. Serial puncture is used to treat fine rhytides such as perioral wrinkles and minimally shallow nasolabial wrinkles and depressions such as acne scars. A 30- or sometimes 32-gauge needle is commonly employed. The needle is directed at an upright angle (90 degrees or less) and just when the bevel of the needle is fully inserted into the skin or slightly more deep, a tiny droplet of material is injected. Injections are spaced very closely apart, similar to a string of beads. Gentle molding can be performed afterwards to evenly spread out the filler and avoid unwanted papules.

Serial threading

This is an intermediate placement technique between serial puncture and linear threading. Unlike linear threading, the body of the needle is partially placed into the skin and the material slowly injected. The injector has the choice of either withdrawing the needle if placement was done at a 30° angle or injecting a larger droplet of material similar to serial puncture if the needle was inserted more upright.

Cross-hatching and fanning

This technique is useful for covering a wide area such as the cheeks for lipodystrophy and where a larger amount of filler is required. Cross-hatching and fanning is used primarily for volumetric enhancement and facial contouring. One commonly used filler for cross-hatching and fanning is poly-L-lactic acid. A series of retrograde injections are performed into the deep dermal or subdermal layer or in a unidirectional fashion. This is followed by another series of retrograde injections in a direction perpendicular to the initial set of injections. For example for injecting a very prominent nasolabial fold with this technique, a series of short retrograde injections are performed 90 degrees across the nasolabial fold throughout its length. Another set of longer retrograde injections is then performed through the length of the fold perpendicular to the first set of injections.

Deep depot

This technique is utilized for facial contouring and volumetric enhancement. Deep depot is used with certain fillers such as those containing calcium hydroxyapatite. For example, to augment the malar eminences, a larger bore needle such as a 26- or 27-gauge needle is deeply inserted perpendicular into the skin over the zygoma until the tip touches the periosteum. A droplet of filler is injected over the periosteum of the zygoma until noticeable visible enhancement is seen. A series of injections is performed over the zygoma followed by gentle molding.

The patient should be seated comfortably on the
examination chair in an upright to semi-upright position to allow for normal downward sagging of the face to occur with gravity. Critical features of the folds will be more evident in a more upright position. If the patient is placed prone on the table, then essential details of rhytides, particularly in the midface, will not be as clearly evident as they will be partially lost due to backward forces. Therefore, the prone position is not recommended for injected fillers into the face. Good light is essential and sometimes folds may become more prominent and easier to visualize if the light is adjusted at an angle to cast shadows on the wrinkles.

Consent forms authorizing the injector to perform the procedure are required for the patient to read, understand, and sign. The risks and benefits as well as reasonable outcomes should be detailed in the consent form. Dispensing post-procedural handouts explaining what the patient should or should not do at home following the injections is a good practice.

The patient should be told that injections with soft tissue fillers elicit pain. Some of the fillers are already pre-mixed with lidocaine to minimize discomfort during the course of injections. Other fillers can be combined with lidocaine manually by connecting the syringe containing the filler to another prefilled syringe containing the appropriate volume of lidocaine through a Luer-lock connector and mixing the two together by alternatively depressing the syringe plungers. Most patients require application of a topical anesthetic preparation containing different combinations and strengths of lidocaine, prilocaine, tetracaine, or benzocaine to the areas to be injected. Typical application times are 30 minutes to 1 hour. One should note that the skin and tissue surrounding the folds and wrinkles frequently swell when anesthetic creams are applied and the features of the rhytides may become distorted or lost. Therefore, critical examination of the areas to be injected as well as preprocedural photographs are essential prior to application of the anesthetic creams. Marking the injection sites with an easy to remove marker pen or pencil may be beneficial. Regional nerve blocks are usually unnecessary unless the site to be injected is particularly sensitive. Injecting fillers into the body of the lips can be quite painful and an infraorbital and submental nerve block can be performed. The absence of epinephrine in performing nerve blocks is recommended to allow for the anesthesia to retreat faster after completion of the injections and minimize the duration of numbness for the patient afterwards. The placement of ice or cold compresses before, during, and after the injections can be utilized to provide comfort to the patient and to induce partial vasoconstriction locally and minimize purpura. Following injections, gentle molding and massaging may be performed to evenly distribute the filling agent beneath the skin. Immediate post-procedural photographs are also recommended. The patient should be told not to excessively touch the injected areas and minimize exaggerated facial expression for the next 24 hours. Transient swelling and bruising should be warned to the patient beforehand and are natural to occur and frequently inevitable. The occurrence of any unwanted bumps or unevenness is a risk of any filler agent and is usually due to faulty technique. The patient should call and follow-up in the office should this occur and corrective actions should be exercised.

Finally, during the course of injections, the degree of patient discomfort should be noted throughout the procedure. In the event that the patient experiences sudden extreme pain, then injections should be immediately halted due to the possibility of vascular occlusion which can result in subsequent tissue necrosis. The possible occurrence of blanching of the skin should be inspected for at all times. Should this happen, application of a topical mixture containing nitroglycerin is recommended in order to induce vasodilatation and minimize the incident of necrosis.

Areas of injection

Although soft tissue fillers may be injected almost in any part of the body, only the face and dorsum of the hands will be discussed. For practitioners who casually inject fillers, the nasolabial folds are the most common location. Advanced injectors address other areas of the face including upper, mid, and lower face as well as the dorsum of the hands. Soft tissue fillers may be utilized as monotherapy for rejuvenation or is frequently used in combination with other minimally invasive procedures such as neurotoxins, laser therapies, and chemical peels.

Upper face

Injection of soft tissue in the upper areas of the face is limited. The skin is thinner and the risk of unwanted adverse events is higher than in other
parts of the face. For atrophy of the temporal area, non-permanent: 1) or semipermanent fillers may be injected for volumetric enhancement. Care must be taken to avoid injury to the temporal nerve. A small retrospective study was conducted for treating temple volume loss and orbitofacial asymmetry.\(^1\) Patients initially received approximately 1 mL of a hyaluronic filler injected into the superficial fascia of each temple which was injected behind the frontozygomatic process to soften the bony contour of the lateral orbital rim. The majority of patients who enrolled in the study were very or moderately satisfied with the results.

Preperiosteal placement of hyaluronic acid fillers may be placed at the superior orbital rim to achieve a nonsurgical “brow lift”. Approximately 0.4 cc can be injected per upper eyelid inferior to the lateral edge of the upper eyelid to enhance the contour of the upper eyelid and brow.\(^2\)

Injection with neurotoxins is the most common minimally-invasive treatment method to treat dynamic rhytides of the upper face including the glabella, forehead, and periorbital rhytides (crow’s feet). However, residual wrinkles may persist despite maximum muscle relaxation elicited by botulinum toxin. In these situations, lower viscosity, nonpermanent fillers such as hyaluronic acid or collagen-based products may be injected to minimize the residual rhytides remaining after botulinum injections. Caution must be exercised when injecting fillers in the glabellar area, forehead, and crow’s feet because the skin is relatively thin and resides over bony prominences. If injected too superficially or excessively, unevenness and lumpiness may occur. In addition there are case reports of local necrosis and occlusion of the retinal artery branch resulting in blindness have occurred when fillers were injected in the glabellar area.\(^3\)-\(^5\) Nonetheless, soft tissue filler injection when injected conservatively and using the appropriate non-permanent low-viscous filler may allow for correction for residual rhytides after neurotoxin injections. The glabellar area is also quite porous and the filling agent often times has a tendency to extrude through these dilated pores.

**Midface**

The midface is the most commonly injected area of the face for soft tissue fillers. Because of the inherent sagging of the midface that naturally occurs with photoaging, treatment of the nasolabial folds is the most prevalent requested location. Depending on the depth and length of the nasolabial fold, 1-2 cc of the appropriate filler is of adequate volume for restoration. Occasionally, more than 2 cc is required for deeper, prominent folds. The direction of injection may be superior to inferior starting at the perialar area and proceeding inferiorly to the corner of the mouth or in a \textit{vice-versa} direction. The perialar area is the most sensitive part of the nasolabial fold and the author tends to start at the most inferior aspect of the nasolabial fold and proceed superiorly. Frequently the triangular portion of the nasolabial fold in the perialar area is quite prominent and larger volumes of filler are necessary to correct this area. Linear threading (retrograde or anterograde) is the most common technique to inject the nasolabial fold but serial puncture can be used if the fold is quite thin or superficial. Some injectors also use the cross-hatching technique to fill the nasolabial folds, especially when they are very deep.

The ability to correct nasal defects non-surgically has expanded the utility of filling agents. The more commonly used agents have been hyaluronic acid and calcium hydroxyapatite.\(^6\)-\(^8\) However, caution must be exercised as there have been case reports of tissue necrosis occurring in the areas of the nose where a filler was injected, particularly in the nasal tip and ala.\(^5\), \(^6\), \(^9\)-\(^11\) While such occurrences are rare, restricting the use of fillers to the nasal dorsum and sidewalls minimizes complications.\(^6\) Whether the nasal defects are congenital, traumatic, or iatrogenic, injections should be performed in the subdermal plane above the perichondrium and periosteum. This is to minimize visible or palpable nodularity. Injecting small boluses of filler through the serial threading/puncture technique usually provides the best outcome. Low nasal tip projections (drooping nose tip) are common defects that patients seek consultation for correction. Injections of a filling agent such as hyaluronic acid into the medial crura area and anterior nasal spine can provide partial, but noticeable leveling of the nasal tip.\(^12\) Non-surgical rhinoplasty of the nose can be accomplished with the injection of various soft tissue fillers such as hyaluronic acid. Contouring the nasal defect involves small bolus injections of the filler into the superior aspect of the nasal dorsal bridge and sidewall to mask the appearance of the prominent nose.\(^6\)-\(^9\)

The malar and submalar areas of the midface are
very commonly corrected with volumizing agents. Intrinsic lipoatrophy of the cheeks due to aging or induced by certain medications (particularly for HIV) are ubiquitously requested areas to be enhanced. Volumetric rejuvenation in these areas is best corrected with fillers of longer duration or semipermanent agents. These include fillers containing hyaluronic acid fillers with higher viscosity and greater cross-linking, calcium hydroxyapatite, and poly-L-lactic acid. There are various techniques to volumize the malar and submalar areas and the practitioner can employ a single technique or a combination of techniques in the same patient to attain the desired results. Correction with the poly-L-lactic acid suspension involves injecting the product in fanlike sweeps across the length of the defect which is followed by series of cross-hatching injections in a perpendicular direction for even distribution. Injection with calcium hydroxyapatite can also be utilized in the same manner as an alternative to poly-L-lactic acid. A non-surgical malar lift can be accomplished with volumizers. This method has provided greater versatility and utility to treat the sagging face or persons with lower cheekbones and patient satisfaction is generally high. Either calcium hydroxyapatite or high viscosity hyaluronic acid may be utilized to enhance the malar eminences. A series of droplets of product using the deep depot technique are injected over the zygomatic area to produce instantaneous enhancement. Both techniques can be used in the same patient to augment the malar eminences and to correct the lipoatrophy in the cheeks with various agents. The versatility of combining soft tissue fillers in different areas of the face is clearly manifested here.

Hyaluronic acid fillers can also be injected into the earlobe to enhance its appearance and volume. Care should be exercised not to inject excessive amounts due to potential, although unlikely, occurrence of tamponade.

**Lower Face**

The lower area of the face is another common location for correction with soft tissue fillers. The treatment of vertical perioral rhytides is a frequently requested procedure. However, such fine rhytides are difficult to correct fully. The three most common modalities to treat perioral rhytides are fillers, neurotoxins, and laser resurfacing. Most often a combination of methods is necessary. A lower viscosity, small particle sized hyaluronic acid filler or a collagen based filler is frequently used to treat perioral rhytides. The serial puncture technique is the best method to used and either a 30- or 32-gauge needle is used. Either topical anesthesia or a regional nerve block may be utilized to minimize discomfort.

Increasing the volume of the lips is a commonly requested aesthetic procedure, especially among women. In general, the bottom lip is one-third fuller than the upper lip. Preserving or reestablishing natural symmetry on both contralateral halves of the lips is essential for a proper appearance. For the most part, most women want a natural, subtle enhancement to their lips and do not desire disproportionate or excessively full lips. Occasionally, a woman will request unnaturally fuller lips and it is up to the practitioner whether to fulfill that request or not. Because injections into the lips are quite painful, an infraorbital and submental nerve block are recommended for the top and bottom lip. Enhancing the lips requires a delicate touch and finesse to attain natural looking results. Linear threading in a retrograde or anterograde manner is the most common technique. The most common location to inject is in the vermilion border (white roll) of the upper and lower lips. The philtrum columns (cupid’s bow) can also be accentuated and redefined by injecting fillers to produce aesthetic results.Injecting into the body of lip (wet roll) requires subtlety but if properly performed by injecting a larger amount in the midzone of the lip and a lesser amount in the lateral aspects of the lip will lead to fuller, slightly upturned lip without producing the “duckbill” look. It is not recommended to inject semipermanent or permanent fillers into the lips due to the higher potential for adverse events which sometimes can be permanent and catastrophic such as palpable or visual nodules, granulomatous reactions, and excessive, undesired fullness. The most common fillers utilized are non-permanent such as those that are hyaluronic acid- or collagen-based.

The marionette lines are a very common location to correct in the lower half of the face. Because of intrinsic photoaging, the corners of the mouth turn in a downward direction that patients attribute to as appearing sad or looking old. The goal in correcting marionette lines is not only to fill them, but also to turn the corners of the mouth upward. Injecting into the lateral commissures will provide support at
the corners of the lip to attain a slight upward curvature of the mouth. In addition, injecting a few units of botulinum toxin into the depressor anguli oris in combination with the filler agent will also reverse the sagging mouth. One cardinal feature in correcting the marionette lines is to inject slightly more medial in the folds rather than directly into the fold or laterally. If improperly performed, the marionette lines may actually be accentuated which is not the desired outcome.

Other areas in the lower face that are addressed frequently are the prejowl sulcus area. A nonpermanent or semipermanent filler may be injected in those areas by using the serial threading or deep depot method. Some patients are bothered with a prominent mental crease that runs across the chin. This can be a difficult area to correct and a nonpermanent filler such as a hyaluronic acid agent be injected by using a linear threading or serial puncture method.

Dorsum of Hands

In addition to the face, the dorsum of the hands frequently undergoes lipoatrophy due to intrinsic aging that patients become self-conscious about. Hand volume restoration has recently become more popular and various filler agents are available to restore fullness.\(^{14-17}\) Calcium hydroxyapatite is probably the most common filler to restore volume to the hand.\(^{14,15}\) Hyaluronic acid has also been utilized to correct lipoatrophy of the hands.\(^{16,17}\) Techniques to inject both types of fillers are similar. On the average, approximately 0.65 to 1.3 cc of product is needed to restore volume in the dorsum of each hand.\(^{14-17}\) The filler is injected into the deep dermal plane by depositing a globular droplet into the intermetacarpal spaces using serial threading. The bolus of the filler agent is then massaged and molded gently to achieve uniform distribution and a series of injections are performed throughout the length of the intermetacarpal spaces. Care needs to be taken to ensure no palpable or visible nodules are present.

Complications

When obtaining informed consent from a patient who desired treatment with a filling agent, the benefits and the potential risks must be discussed. Common adverse events such as swelling and bruising are expected sequelae of injections and are considered not to be true complications and this needs to be explained to the patient. Minimizing edema and purpura can be accomplished through the application of ice packs and cold compresses prior, during, and after the procedure. The patient can be instructed to apply cold packs to the injected areas as home as well. If patient are on anticoagulants such as aspirin, warfarin, or Plavix, the risk of bruising is higher and should be discussed with the patient. The author generally does not instruct patients to stop anticoagulants prior to injection. Complications can arise to due faulty technique or they may arise due to local tissue reaction to the filler itself. For the most part, true complications are not common with soft tissue fillers if proper injection technique is performed and the appropriate patient is selected.

Asymmetry is probably the most common complication. This can be easily rectified with touch up injections to circumvent the complication, either at the patient or physicians’ cost. The author does not recommend saving and storing leftover filler agents for future usage with one exception (Sculptra – product label storage time after reconstitution).

Unevenness, ridging, papules, and nodule formation can occur with any filler agent and arise due to faulty and improper injection technique. Common reasons for inducing bumps are injecting too superficially, failing to stop injecting just when the needle exits the skin during retrograde injection, or selecting the wrong filler type (injecting a heavily crosslinked/viscous filler or a semipermanent filler into the papillary dermis as well as in a location where the skin is thinner). When caught immediately after injection, massaging the bump can be performed to even it out. Hyaluronidase preparations can be administered into undesired bumps where hyaluronic acid fillers were injected to enzymatically break down the polymer. Injections with hyaluronidase agents often times diminishes the bumps within 24-48 hours. For bumps that were induced by semipermanent fillers that do not resolve, physical extraction and excision may be the only alternative to correct the complication.

Allergic reactions to the filler material or one of its components are rare but have been reported. Skin testing is required for bovine based products but not porcine based. For true allergic reactions, treatment with a topical steroid may suffice for mild reactions but systemic steroids or other immunosuppressive agents such as cyclosporine may be necessary to
reduce more severe allergic reactions. Granulomatous reactions are rare but have been reported with permanent filler materials. Such occurrences are a delayed-type hypersensitivity reaction than can happen months to years after initial injections.

**Botulinum toxin**

Dynamic facial wrinkles can be interpreted as manifestations of negative emotions, fatigue, stress, and perceived aging. Such rhytides result as a combination of intrinsic skin aging, ultraviolet damage, and repetitive action of facial muscles. Of these, the most contributing force for the persistence of facial wrinkles is the repetitive contractions of the intrinsic muscles for facial expression. There are a variety of different treatment options available for this facial lines including the use of filling agents, ablative and non-ablative laser surgery, dermabrasion, and chemical peels. However, these procedures do not adequately address the underlying cause of dynamic wrinkles as evidenced by the persistence of facial lines after treatment. The understanding that muscular contraction contributes to etiology of facial lines, wrinkles, and furrows has broadened the treatment options for these facial cosmetic blemishes.

Botulinum toxin type A (BTX-A), a potent neurotoxin that irreversibly blocks presynaptic acetylcholine release, has been successfully employed to treat a variety of hyperkinetic facial lines such as glabellar lines, crow’s feet, horizontal forehead lines, vertical perioral rhytides, and marionette lines have been successfully treated with BTX-A. Currently there are three commercial formulations of BTX-A, Botox, Dysport, and Xeomin approved in the United States. In 2002, Botox was FDA approved for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients aged 65 years or less. In 2009, Dysport was FDA approved for the same cosmetic indication as Botox. Xeomin is another BTX-A formulation that is was recently approved in the United States for the treatment of glabellar lines in adults younger than 65 years of age.

Likewise, botulinum toxin type B (BTX-B) is another potent neurotoxin that has been employed to treat spastic conditions such as cervical dystonia. Myobloc, the only commercial formulation for BTX-B and is FDA approved for the treatment of cervical dystonia but currently not approved in the United States for any cosmetic usage. A variety of hyperkinetic facial lines have also been treated successfully with BTX-B.

**Structure and mechanism of action**

There are seven serologically distinct types of botulinum neurotoxins, designated types A through G, which corresponds to the strain of Clostridium botulinum that produces the specific toxin. These serotypes are all synthesized as single chain polypeptides with molecular weights of approximately 150 kD and share a common structural organization which consists of one heavy chain (100 kD) and one light chain (50 kD) polypeptide that is linked by a single disulfide bond. All botulinum toxins inhibit acetylcholine release at the neuromuscular junction in a three-step process. The single-chain polypeptides are activated by proteases which are cleaved into a double chain consisting of the heavy chain and the light chain moieties. Upon cleavage, the heavy chain binds to a high affinity receptor on the presynaptic nerve terminal which enables the internalization of the bound toxin into the cell. The light chain moiety is a zinc-dependant endopeptidase that cleaves membrane proteins that are responsible for docking acetylcholine vesicles on the inner side of the nerve terminal membrane. The cleavage of these proteins inhibit the fusion of the vesicles with the nerve membrane, thereby preventing release of acetylcholine into the neuromuscular junction.

The intracellular target of BTX-A is the SNAP-25 (synaptosome-associated protein of molecular eight 25 kD) which is a protein essential for the successful docking and release of acetylcholine vesicles with the pre-synaptic vesicle. In contrast, BTX-B cleaves VAMP (Vesicle Associated Membrane Protein), which is also known as synaptobrevin. Like SNAP-25, VAMP is essential for the docking and fusion of the synaptic vesicles to the presynaptic membrane for the release of acetylcholine.

**Types of botulinum toxins**

The various types of botulinum toxin formulations will be discussed and clinical data supporting their utilization will be detailed here.
**Botox**

Botox was the first type A botulinum toxin to be approved by the FDA in the United States. The product is supplied as a vacuum-dried lyophilized powder in vials containing either 50 units or 100 units of Botox. Unreconstituted Botox should be stored at 2-8 degrees Celsius. The official recommendation by the manufacturer is to reconstitute Botox with 2.5 ml of 0.9% nonpreserved saline for the 100 unit vial (1.25 mL for the 50 unit vial) to a final concentration of 4.0 U/0.1 mL. Practitioners have also used other different dilutions ranging from 1 to 10 mL/100 units and have reported that dilution at higher volumes can result in more diffusion. In addition, reports have demonstrated no decrease in efficacy using preserved saline to dilute the Botox that there is less pain associated upon injection using preserved saline. The manufacturer recommends avoided aggressive agitation of the vial upon mixing to prevent denaturation of the product. The reconstituted product should never be frozen and can be stored for up to six weeks at 4 °C.

Tuberculin or insulin syringes are frequently used for injecting Botox since they there is no potential space in the hub and result in less waste of the product. 30- or 32-gauge needles are the most commonly used needles to inject Botox. Topical anesthesia is not required but some patients may request their use to minimize discomfort. The use of ice can also reduce pain and also minimize purpura formation by constricting the blood vessels prior to injection.

Prior to treating the patient with Botox, a complete medical history should be attained to prevent unwanted reactions. Medications and food products that inhibit platelet aggregation and increase clotting time should be discontinued for 10-14 days prior to the procedure. These include aspirin, nonsteroidal anti-inflammatories, garlic, fish oils and similar. Some medical condition that are contraindicated for botulinum toxin injections include peripheral motor neuropathic diseases or neuromuscular functional disorders such as myasthenia gravis and Eaton-Lambert syndrome. Patients who are currently on aminoglycoside antibiotics such as gentamycin may develop increased inhibition of neuromuscular transmission and concomitant usage together with botulinum toxin is contraindicated. The presence of any infection or inflammation on the skin at the site of injection is also a contraindication. Finally, females who are pregnant or lactating should not receive injections of botulinum toxin.

The upper face.—Facial wrinkles involving the forehead, glabella, and lateral periorbital regions are common aesthetic areas where botulinum toxin is injected. In treating the glabella, botulinum toxin targets the bilateral corrugators, depressor supercillii, and the central procerus muscles that are responsible for the glabellar lines. Usually, two injections are administered per corrugator muscle and one injection in the procerus. The first phase 3 study demonstrating the efficacy of Botox for the treatment of glabellar lines was published in 2002. Patients with moderate to severe glabellar lines at maximum frown received intramuscular injections of 20 U Botox or placebo into 5 glabellar sites. Patients were followed up for 120 days after injection. Outcome measures were physician rating of glabellar line severity at maximum frown and rest, patient assessment of improvement, and vital sign and adverse event monitoring. 264 patients were enrolled with 203 on Botox and 61 in the placebo group. There was a significantly greater reduction in glabellar line severity with BTX-A than with placebo in all measures ($P < .022$) and the effect was maintained for many patients through day 120. The recommended dosage for the treatment of glabellar lines is 20 units but can vary from 15-30 units depending on the strength of the corrugator and procerus muscles. Typically, men may need higher doses of botulinum toxin versus women given the greater strength of the muscles.

The treatment of the glabellar region with botulinum toxin results in a slight brow lift by weakening the central frontalis effect of brow elevation and thus proportionately increasing the frontalis effect of lateral brow elevation. An advanced technique that can be utilized to attain a lateral brow lift by weakening the lateral lid depressor muscles is to inject 1-2 units of Botox into the lateral-superior orbicularis muscle just below the lateral brow but above the superior orbital rim.

A single-center, prospective, double-blind, randomized, dose-comparison study was conducted in female patients between the ages of 18 to 65 years of age for the treatment of glabellar, forehead, and periorbital rhytides with Botox. Eligible patients were assigned randomly to one of 3 treatment groups representing total doses of 32, 64, or 96 U and were followed up for up to 52 weeks. Patients were re-
quired to have upper facial wrinkles that met the following specifications on a 4-point facial wrinkle scale (FWS) (0 = none; 1 = mild; 2 = moderate; and 3 = severe) as determined at maximum attempted muscle contraction by a trained observer: moderate or severe glabellar lines; mild, moderate, or severe forehead lines; and bilaterally symmetric moderate or severe crow’s-feet. The total dose was divided evenly among 16 injection sites: 5 injections in the glabellar, 5 injections in the forehead, and 3 injections in each lateral canthal area for the periorbital wrinkles. Botox treatment, used in total doses of 32, 64, or 96 U, was shown to be safe and effective for treating multiple upper facial rhytides in female patients in single sessions. Overall, each dose resulted in significant improvement in the appearance of facial rhytides, but a dose-response relationship emerged based on duration of effect and on between-group differences on a substantial number of the measures that were assessed. The principal differences between the groups were in the duration of the effect, although in some individuals, some areas wore off more rapidly than other areas. Based on anecdotal information, some physicians hypothesize that a longer duration of rhytide effacement may be achieved through treatment of multiple areas, as this eliminates any potential for adjacent muscle recruitment.

When using botulinum toxin to treat forehead rhytides, typical doses of 15-30 units of Botox is injected into the frontalis muscle. Because the forehead is the primary brow elevator, care and caution must be exercised not to lower the eyebrows and flatten them when treating forehead wrinkles, especially in women where an arched brow is of aesthetic importance. To avoid lowering the brow, injecting higher up in the forehead can minimize this tendency as well as treating the glabella concomitantly. When treating the forehead for the first time, practitioners may reserve treating of the forehead area for 2 weeks after injecting the glabellar area first and also utilize a lower dose for the forehead to reduce the chance of depressing the brow excessively.

Typically, 3 injections are performed on each side of the lateral orbital of the eye to target the lateral orbicularis muscle to treat crow’s feet. Two-three units of Botox are used per injection. The distance from the lateral canthus to the area of injection should be around 1 1.5 cm to minimize the rare occurrence of diplopia. In addition, the area around the lateral orbit is enriched with blood vessels and this is a site more prone to purpura. Care should be exercised to closely examine for the presence of blood vessels prior to injection. Sometimes after successful treatment of the crow’s feet, patients may note increased crinkling and fine rhytide formation immediately below the infraorbital area due to muscle recruitment. Should this occur, 1 unit of Botox can be placed in the area of new wrinkle formation to obviate this effect. A study was conducted to compare the efficacy and safety of 4 doses of Botox with placebo to treat crow’s feet. Subjects received a single bilateral treatment of 18, 12, 6, or 3 U of BTX-A or placebo injected into the lateral aspect of the orbicularis oculi muscle. Investigators and subjects rated crow’s feet severity at maximum smile on day 7 and at 30-day intervals from days 30 to 180. As observed by both investigators and subjects, all doses of BTX-A resulted in improvements in crow’s feet severity when compared with placebo. A dose-dependent treatment effect for efficacy was observed, with higher doses having an increased magnitude and duration of effect. However, a clear differentiation between the 18 U and 12 U doses was not apparent. It was concluded that BTX-A was safe and effective in decreasing the severity of crow’s feet, with 12 U per side suggested as the most appropriate dose.

Mid and lower face.—The mid and lower face is not a common area to treat with botulinum toxin when compared to the upper face. Caution must be exercised in these areas since diffusion of toxin and inadvertent injection of adjacent musculature can result in functional deficits and unwanted limited motion.

Nasal wrinkles on the dorsum of the nose can frequently be treated with botulinum toxin by injecting a few units into the nasalis muscle. Between 2 and 5 U of botulinum toxin have commonly been used. A study was conducted to determine the efficacy of Botox in the treatment of nasal wrinkles of the superior nose (bunny lines); 250 patients with nasal rhytides were treated and 3 units of Botox were injected bilaterally into the nasalis muscle. Patients were seen at 1 month for follow-up, and the remaining rhytides were documented. 40% of patients had satisfactory treatment of nasal wrinkles with the initial bilateral 3 U injections. Sixty percent of subjects had remaining nasal rhytides following the nasalis muscle injections. Thirty percent of subjects had persistent wrinkles at the root of the nose (nasal orbicular wrinkles), and 30% had wrinkles at the nasal root and between
the eyes (nasociliary wrinkles). The injection of botulinum toxin into additional locations according to the anatomic differences of each person showed excellent resolution of the rhytides without complications.

A common area in the lower half of the face to treat with botulinum toxin are the vertical perioral rhytides. These lines are caused by repeated contraction of the orbicularis oris. Several injections of 2 units of Botox can be placed along the upper and lower lip to minimize lip furrows. A study was conducted where 18 patients were injected with BTX-A into the vertical lip rhytides. The effect of treatment was evaluated at 2 to 3 weeks after procedure and smoothening of hyperfunctional lines and upper lip fullness/eversion was observed in patients treated with BTX-A injections.43

Another usage of botulinum toxin injections is to target the depressor anguli oris muscle of the mouth to elevate the corners of the mouth.44 The depressor anguli oris pulls down on the lateral oral commissures and excessive function causes the corners of the mouth to droop (marionette lines). The downward angle of the marionette lines can be improved by injecting 2.5 U of Botox intramuscularly approximately 8-10 mm lateral to the oral commissure and 8-15 mm inferior to this point.

Relaxing the muscles of the mentalis can reduce the involuntary convolutions or dimpling of the chin when performing speaking or performing other mundane activities of the face.44 In addition to softening the pebbling of the chin, injection of botulinum toxin into the mentalis can reduce the deep transverse labiomental crease that runs horizontally across the chin. 5-8 U of Botox is typically used to inject the mentalis muscle.

Cosmetic uses of botulinum toxin in the neck is primarily for the treatment of platysmal banding which are the vertical bands found in the central neck.45 There are also horizontal rhytides caused by contraction of the platysmal muscle, usually seen laterally, which can be treated with botulinum toxin injections. The proper method to inject the platysma is to have the patient seated upright and contract the platysma. By doing so, the practitioner can grasp the platysmal band between the thumb and index finger with the non-dominant hand and inject 2-4 U of Botox in the lower dermis per injection site along the vertical extent of the band, starting approximately 2 cm below the inferior border of the mandible. The injections are repeated at 1.5 to 2 cm apart from each other descending down the neck toward the border of the clavicle. Most patients will require several injection points to treat a platysmal band. It is advisable to inject no more than 40 to 50 U of Botox total per treatment session for the platysmal bands.

**Dysport**

Dysport was the second BTX-A to be approved in the United States and is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients less than 65 years of age.46 The recommendation for reconstituting Dysport for glabellar lines in the 300 U vial is with 2.5 mL or 1.5 mL of unpreserved normal saline. The recommended dosage for treating glabellar lines is a total dose of 50 Units of Dysport divided in five equal aliquots of 10 Units each to the procerus and corrugator muscles. Re-treatment with Dysport at standard strength should be administered no more frequently than every three months. The potency units of Dysport are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of Dysport cannot be compared to or converted into units of any other botulinum toxin products.47

The same anatomic areas that were described above to treat rhytides with Botox can also be applied with Dysport. A study was conducted to compare the efficacy and tolerability between Botox and Dysport in the treatment of moderate to severe glabellar lines.48 Sixty-two patients with moderate or severe glabellar lines at maximum contraction were randomly assigned to receive 20 U of Botox or 50 U of Dysport (20% in the procerus muscle, 80% in the corrugator muscles). The incidence of patients with at least a 1-grade improvement in the severity of their glabellar lines at maximum contraction peaked at week 8 in both groups. However, the duration of this improvement was generally more prolonged with Botox than with Dysport with the overall incidence of such improvement being 77% versus 59% at week 12 and 53% versus 28% at week 16. In addition, at week 16, the incidence of patients whose glabellar line severity was none or mild between Botox and Dysport was 23% versus 10% for all patients (not statistically significant) and 50% versus 13% (P=0.05) for patients with moderate glabellar
lines at baseline. Throughout the 16-week follow-up, patients’ mean scores for how attractive they felt and how satisfied they felt with their appearance were consistently higher with Botox than Dysport, with statistical significance achieved for both at week 12. There was no significant between-group difference in the incidence of treatment-related adverse effects. It was shown that Botox offers more prolonged efficacy than Dysport when the two products were compared in a 2.5:1 dose ratio. At the 2.5:1 dose ratio, the results of the study presented herein suggest that Botox offers more prolonged efficacy (and comparable tolerability) relative to Dysport. The data suggest that the dose of Dysport may need to be higher than the 50-U dose suggested for the treatment of glabellar lines to achieve a duration of effect and level of patient satisfaction that is comparable with Botox.

The results of five phase III studies of Dysport for the treatment of glabellar lines were recently published.49 Three double-blind, multicenter, randomized, placebo-controlled studies enrolled ethnically diverse healthy adults with glabellar lines of at least moderate severity at maximum frown. In these studies, patients were followed for up to 180 days after treatment. The fixed-dose, single-treatment study randomized 158 patients to receive placebo or one dose of Dysport at 50 U. The fixed-dose, repeat-treatment study randomized 311 patients to assess treatment following the prior Dysport treatment of 50 U. The variable-dose study randomized 816 patients to receive placebo or a single variable dose (50-80 U, based on gender and assessment of muscle mass). Clinical evaluations were performed on days 14 and 30 and monthly thereafter. The primary endpoint was a response defined as a composite 2+ grade improvement, at day 30 from baseline, on the wrinkle severity rating scale from 2 to 0, or from 3 to 0 or 1 (where 3=severe wrinkles/severe, 2=moderate wrinkles/moderate, 1=mild wrinkles/mild, and 0=no wrinkles/none), for both the blinded evaluator’s/blinded investigator’s and patient’s assessments. Patients (1116 total; 720 Dysport, 396 placebo) given Dysport received 50 to 80 U of treatment. The median duration of response was 85 days for fixed dosing and 109 days for variable dosing. Similar efficacy occurred at doses adjusted for gender and muscle mass, although males required higher doses than females in the variable-dose study. Responses appeared as early as 24 hours, with a median time to onset of 3 days. Extension studies evaluated 1200 patients for 13 months and 768 patients in an interim analysis for 24 months. Maintenance of efficacy was seen after multiple cycles, indicating a lack of tolerance. It was concluded that Dysport significantly improved moderate to severe glabellar lines compared with placebo, with onset seen as soon as 24 hours after treatment and a median duration of effect of 85 or 109 days for fixed or variable dosing, respectively.

Another study examined the efficacy of Dysport to treat crow’s feet in a double-blinded placebo controlled trial.50 Subjects with moderate to severe crow’s feet at maximum smile (mild to severe at rest) were randomized to a single bilateral Dysport treatment (15, 30, or 45 U) or placebo. Independent panel assessments (Week 4) showed that all Dysport doses resulted in significant improvements in crow’s feet severity at maximum smile (P<0.001); a clear dose-response effect was seen. Improvement over placebo was seen in the 30-U and 45-U groups to Week 12. Investigator assessment showed significant improvement for all doses for 12 weeks at maximum smile and rest (P≤0.01). Patient satisfaction was significantly greater for all doses than for placebo for 16 weeks (all P<0.05).

Xeomin

Xeomin is the third BTX-A to be approved in the United States in 2011 and is indicated for the treatment of glabellar lines in adults younger than 65 years of age. Unlike other neurotoxins, Xeomin does not contain protein complexes including bacterial proteins. Clinical trials have demonstrated that Xeomin is well tolerated and highly effective in treating the glabellar lines and does not require refrigeration either during transport or in storage.

Myobloc

Myobloc is available in the United States and is supplied as a sterile liquid formulation of the purified neurotoxin. Each vial contains 5000 units per milliliter of botulinum toxin B in 0.05% human serum albumin, 0.01 M sodium succinate, and 0.1 M sodium chloride at a slightly acidic pH of approximately 5.6. Myobloc is available in three different total dosage strengths, 2500, 5000, and 10,000 units. The recommended storage condition for Myobloc is 2° to 8° C for up to 21 months and must not be frozen. Myobloc may be further diluted with normal
saline. Myobloc is FDA approved for the treatment of cervical dystonia but not for cosmetic uses.

While not used as extensively as Botox or Dysport for cosmetic purposes, Myobloc may be used to treat facial rhytides in instances where patients develop loss of response to BTX-A. Repeated injections with BTX-A may result in the formation of neutralizing antibodies that may reduce the effectiveness of subsequent treatments with BTX-A by inactivating the biological activity of the toxin. However, the rate of formation of neutralizing antibodies in patients receiving BTX-A has not been well studied and the critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that botulinum toxin injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. In situations where patients develop intolerance to BTX-A, transitioning to Myobloc may lead to improved outcomes in the treatment of facial rhytides. A report demonstrated that BTX-B is an effective treatment modality for glabellar rhytides refractory or exhibiting decreased clinical efficacy to BTX-A.51

A study was published to observe the effects of BTX-B in comparison to BTX-A, on patients with brow furrows assessing initial efficacy and duration of effect.52 Patients were injected with BTX-B in two different dose conversions against BTX-A to the corrugator-procerus complex. Some patients received a conversion of 50 units of BTX-B (total of 1000 units) to one unit of BTX-A while others received a conversion of 100 units of BTX-B (total of 2000 units) to one unit of BTX-A. The patients treated with BTX-A received a total of 20 units. Both types of botulinum toxin were effective at improving glabellar frown lines. The onset of actions occurred slightly sooner (2-3 days) with BTX-B than with BTX-A (3-7 days). Duration of effect with BTX-A was at least 16 weeks. The duration of response was dose dependent with BTX-B with 1000 units of lasting 6-8 weeks and the higher dose at 2000 units lasting 10-12 weeks. At least with the doses used, BTX-B has a quicker onset of action but BTX-A has longer benefit for glabellar wrinkles. These data strongly suggest that further dose ranging studies of BTX-B are necessary and indicated in controlled double blind studies in a larger patient population. In addition, there is a higher complaint of pain upon injection with Myobloc compared to Botox, presumably due to the lower pH of Myobloc.22, 53

Other studies have also investigated the treatment of glabellar wrinkles with BTX-B and have observed a rapid onset of action but a shorter duration. A total of 1800 units of BTX-B was used for the glabellar area and mean onset of 1.5 days and a mean duration of 8 weeks was observed.28 At higher doses of BTX-B used by the same investigator in a follow-up prospective study, the duration of response was 9.6 and 10.4 weeks with 2400 and 3000 units respectively.12 The onset of action was seen within 2 to 3 days. Another study looked at three different dosages of BTX-B for the treatment of glabellar lines. Patients received either the low dose of 1875 units, the medium dose of 2500 units, or the high dose of 3125 units.23 Most patients at all doses showed some evidence of paralysis at 2 months. At 3 months after injection, only subjects in the high dose maintained a significant response with BTX-B. The authors concluded that at the doses utilized in their study, the effect of BTX-B does not generally appear to last as long as BTX-A. However, similar to the other studies, the onset of action was sooner with BTX-B.

Safety of botulinum toxin

Cosmetic treatment with botulinum toxin injections has become one of the most common nonsurgical procedures performed by practitioners. It has been proven as safe and effective for the treatment of glabellar lines and other rhytides in the face and neck. Nonetheless, given its long safety track record and high usage in millions of patients, knowledge of any potential adverse effect associated with botulinum toxin is essential for any practitioner who performs such injections. Generalized reactions that have idiosyncratically occurred from botulinum toxin injections include nausea, fatigue, malaise, flu-like symptoms, and rashes at sites distant from the injection but the instances of these events occurring is rare.

Age Considerations

It is difficult to tell for sure whether patients over the age of 65 respond differently to BTX-A than younger patients since there have been no studies investigating cosmetic uses of BTX-A specifically in the elderly, and there have not been enough elderly patients enrolled in clinical studies to make any meaningful comparisons.54 Since the elderly
are more likely to have thinner and less elastic skin, weaker facial muscles, and wrinkles that over time are caused by gravity-induced tissue sagging rather than muscle contraction, the elderly are not expected to respond as well to BTX-A treatment.\textsuperscript{55} The site of injection also warrants special considerations in the elderly. Treatment of forehead lines, for example, would require injections to the frontalis muscle, which many older people use to raise their eyebrows and eyelids to see. Older patients may also have redundant skin under the brow (pseudoptosis) which could be worsened by BTX-A treatment. Older patients who receive BTX-A for glabellar lines may be more at risk for complications such as eyelid ptosis if they have a reduced or absent orbital septum.\textsuperscript{56} Conservative dosing, injection of low volumes, and proper placement of the injection can reduce the possibility of spread of the toxin to unintended muscles. A prudent caution is to start at the lowest possible effective dose for elderly patients.

**DIFFUSION**

The effects of botulinum toxin effects, in some cases, may diffuse beyond the site of local injection.\textsuperscript{57} The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, and breathing difficulties. These symptoms have been reported hours to weeks after injection. To date, no definitive serious adverse event reports of distant spread of toxin effect associated with cosmetic use of botulinum toxin has been reported.

**PRE-EXISTING NEUROMUSCULAR DISORDERS**

Patients with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin.\textsuperscript{58} Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of botulinum toxin injections.

**DRUG INTERACTIONS**

Concomitant administration of botulinum toxin and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like non-depolarizing blockers, lincosamides, polymyxins, quinidine, magnesium sulfate, anticholinesterases, succinylcholine chloride) should only be performed with caution as the effect of the toxin may be potentiated and result in excessive neuromuscular weakness.\textsuperscript{59}

**PREGNANCY AND LACTATION**

Administration of botulinum toxin is not recommended during pregnancy. There are no adequate and well-controlled studies of botulinum toxin in pregnant women. Caution should be exercised when botulinum toxin administered to a nursing woman because it is not known whether this drug is excreted in human milk.\textsuperscript{59}

**PTOSIS AND ASYMMETRY**

Transient ptosis is the most frequently reported complication and has been reported in the literature in approximately 5% of patients.\textsuperscript{56, 60} Ptosis of the eyelid results from migration of the botulinum toxin to the levator palpebrae superioris muscle. The levator allows the eyelid to open properly and fully. To avoid ptosis, injections should occur at least 1 cm above the eyebrow and should not cross the midpupillary line. A therapy recommended to treat ptosis from administration of botulinum toxins A and B is the use of apraclonidine 0.5% eye drops. The most common dosing scheme used for apraclonidine is one or two drops three times daily until ptosis resolves.

The most significant complication of treatment of the frontalis is brow ptosis. Injections in the forehead should always be above the lowest fold produced when the subject is asked to elevate their forehead (frontalis). If the patient has a low eyebrow, treatment of the forehead lines should be avoided, or limited to that portion of the forehead 4.0 cm or more above the brow.

The most common reported complications in the crow’s feet area are bruising, diplopia, ectropion and an asymmetric smile due to injection of zygomaticus major.\textsuperscript{56} If severe lower lid weakness occurs, an exposure keratitis may result. Treatment is symptomatic. These complications are avoided by injecting at least 1 cm outside the bony orbit or 1.5 cm lateral to the lateral canthus, not injecting medial to a verti-
cal line through the lateral canthus and not injecting close to the inferior margin of the zygoma. Violating these boundaries has on occasion also resulted in diplopia due to medial migration of Botox and resultant paralysis of the lateral rectus muscle. Covering or patching the eye will alleviate some of the double vision.

**Conclusions**

The aforementioned therapeutic uses of the various types of fillers and botulinum toxin formulations have expanded the ability of practitioners to treat various rhytides of the face and to restore volume due to atrophy. When used as monotherapy or in combination, the use of fillers and botulinum toxin is a simple, minimally-invasive procedure that has minimal to no downtime, minimal adverse events, and has turned back the clock on millions of patients.

**Riassunto**

**Riempimento dei tessuti molli e tossina botulinica, tecniche di trattamento**

Sono state impiegate una molteplicità di tecniche non invasive nel miglioramento delle alterazioni cutanee causate dal fotoinvecchiamento. Tali metodi comprendono peeling chimici, microdermoabrasione, laser ablativi e non ablativi e varie fonti di luce rigenerante. Tuttavia, le procedure cosmetiche minimalmente invasive maggiormente utilizzate nella correzione delle rughe indesiderate e nella valorizzazione dei tratti del viso attraverso la modellazione e la volumizzazione sono le iniezioni di tossina botulinica e il riempimento dei tessuti molli. La loro sicurezza a lungo termine e la relativa facilità di tecnica da parte dei tecnici hanno portato a elevati livelli di soddisfazione in tutto il mondo. Nondimeno sono indispensabili per garantire un esito eccellente e sicuro un training adeguato sui fondamentali dell’arte di iniezione, la scelta del candidato idoneo e la conoscenza di potenziali eventi avversi.

**Parole chiave:** Botulino, tossine - Ringiovanimento - Cute, invecchiamento.

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Cosmetic applications of sclerotherapy

D. M. DUFFY

The aim of this study was to broaden practitioner perspectives regarding the scope, safety, and efficacy of sclerotherapy for cosmetically unattractive veins and other conditions involving a variety of anatomical sites. The author wrote a review of results obtained following cosmetic sclerotherapy for both veins and in other applications is presented. This study involves hundreds of patients treated in a private phlebology practice spanning 33 years along with a brief review of pertinent literature. Since treatment of dilated veins involving the dorsa of the hands and face are rarely discussed, and widely performed, their treatment will be emphasized. The largely historical usefulness of sclerotherapy for other applications is also reviewed. As with lower extremity veins there was a great deal of both regional and patient-to-patient variability in terms of sensitivity to sclerosants and response to treatment. However, sclerotherapy carried out for cosmetic purposes has routinely produced satisfactory results for various applications and in a multiplicity of locations. Potentially serious complications and treatment failures were rare in properly selected patients. Patient satisfaction with a few exceptions was uniformly high. The addition of cosmetic sclerotherapy to an established phlebology practice can be a rewarding and highly satisfactory application of this versatile technique. Both treatment site, lesion type and the cosmetic nature of this therapy affects every aspect of treatment; legal, ethical, and procedural. Experience suggests that each area and type of lesion treated exhibits predictable patterns of response and risks. Vein treatment outcomes varying with anatomical site may reflect: 1) evolutionarily adaptive processes which have produced veins specialized for specific environments; 2) differences in patterns of cytokine recruitment and apoptotic processes. It should also be noted that potential complications reflect area specific patterns of venous anastomoses, nerves, vital structures, and the complexities of arterial architecture.

**KEY WORDS:** Sclerotherapy - Cosmetics - Veins.

Although the term sclerotherapy was coined in the 1930s by H.I. Biegelsen 1-4 to describe palpable firmness resulting from fibrotic replacement of vascular tissue; the notion of fibrosing these hollow organs “from the inside” using an extraordinary range of sometimes brutal therapies has been around for millennia. Hippocrates traumatized varicose veins by employing a slender piece of iron to induce thrombosis.5 While intravascular therapy for varicose veins was first performed in 1840 using absolute alcohol; the modern approach to sclerotherapy probably began in 1851 when Pravaz employed a modified syringe to inject ferric chloride into a varicocele. More than 160 years later sclerotherapy is still being used for this purpose.5, 6 Over time more than 24 sclerosants have been employed empirically without oversight and were subsequently abandoned due to horrific complications, as safer and equally efficacious

_**Conflicts of interest.**—None._

_**Acknowledgements.**—I am always honored to be asked to publish in a journal as prestigious as Giornale Italiano di Dermatologia e Venereologia. I’ve enjoyed presenting this report and hope that those who carry out these procedures will share their experiences with me. I could not have completed this article without the generous and absolutely essential assistance of Peggy Goodwin, as well as the tolerance of my staff and the patience of the editors of this journal._

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agents became available. Although a number of different types of sclerosants are still employed, by the mid the 20th century two detergent sclerosants sodium sotradecol sulfate (STS), and polidocanol (POL), although by no means perfect, established sclerotherapy in good hands as a relatively predictable, safe and effective treatment for lower extremity varicose and telangiectatic veins. Some of the drawbacks associated with both of these sclerosants in specific applications will be discussed in more detail.

Historically the ability of injectable sclerosants to produce controlled fibrosis has also been exploited to treat a large number of nonvascular syndromes including rectal prolapse, low back syndrome, hypermobile joints, inguinal hernias, prostatic hypertrophy, glaucoma and thyroid enlargement. Sclerotherapy is still being used to treat conditions as varied as snoring, spermatoceles, ganglions, and pyogenic granulomas. Conceptually mesotherapy is based on the same principles underlying sclerotherapy.

**Cosmetic sclerotherapy – Future prospects**

There are a number of reasons why certain applications of cosmetic sclerotherapy may inevitably become more popular: 1) women, and increasingly men, who have come of age in an era which provided expeditious solutions to almost every aesthetic complaint are increasingly unwilling to accept either real or perceived flaws in their appearance. These “defects” in times gone by would have been considered to be the benign stigmata of an aging process to be “suffered gracefully”. Perhaps some measure of increasing patient dissatisfaction with the ageing process (and determination to do something about it) can be found in a lay publication, which describes hands as the “The last virgin body part” “Which can give away your age like the rings of a tree.” It also notes that “Women who have peeled, suctioned, lifted, and tucked away years of facial and body wear and tear are demanding equal opportunity for their hands”; 2) wider applications of cosmetic sclerotherapy have also been facilitated by the development of more sophisticated techniques and FDA approval for the use of POL to treat lower extremity telangiectasia, reticular and small varicose veins whose treatment rationale is often cosmetic; 3) heavily promoted lasers and other devices have often failed to be as cost effective, efficacious or as comfortable to use as a simple technique dependent procedure such as sclerotherapy. Lasers have exhibited a particularly striking inability to replace sclerotherapy as the treatment of choice for both lower extremity telangiectasia and reticular veins; 4) finally, more practitioners are available both skilled and unfortunately unskilled who are incorporating cosmetic procedures into their practices as a matter of financial necessity.

**Treatment considerations – A new philosophical paradigm**

Challenges facing practitioners who carry out elective procedures involve issues that are as much philosophical as procedural. In the case of sclerotherapy the incorporation and application of treatment modifications based upon anatomic site and lesion type can easily be mastered by experienced phlebologists who are anatomically knowledgeable, aware of the shortcomings of various sclerosants, and adept at recognizing signs of impending complications. Making decisions about whom you should or shouldn’t treat is often more difficult than actually carrying out the procedure. Patients who seek cosmetic improvements often differ from patients who undergo sclerotherapy as a matter of medical necessity both in terms of motivation and sometimes unrealistic expectations. Their interest and understanding of these procedures may be fueled by advertisements, lay publications, and internet information. These sources often gloss over the possibility of complications and treatment failures. The ability to address patient needs in the United States may be further complicated by regulatory issues, malpractice concerns, and patient ignorance involving insurance benefits. Phlebotomists here who intend to perform cosmetic sclerotherapy without exposing themselves to the possibility of regulatory infractions, malpractice inadequacies, or potential lawsuits must disabuse patients of their misconceptions, acquire a clear understanding of regulations governing these procedures, and determine the extent of their malpractice coverage. The USFDA considers sclerotherapy carried out for any purpose other than to treat lower extremity venous disorders as legal but off label. The essence of “off-label” status has to do with the creation of alternative (“innovative protocols”) which employ FDA approved medications for unapproved purposes on an individual basis.
practice cannot be promoted broadly or advertised. Moreover, the patient must be fully informed as to the FDA status of the procedure. To add to the complexity state regulations governing the off-label use of approved drugs sometimes conflict with federal standards. Torres 18 outlines the niceties promoting and using off-label medications in the United States.

Medical establishments’ response – Sometimes less than welcoming

Finally, those who intend to embrace cosmetic sclerotherapy must be prepared to encounter some degree of opprobrium from certain colleagues who regard any cosmetic procedure associated with potential risks as frivolous, unnecessary and potentially disastrous. The disparity between patient’s interests and colleague approval can be a source both of irritation and limited referrals. Communications sent to colleagues regarding your interest in carrying out cosmetic sclerotherapy must be accompanied by a reasonable summary of contraindications, complications, and expected results. Including a peer reviewed article or two will help to substantiate both the validity of the procedure and your ability to carry it out. It also does not hurt if you are well known as an experienced phlebologist in your own community.

Getting started

In the late 1980s at least two major obstacles confronted any American phlebologist who chose to carry out cosmetic sclerotherapy. The first was the absence of any published treatment guidelines. The second, which faced all phlebologists here was an impoverishment of choices among the few sclerosants legal to use in the United States.

Sclerosants American style

Physicians here faced an astonishing example of hippocratic dissonance in which the legality of using highly toxic, older sclerosants was largely unrelated to the risks they presented. Bureaucratic inertia discouraged the introduction of safer sclerosants which prolonged the use of outmoded agents such as sodium morrhuate and ethanolamine oleate, which were vastly more dangerous than sclerosants widely used abroad. POL which was illegal to use in the United States until 2010, was demonstrably as efficacious and a great deal safer than many of the agents approved or sanctioned solely on the basis of long term use.8 Finding a sclerosant was like choosing a politician; your choice was limited to the one you feared the least. There were several issues of particular concern, they included the risk of allergies, tissue necrosis and the liabilities of employing a safer, non FDA approved product for which malpractice insurance may be invalid, not to mention the possibility of federal prosecution.

Detergent sclerosants

POL and STS (which is 2-3X more potent), have been used for many years and are well characterized. Both have numerous advantages and a few drawbacks. Particularly when using high concentrations detergent sclerosants can cause life threatening allergies, embolic phenomena, tissue necrosis and serious neurological complications. They also have the potential to cause unintended sclerosis in contiguous veins many centimeters from the intended target. STS has the additional drawback of routinely causing extravasation necrosis in concentrations of 1% or greater, while 3% POL, the equivalent concentration appears to be much less tissue toxic.19 Both agents are reputed to exhibit a similar rate of allergies when the concentrations are matched. The use of POL is also very rarely associated with cardiotoxicity.8

Detergent foams

Detergent foams are considered to be significantly (up to 3X) as potent as equivalent concentrations of liquid sclerosants.20 When these preparations first came into wider use for the treatment of large refluxing veins, they were found to cause an unexpectedly high incidence of certain types of complications. These included sclerosis of interconnected nontargeted veins at an even greater distance than seen with potent liquid sclerosant, increased neovascularization, and pigmentation. Neurologic phenomena (transient ischemic episodes and strokes) are also more common.21-25 One mechanism considered to be contributory to these neurologic events is the presence of an
open foramen ovale (which afflicts 25% of the population), and permits P.F.O. foam to enter the cerebral circulation via a right to left shunt. This condition is also associated with migraines and an elevated risk of cardiovascular disease.  

**Addressing potential complications**

**Allergies**

Although STS was considered to be generally safe, was FDA approved, and had a reported low incidence of serious allergies, personal enthusiasm for using it was tempered by a letter received from a colleague who reported an incident in which a patient died shortly after the administration of a “test dose” of 0.5 cc of STS. The cause of death was never clearly established, however an experimental laboratory analysis indicated the death was due to an allergic reaction [Lakeview Clinic, Ltd. 424 State Hwy, Waconia MN 55387. Lehmann JD, MD, personal communication].

HS, approved as an abortifacient, was legal to use “off-label”. Its only virtue was its non allergenicity. Uncomfortable to use, and extraordinarily prone to causing extravasation ulcers with the slightest technique mishap, it was also too weak to use for larger veins.

**Tissue necrosis**

A study carried out in this office compared the ability of equal volumes of 3% POL, 1% STS, and 23.4% HS and sodium morrhuate to produce tissue necrosis following deliberate mid-dermal injection. POL, alone among these agents, did not produce tissue necrosis. It was surmised from this study that high concentration POL was minimally tissue toxic. This finding has been confirmed in a number of other reports. In an earlier investigation, the injection of 0.4 cc of 3% POL into the authors forearm did not result in tissue necrosis although mild pigmentation was noted. Sodium morrhuate produced a large ulcer associated with so much pain that it required immediate intervention. What is known now is that all sclerosants can under certain circumstances cause tissue necrosis by multiple mechanisms. Factors associated with tissue necrosis include the anatomical location of the treated veins, AV malformations, concentration and type of sclerosants, depth of injection, injection force and volume. Certain sites are particularly susceptible to tissue necrosis and localized or distant neurologic phenomena. The medial malleoli are particularly prone to tissue necrosis as are certain regions of the face and hands. The occurrence of ulcerations and localized neurological problems led to the discontinuance of injection of the dorsoradial hand veins. Sclerotherapy for facial telangiectasia particularly on the cheeks, hands and nose may also be associated with an increased incidence of tissue necrosis.

**Clinical applications - Varicose and reticular hand veins**

The first peer reviewed article describing the treatment of dorsal hand veins published in 1999 did not result in a tidal wave of interest or publications. Criticism in the form of letters to the editor were proffered by those who considered dilated veins on the dorsum of the hands to be “normal”. Quite reasonably, more thoughtful commentaries stressed the importance of preserving hand veins which were essential to provide potential lifesaving venous access should medical emergencies occur or the need for long-term IV medications arise. Some of the most pointed criticisms mocked both the patients motivation for having the procedure carried out and the doctors willingness to perform it. Despite these concerns, there’s nothing in the published literature to suggest that sclerotherapy for the treatment of hand veins (provided some are spared for emergencies), is ineffective or carries with it a significant incidence of serious immediate or delayed complications.

**Hand veins unique features**

Reticular and varicose veins situated on the dorsa of the hands are exposed to an extraordinary combination of environmental conditions which exist almost nowhere else on the body. They are subjected to frequent rapid changes in position (elevation and dependency), as well as muscular activity which combine to produce dramatic fluctuations in both arterial and venous flow. Sun exposure, trauma and the aging process complicate their environment even more. Perhaps because of this they often require considerably higher concentrations of sclerosants than those that would ordinarily be needed to treat vessels of the
Examination and clinical approach – The importance of pre-existing problems

The hands are carefully examined for symmetry, muscle mass, hand strength, atrophic changes in muscle and bone as well as skin laxity. Patient hand strength is assessed by having the patient squeeze the examiner’s finger. Dexterity should also be evaluated. Preexisting weakness or any other abnormality if not acknowledged by the patient before treatment will surely be attributed by both the patient (and perhaps an attorney), as an unexpected complication of treatment.

Doppler evaluation

Patients with anomalous distribution of dorsal hand veins may have unpredictable, dangerous to
treat circulatory abnormalities. One patient presented with a thick walled 4mm distended vein on the thenar eminence of the right hand. Doppler evaluation suggested that this was an artery, however, Doppler evaluation of this area is difficult to interpret because of a great deal of extraneous arterial background noise.

Patient selection

A suitable candidate for the treatment of hand veins is healthy, mobile, exhibits normal anatomical distribution of the dorsal hand veins, with no existing deformities of the hands, chronic pain syndromes and has adequate symmetrical hand strength and coordination. The entire protocol “warts and all” is explained in detail and this explanation is supplemented by a written handout, careful pre treatment photos, and consent form. Digital photos are taken with the hands in a dependent position, both in direct view and tangentially using side lighting to document the size of the vessels and degree of protuberance is noted. The veins are measured both in dependency and el-

Table V.—Contradictory approaches to treatment of facial veins.

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Sclerosant and Rationale</th>
<th>Concentration of sclerosant</th>
<th>Volume</th>
<th>Intended outcome</th>
<th>Technique</th>
<th>Success rate percentage</th>
<th>Minor side effects</th>
<th>Serious complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green (39)</td>
<td>Higher concentrations of detergent solutions are safe and more effective than osmotic or low concentration sclerosants</td>
<td>0.75 – 1% STS</td>
<td>1-3cc</td>
<td>Vessel obliteration</td>
<td>Massage after injections/ compression. Manual external compression along the malar margin of the orbit during treatment. Compression after delivery of solution</td>
<td>100% One treatment only</td>
<td>Mild erythema and edema persistence 2 days. Bruising</td>
<td>None</td>
</tr>
<tr>
<td>Weiss (53)</td>
<td>Rapidly acting detergents minimize bleeding time, damage/swelling occurs more quickly</td>
<td>Sotradecol 0.2% Polidocanol 0.5 – 1% or saline and dextrose (Sclerodex™ rarely hypertonic saline 23.4% STS .2% Polidocanol 0.5 – 1%</td>
<td>“Use only a few drops” We typically utilize 0.2 – 5% Sotradecol volumes of no more than 0.1 - 0.2 cc</td>
<td>Reduce vessel size rather than “completely obliterate them”</td>
<td>Pressure over treated area for 10 minutes to minimize bruising</td>
<td>Greater than 50%</td>
<td>Bruising 50 – 75%</td>
<td>None</td>
</tr>
<tr>
<td>Bowes/Goldman</td>
<td>Osmotic (Sclerodex, hypertonic saline) detergent solutions may travel many cm from the site of injection causing potential injury</td>
<td>Sclerodex undiluted. Hypertonic saline 23.4%</td>
<td>Sclerodex up to 2cc</td>
<td>Obliteration or partial obliteration</td>
<td>Gentle pressure post treatment. Multiple treatments</td>
<td>63 – 75%</td>
<td>Bruising, matting</td>
<td>None</td>
</tr>
</tbody>
</table>

Comment: Green (39) employs the highest concentrations and volumes of detergent solution, reports the greatest success with the fewest number of treatments. He believes that no direct connection between facial veins and ophthalmologic or neurological structures exists noting that the blood in the face drains down towards the neck into the internal and external jugular veins not into the ocular or cerebral circulation. Four criticisms have been directed at his approach. 1) Injections in this area could theoretically produce blindness or neurological injury via multiple anastomoses. 2) “Common sense dictates the use of small volumes of sclerosant which minimizes the risk of blindness or neurologic injury”. 3) Manual external compression on the lower margin of the orbit after delivery of sclerosant solution could force the solution into the orbital vessels. 4) Osmotic sclerosants advantages and disadvantages. 1) Sclerodex is less prone to cause tissue necrosis and is more comfortable than hypertonic saline. 2) These agents are relatively weak sclerosants and may not work as effectively as higher concentration / volumes of detergent sclerosants.
Choosing sclerosant concentrations/types/foam vs. liquids

Dorsal hand veins can be notoriously resistant to low concentrations of sclerosants; 23.4% HS and STS under 1% are generally ineffective even when treating smaller vessels on younger patients. The occurrence of treatment failures employing sclerosant concentrations which would be effective on the lower extremities led to the employment of 3% POL solution for most of the patients treated. The use of foams was reserved for patients who did not respond to 3% POL solution for reasons discussed later.

Although vessel diameter and sclerosant dilution associated with it are generally considered to be a major criterion for choosing a particular concentration of sclerosant, the volume of blood within veins can be reduced simply by raising the hands. Accordingly, the thickness of the vessel wall and robustness or fragility of the overlying dermis play a major role in the choice of appropriate sclerosant concentrations. Elderly patients with atrophic skin and thin walled veins up to 3mm in diameter can have been effectively treated using 0.75% - 1.5% POL solution or alternatively 0.25-0.5% STS solution.

Figure 1.—Sclerotherapy carried out in the area indicated by the circle in this diagram appears to pose a significantly higher risk for nerve damage.

Common complications particularly bulky thrombi (which usually need to be incised and drained) are carefully discussed. Patients are also told that these thrombi which typically occur in veins following treatment are not dangerous, do not break loose, and represent expected treatment outcomes indicating that the vein will need no further treatment. Because thrombi (we call them “trapped” blood to allay patient anxiety) can occur or recur up to three weeks after treatment, the patients are asked to refrain from travel during that time frame. Patients who seek treatment often present with large numerous, easily cannulatable veins on the forearms and upper arms as well, noting that many members of their families are also “veiny”. These patients are good candidates for this procedure. Those who do not have other easily accessible veins should not be treated.

Foam preparations

Foams are prepared using room air at 1:4 dilution employing two syringes and a coupling. Concentrations from 1%-3% POL foams have been employed as have STS foams 1% - 2% strength. They are often
injected using a larger diameter needle as quickly as possible after being prepared because of foam degradation. Foams have the additional disadvantage of being very difficult to aspirate, and an increased risk of bulky and recurrent thrombi (often involving the forearms), and a well-recognized risk of cerebral neurological complications. Most of the patients who required foam were younger patients with thick walled veins and abundant dermal support.

Sclerosant volumes

Although up to 5 cc of polidocanol 1.5-3% liquid, or 1% STS liquid have been employed, generally 1-2 cc is all that is necessary per treatment. When using foam a smaller volume massaged into the vein is often effective and minimizes the risks of excessive thrombosis and neurological phenomena.

Technique

Ordinarily only one half of the veins on each hand is treated at each session to minimize edema. When the patient returns the other half of each hand is treated before incision and drainage of thrombi is carried out. For patients who are not in a hurry one vein at a time can be treated. In this case, compression is not necessary but the treatment process is prolonged. Prior to treatment patients are asked to remove all jewelry and refrain from taking aspirin or other agents which would increase bruising. Small vessels involving the phalanges can also be treated but this is technically more difficult. After cleansing the treatment areas with alcohol, patients are treated in the recumbent or seated position with the treated hand placed below the level of the treatment table to facilitate vein distention. A tourniquet may be used if the room is cold and the veins are constricted. A 3 cc luer-lock plastic syringe which is only half full (which permits better control of the injection process) is attached to a half inch 30 gauge needle. Before initiating injections the patient makes a fist which stretches the skin more tightly over the veins stabilizing them during the cannulation process. After cannulation the hand is elevated and sclerosant is slowly injected into empty veins. The direction of the injections proximal to distal or distal to proximal doesn’t seem to matter. During the injection process the veins are filled to the dorsum of the wrist where the vessels are occluded digitally either by the patient or an assistant, or by a tourniquet to minimize thromboses in this area which is a frequent cause of post-treatment discomfort. Immediately after treatment with the hand elevated an ice bag (McKesson Medi-Pak Instant Cold Compress Richmond VA 23228) is applied for several minutes while the patient opens and closes the hands.

Post-treatment protocols

Compression

A compression dressing consisting of an ace bandage applied over cotton balls or a sanitary napkin is applied immediately after treatment up to the wrist when using liquid sclerosant. When using foams the dressing is extended the length of the forearm and applied after the hand has been elevated for several minutes to allow dissipation of the foam distally. Experience has taught us that prolonged elevation of the hands to at least the level of the chest for as much of the time as possible for several days after treatment combined with opening and closing the hands often enhances patient comfort, reduces edema, and minimizes thrombotic bulk more effectively than any form of compression. We now leave compression dressings on for no more than 12 hours. Patients are also asked to refrain from heavy lifting, vigorous clapping, or physical activity that requires the hands to be subjected to prolonged episodes of dependency for at least a week. When using computers patients are advised to adjust their seating arrangements so that their hands are above the waist while they are working. Table II discusses contraindications specifically related to the treatment of hand veins.

Pain tolerance – A warning that is sometimes ignored

Patients are carefully quizzed regarding their ability to tolerate pain. Those who proudly admit to be-
Personal observations

Since 1987 in excess of 250 patients with hand veins varying between 1.5-6mm in size have been treated in this office. Treatment failures were rare, serious complications were even rarer. Most patients were delighted. Patients are provided pretreatment photographs to document improvements. Results were long lasting (longest follow-up at this writing is 15 years). Recurrences were uncommon although new smaller veins developed particularly in those who lifted weights or performed hard manual labor.

Treatment details

The second phase of an ongoing study which began in 1990, essentially duplicated results seen in an earlier study,8 with the exception of absence of neo-vascularization (matting), neurologic complications or tissue necrosis. Low concentrations of sclerosants were often associated with a high incidence of treatment failures (80%). The use of 3% POL liquid or foams up to 3% concentration produced good results in 95% of treated patients. Treatment of veins involving the dorsoradial hand near the thenar web are no longer carried out. Patients with migrainoid symptomology or other neurological conditions are carefully avoided.

Minor adverse events

Adverse events common to sclerotherapy including bruising, edema, and palpable thrombi were observed in 90% of the treated patients (Figure 2).

Swelling, persistent discomfort

One patient developed swelling of the index finger which may have been precipitated by a ring which she put on shortly after treatment. Four patients developed persistent discomfort in several treated areas which resolved over several months. Although there were veins that remained untreated further treatments were deferred. Resistance as measured by lack of response to three treatments has occurred in less than 1% of treated patients and often could be eliminated by increasing sclerosant potency or using foam. Several patients had veins which persisted despite the injection of 3% POL foam further treatments were not carried out.
Superficial thrombophlebitis

Superficial thrombophlebitis involving the forearms has occurred in less than 1% of the treated patients. Immediate relief was afforded by injecting 0.3 cc of 2.5 mg per cc of triamcinolone acetonide (Kenalog™), in 1% xylocaine without epinephrine directly into the thrombi followed by incision and drainage. In one case, this was followed by transient pseudo atrophy.

Potentially serious complications

Allergic phenomena and embolization were not observed. Two patients developed scintillating scotomata. Both denied the previous existence of migrainoid symptomatology. Neither of them had patent foramen ovale as determined by cardiac evaluations. Both occurred prior to 1999.

Tissue necrosis/Localized neurological complications

Treatment of veins involving the dorsoradial surface of the hand may damage superficial sensory branches of the radial nerve which lie in the superficial subcutaneous tissue. Two cases of nerve damage (neuropathy) followed the treatment of veins in close proximity to the thenar web. These complications followed injections of less than 1 cc of 3% POL solution associated with immediate development of paresthesias, pain, and blanching of the thumb, index and middle finger. Both patients developed transient superficial ulcerations which healed without scarring. In one case there was no persistent sensory defects. In the other case mild numbness involving the distal thumb which had improved with time was still noted at 2 years. The etiology of nerve damage was speculative. It may have occurred following extravasation of the sclerosing agent, the inadvertent injection of an AV malformation, or a neurovascular reflex. Avoidance of treatment of the dorsoradial hand has to date eliminated this problem.

Reported complications

Lawsuits have been filed because of persistent, intermittent swelling, continuous pain and discomfort, as well as the beginning stages of carpal tunnel syndrome and a noticeable deep maroon color of the treated hands.

Forearms/Bicepital veins

Fifteen patients were treated for “excessiveness veininess” involving the forearms and biceps. All had excellent alternative veins involving the antecubital fossae which were spared. Treated veins varied in size from 2.5 mm to 6 mm in diameter and were treated with 1.5-3% POL. Treatment failures following the treatment of the larger veins were noted in four of the patients treated. No complications other than transient edema and bruising were noted in any of the patients. Multiple (up to 3 treatments) were the rule. Patient satisfaction was very high. One patient pre-
permitted their use are also obtained (Figures 3-5). In addition, a written summary is provided detailing the occurrence of common complications including bruising and swelling as well as the existence of a therapeutic conundrum. Patients are told that although high concentrations and volumes of sclerosants have been employed resulting in a 100% success rate without complications, the risks of employing such a treatment protocol may outweigh its benefits necessitating the use of lower, safer concentrations. As a consequence of using lower concentrations, in approximately 50% of patients treated vessel diameter is substantially reduced but the vessels are not completely obliterated. Two treatments carried out at four-week intervals are performed. If further treatment is required it is carried out at two months. Patients are told that the upper eyelids, and the central forehead, and reticular veins involving the temple area may present increased risks and they are not treated. One patient complained bitterly when a 2.5-mm thick walled “vein” located on the temple was determined by Duplex scanning to represent an artery. She was angry that treatment had to be deferred despite the obvious risks associated with it.

**Facial reticular veins**

As with hand veins, very little has been written since Green published a highly quoted peer-reviewed article in 2001 exclusively devoted to the treatment of periocular reticular veins. His use of relatively large volumes of 0.75% STS provoked a torrent of polemical commentary. The upshot, “The safety of periocular vein sclerotherapy was not established by this report”. It was clear that the reviewers felt that the potential risks (blindness and neurological complications), far outweighed potential benefits. In addition, specific aspects of the technique employed including sclerosant type, volume, concentration and post treatment manipulations were criticized as being intrinsically dangerous. Table V presents differences in opinions and approaches to the treatment of these veins.

**Facial reticular veins unique features**

First, the presence of the multiple arterial and venous anastomoses and ocular adnexa make the possibility of visual loss, cavernous sinus thrombosis, and tissue necrosis resulting from inadvertent arterial injections are a major concern. Secondly, venous pressure is low and theoretically intravenous injection could reach the orbit where there are no valves. Third, one publication suggests the use of sclerodex (an osmotic sclerosant) which confines sclerosant damage to a small area. Finally, treatment of each region of the face is associated with the possibility of specific types of complications and treatment outcomes.

**Examination and clinical approach**

As with hand veins, a careful explanation of the theoretical risks are carefully discussed with the patient. Digital photographs and consent forms to permit their use are also obtained (Figures 3-5). In addition, a written summary is provided detailing the occurrence of common complications including bruising and swelling as well as the existence of a therapeutic conundrum. Patients are told that although high concentrations and volumes of sclerosants have been employed resulting in a 100% success rate without complications, the risks of employing such a treatment protocol may outweigh its benefits necessitating the use of lower, safer concentrations. As a consequence of using lower concentrations, in approximately 50% of patients treated vessel diameter is substantially reduced but the vessels are not completely obliterated. Two treatments carried out at four-week intervals are performed. If further treatment is required it is carried out at two months. Patients are told that the upper eyelids, and the central forehead, and reticular veins involving the temple area may present increased risks and they are not treated. One patient complained bitterly when a 2.5-mm thick walled “vein” located on the temple was determined by Duplex scanning to represent an artery. She was angry that treatment had to be deferred despite the obvious risks associated with it.

**Reasons to be concerned when injecting facial veins**

Although at this writing no serious complications have been reported following cosmetic periocular reticular vein sclerotherapy; monocular blindness has been reported after STS was injected into a venous malformation partially located in the orbit. Blindness has also been reported due to embolic occlusion of the ophthalmic artery as a complication of nasal steroid injections. In another case severe visual loss followed the injection of steroids into a chalazion. Because it is not a suspension, distal embolic phenomena with detergent sclerosants should not be expected. Some of the conflicting opinions regarding technique specifics are presented in Table V.

**Facial sclerotherapy - Personal observations**

Despite the theoretical possibility of horrific complications, I have neither personally observed in the treatment of over 50 patients nor reviewed articles in which serious problems occurred following cosmetic injection of reticular veins located on the lower lid, medial cheek and mandible.
Immediately after injection, gentle pressure is applied to minimize bruising for a full five minutes. Subsequently an ice bag may be used both in the office and at home for 5-10 minute intervals to reduce discomfort and swelling. Patients are instructed to use two pillows while sleeping, avoid strenuous exercise and alcohol for 2 days post-treatment.

Long- and short-term results - Personal observations

Complete or partial sclerosis following the injection of reticular veins on the face is often quite gradual mimicking the effect one sees when treating lower extremity telangiectasia using low concentrations of sclerosants. Bruising, transient swelling and treatment failures have been the only complications observed following the treatment of the veins involving the lower lid and medial cheek. Treatment failures after two treatments occurred in approximately 25% of 100 patients treated. Another 25% of patients treated developed new smaller veins in the same area over a period of 10 years.
Temporal reticular veins – A high-risk treatment area

Although initially temporal veins were treated without problems other than the occurrence of a thrombus in one patient which developed after injection of a 1.5 mm reticular vein which required incision and drainage. Treatment of reticular veins in this area was discontinued following the occurrence of three frightening events. In one case 0.75% POL failed to affect temporal veins measuring 1.5 mm in diameter. A second treatment was carried out using 0.25cc of 1.5% POL (a concentration which may be dangerously high for the treatment of this area). Two weeks after the second treatment the patient developed a 2.5 x 2.5 cm area of crusting superior to the injection site which was followed by a shallow ulceration of the same size which was surrounded by a transient loss of hair over a two month period. Examination revealed exclamation point hairs suggestive of alopecia areata at the perimeter of the ulcer. Hair regrowth and complete healing of the ulcer was noted at 6 months. On two other occasions patients undergoing temporal vein injections developed widespread blanching and ecchymosis, both of which responded to topical nitroglycerin, and prophylactic SecondSkin™ (Spenco Medical Corp., Waco, TX, USA). When symptoms of impending tissue necrosis are observed, Hyaluronidase (Vitrase™ ISTA Pharmaceuticals, Irvine, CA, USA) as outlined in a recent article could also be employed. It’s possible that blanching which sometimes precedes tissue necrosis may represent a neurovascular reflex unrelated to the presence of an AV malformation or intraarterial injection. Commentaries on both phenomena have appeared in the literature (Figures 6-9).

Temporal reticular veins/Published complications

A lawsuit was filed on behalf of 40-year-old woman who underwent sclerotherapy for superficial temporal veins, the first treatment proved ineffective and a second treatment was carried out using 0.25 cc of 0.25% sotradecol. Several hours later the patient complained of nausea, and “severe” migraine. Several weeks after treatment, the patient noted first crusting in the scalp, hair loss, and a little later a large ulceration 6 inches distal from the point of injection. This hair loss was permanent. Arterial studies carried out in the area injected revealed complete occlusion of the anterior branches of the superficial temporal artery suggesting the presence of an AV malformation (Figures 10,11).

Facial telangiectasia

Periodically peer reviewed articles and texts discuss the usefulness and comparative advantages and disadvantages associated with sclerotherapy for facial telangiectasia. In years past before the advent of light based devices (lasers, intense pulsed light) facial telangiectasia were routinely treated in this office employing sclerotherapy. Sclerotherapy is not and never has been the treatment of choice for most
works when other fail. It is particularly useful for large telangiectasia (0.6 mm-1mm in diameter), and considerably less painful than lasers that are used for that purpose. They are also warned that theoretically sclerotherapy for this purpose could cause serious complications but to date they have not been reported. The possibility of mild scarring related to the arteriolar nature of the vessels treated and the risks of treating certain areas (nose and cheeks), are discussed. Patients are told that those areas must be treated very carefully.Bruising which occurs uncommonly is discussed as is the possibility of recurrences which are relatively common varying from person to person. The reasons for special precautions when treating telangiectasia in close proximity to facial arteries (angular, temporal, supraorbital and supratrochlear) are also discussed.

Technique

Essentially the same approach is taken as is for facial reticular veins with the difference being that very small volumes (measured in a few tenths of a cc per injection site) were employed. Currently only 0.5% or 0.75% POL liquid are used.

Personal observations

Two cases of tissue necrosis occurred one involving the cheeks the other the nose which were preceded by blanching following the use of POL the other followed the use of HS. Over 100 patients have been treated. Sclerotherapy is comfortable and extremely effective for treating large (>0.6mm diameter) telangiectasia and is no longer used for patients with large numbers of telangiectasia associated with conditions such as rosacea.

Chest reticular veins

Enlargement of chest reticular veins have been noted to occur in patients who exercise vigorously and may be related to increased estrogen levels following pregnancy, or the use of oral contraceptives. Mondor’s disease may also present as an asymptomatic enlargement of a solitary chest vein. Enlargement of chest veins has also been seen in certain types of malignancies. Two patients developed sternal reticular and telangiectatic veins following cardiac bypass surgery (unpublished observation). Anecdotally they would be expected to result in increased incidence of tissue necrosis. Telangiectasia located in close proximity to facial arteries (angular, temporal, supraorbital and supratrochlear) may be risky to treat.

Examination and clinical approach

Patients are told that sclerotherapy is generally not a substitute for other modalities, but sometimes it was frequently employed in this office for patients who had not responded to electrocautery or had developed hypopigmentation following its use. Currently, facial telangiectasia are better treated using lasers or intense pulsed light. Electrocautery, although uncomfortable, can also be effective in good hands.

Facial telangiectasia unique features

The same circulatory complexities exist for telangiectasia as do for reticular veins; and the same risks are theoretically possible but the use of lower concentrations and volumes make this less probable; finally, facial telangiectasia may be predominantly arteriolar versus venous in character. Treatment might be expected to result in increased incidence of tissue necrosis. Telangiectasia located in close proximity to facial arteries (angular, temporal, supraorbital and supratrochlear) may be risky to treat.
are reported to communicate directly with the cardiac circulation and would be risky to treat.

**Reticular veins involving the breasts**

All the patients treated in this office developed enlarged reticular veins following augmentation mammoplasty. This procedure is regularly carried out. The veins ranged in size between 1.3-2.5 mm in diameter.

**Unique features**

Breast reticular veins respond to roughly the same concentrations and techniques applied for reticular veins on the lower extremities with the exception of compression which does not seem to be of value (unpublished personal observation). Then, the possibility of perforating the breast implant envelopes must be considered, they are often much closer to the surface than may be expected. Finally, pigmentation is rare, as is neovascularization.

**Evaluation and clinical approach**

The rare occurrence of minor complications including transient pigmentation, neovascularization (matting), (which I have never observed), is discussed. The need for possible repeated treatments is also pointed out. The extremely rare occurrence of tissue necrosis, which has never been observed in this office is also detailed.

**Technique**

In the past 23.4% HS was employed; currently 0.75-1.5% POL liquid preparations are used. Volumes never exceeded 2 cc. Care must be taken to avoid perforating the implant envelope, which is sometimes closer to the cutaneous surface than one might expect. Consideration in selecting sclerosant concentration involve included size, vessel wall thickness, and the depth of the treated veins.

**Long- and short-term outcomes**

All patients were satisfied at two years following 1-3 treatments. Recurrence was noted in one of 10 patients followed for more than 10 years. Treatment failures measured by no response to three treatments were seen to occur in less than 2% of the patients treated.

**Complications**

Two patients developed palpable thrombi which required incision and drainage. One patient developed mild superficial thrombophlebitis which responded to nonsteroidal anti-inflammatory agents and incision and drainage. Pigmentation, matting, allergies and embolic phenomena have not been observed.

**Alternative applications**

Only one article describes a wide range of both successful and unsuccessful treatment of both vascular and non-vascular disorders. Sclerotherapy for these conditions is essentially no more than an historical footnote. Cherry angiomata, blue rubber bleb nevus syndrome, and caput medusa have been treated. Reticular veins and telangiectasia involving the inguinal folds were treated effectively as were reticular veins on the dorsa of the feet. Radiation telangiectasia involving the neck was treated and was notable for the lack of good results. Small ulcers were seen at almost every treatment site. Telangiectasia involving the torso, shoulders and back have been treated successfully. Facial venous lakes have responded unpredictably and sporadically after laser treatments had failed. Recurrences were common in the larger venous lakes which filled rapidly after digital compression. The ablative potential of hypertonic saline was employed for the treatment of several punctuate finger tattoos as well as one larger tattoo involving the shoulder. Although the results were satisfactory in terms of what was available at the time they were decidedly inferior than those achieved using lasers. Abdominal caput medusa which followed the use of contraceptives was eradicated using 23.4% hypertonic saline; previous studies indicated that these veins were not essential as a bypass. Kaposi’s sarcoma partially resolved following sclerotherapy. Three patients with a nodular basal cell carcinoma were treated intratumorally with 23.4% hypertonic saline one day before excisional biopsy. In all three cases histological evaluation revealed total destruction of the carcinoma. It was speculated that sclerotherapy might also be useful for the ablation of tumor induced vasculature. Scle-
Sclerotherapy also proved effective for the treatment of epidermal cysts (Figures 12-30).

**Pertinent literature**

Peer reviewed reports in general are optimistic about successes following cosmetic sclerotherapy in all sorts of applications. These reports are often incorporated with other procedures as part of rejuvenation protocols. Serious complications appear to be rare. Bowes reported excellent results following sclerotherapy for reticular and telangiectatic veins on the face and hands. Sclerosants employed consisted of STS, both liquid and foam. One serious complication was reported occurring in a patient who had been treated for telangiectasia <0.4 mm in diameter involving the left breast. 0.5 mL of 0.25% of STS was used. Two weeks after treatment she presented with a 4cm x 6cm full thickness ulceration.
requiring eventual removal of the breast implant to permit closure and subsequent insertion of another implant. In this same article it was concluded that varicose and telangiectatic veins on the face, hands and chest can be treated safely and effectively. For the treatment of these areas no serious complications were reported. No ulcerations, thrombophlebitis, dysaesthesia/paresthesias, motor defects, hyperpigmentation, or telangiectatic matting were reported. They also note that care must taken when injecting the breast. In a later article in 2011 the authors employed STS foam 0.25% or 0.5% polidocanol foam for vessels under 1mm. For vessels 1-3mm they used 0.5% STS foam or 1% POL foam. Schulman reports the treatment of 208 patients with hand veins. He notes that “Patients have been uniformly free of any changes in hand function”. He further notes “There were no serious complications” asserting that “short-term post-sclerotherapy disturbances were limited to localized edema and bruising and always resolved in a matter of days”. There were no treatment failures. Butterwick was optimistic about the treatment of hand veins and reported no serious complications. Lay publications are equally enthusiastic about the potential for this therapy. Shamban reported good results following a variety of techniques to eliminate hand veins. Alone among all the authors reporting she noted “Sclerotherapy may leave hemosiderin stain that may last for several months”, this statement is not backed by any references. For facial veins, Kersten briefly quotes techniques employed by another author. He also asserts there has been “A general reluctance to

Figure 21.—This pretreatment photograph reveals the presence of thin walled varicosities measuring between 0.5-5 mm. 
Figure 22.—Three years post-sclerotherapy with 23.4% hypertonic saline. Patient was very pleased.

Figure 23.—Pretreatment photograph 2 mm vein. 
Figure 24.—Complete resolution noted six months after treatment with 1% POL solution.

Figure 25.—Pretreatment appearance of 0.4-0.6 mm facial telangiectasia. 
Figure 26.—Two weeks post sclerotherapy facial telangiectasia with 0.75% POL. 
Figure 27.—This pretreatment photograph reveals veins between 2-3 mm in diameter involving the dorsum of the foot.

Figure 28.—Results observed following three treatments employing 3% POL liquid and Class II support hose.
Figure 29.—This pretreatment photograph does not clearly reveal the presence of 0.3 mm telangiectasia treated with 0.75% POL solution.
Figure 30.—Blanching was noted at the time of injection followed by crusting and a shallow ulceration two weeks post treatment.
use sclerotherapy for removal of periocular veins because of fear of ophthalmologic and neurological complications”.

Conclusions

Cosmetic sclerotherapy has remained an innovative and fascinating aspect of practice. With the passage of time, new precisely targeted therapies have developed which have rendered sclerotherapy obsolete in some applications. Over time, I’ve become a great deal more conservative. Some of the procedures, particularly caput medusa I would not even attempt at this point. Very little is being written about cosmetic sclerotherapy. I suspect a great deal more is being carried out than is being reported. Periodically I receive a verified phone call from someone or an email which details some almost horrific experience usually involving potential tissue necrosis on the hands. So far none of these have proved to be very serious. One last admonition; training for cosmetic procedures cannot be obtained from lectures. It requires one-on-one instructions from an experienced phlebologist.

Riassunto

Applicazioni cosmetiche della scleroterapia

Lo scopo di questo studio è stato di ampliare le prospettive dei medici riguardanti lo scopo, la sicurezza e l’efficacia della scleroterapia nel trattamento delle vene esteticamente poco attraenti e di altre patologie che coinvolgono una grande varietà di aree anatomiche. L’autore ha redatto una review in cui vengono presentati i risultati ottenuti praticando scleroterapia estetica sia per le vene sia per altre applicazioni. Il presente studio coinvolge centinaia di pazienti trattati con flegologia privata nell’arco di 33 anni insieme a una breve review della letteratura pertinente. Poiché il trattamento delle vene dilatate che coinvolgono il dorso delle mani e il volto è raramente discusso, ma ampiamente praticato, il trattamento stesso viene posto in evidenza. Viene inoltre recensita l’utilità, in gran parte storica, della scleroterapia per altre applicazioni. Come per le vene degli arti inferiori, si è verificata una notevole variabilità sia a livello regionale che da paziente a paziente in termini di sensibilità agli sclerosanti e di risposta al trattamento. Tuttavia, la scleroterapia effettuata per scopi estetici ha regolarmente prodotto risultati soddisfacenti in varie applicazioni e per una molteplicità di aree. Complicanze potenzialmente serie e insuccessi nel trattamento sono stati rari in pazienti opportunamente selezionati. La soddisfazione del paziente, con poche eccezioni, è stata uniformemente elevata. L’aggiunta della scleroterapia estetica a una prassi flegologica stabilita può essere un’applicazione premiante e altamente soddisfacente di questa tecnica versatile. Le aree da trattare, la tipologia di lesione e la natura estetica di questa terapia incide su ogni aspetto del trattamento; legale, etico e procedurale. L’esperienza suggerisce che ogni area e tipo di lesione trattata mostra segni prevedibili di risposta e di rischio. La variazione dei risultati del trattamento delle vene, a seconda dell’area anatomica trattata, può riflettere: 1) processi di adattamento evolutivo che hanno prodotto vene adatte alle diverse aree; 2) differenze nei modelli di reclutamento delle citochine e nei processi apoptotici. Va inoltre notato che le complicanze potenziali riguardano condizioni di aree specifiche di anastomosi venosa, nervi, strutture vitali e la complessità dell’architettura arteriosa.

Parole chiave: Scleroterapia - Cosmetica - Vene.

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Corticosteroids are among the most commonly used drugs, both topically and systemically. Although unexpected and paradoxical, allergic hypersensitivity to corticosteroids is a common finding, delayed-type reactions being much more frequently encountered than the immediate-type ones. With regard to cross-reactions between corticosteroids, based on patch-test results and molecular modelling, we were recently able to simplify the previous classification into 3 different groups, i.e., Group 1: the non-methylated, most often non-halogenated molecules (Group A, D2 and budesonide), which produce most of the allergic reactions; Group 2: the halogenated molecules with a C_{16}/C_{17} cis ketal/diol structure (acetonide Group B); and Group 3: the halogenated and C_{16}-methylated molecules (Group C and D1) that only rarely produce allergy.

**KEY WORDS:** Dermatitis, contact – Cross reactions - Hypersensitivity.

**The skin: main sensitization and elicitation route**

Although sensitization and elicitation mainly occurs via the skin, other routes, among them inhalation of corticosteroids may exceptionally be involved. While few patients are sensitized or do present with allergic reactions when using inhaled corticosteroids personally, exposure to them and to budesonide in particular has been found to be responsible for primary airborne sensitization and/or airborne allergic contact dermatitis in subjects not themselves treated by aerosols containing this CS, but taking care of, or living with, patients who used them regularly because of a chronic respiratory affection. Raison-Peron were the first authors to describe connubial or consort contact dermatitis in the mother of a 3-year old boy being treated for asthma with an aerosol containing budesonide. Moreover, Pontén and more recently also Corraza have reported on airborne contact dermatitis from occupational exposure to them, notwithstanding the extremely low concentrations involved. This type of exposure should be routinely searched for in patients suspected of airborne contact dermatitis or with unexplained positive patch tests to budesonide.

Moreover, also the conjunctival and nasal mucosa,
the respiratory and the digestive tract may be causal routes, although a primary sensitizing contact with the surrounding skin cannot be excluded either.

Not many cases of sensitization and/or allergic reactions due to ocular use of CSs have been reported in the literature. We observed that 6% of patients with a CS sensitization presented with allergic manifestations via this route, particularly to hydrocortisone, the most prescribed ophthalmic CS. Furthermore, besides CSs, multiple positive tests were also observed for other potential allergens present in such preparations, such as topical antibiotics, antiseptics, and even vehicle components.

Clinical presentation: neither specific nor spectacular

The clinical signs of CS allergy are usually minor or display a completely atypical chronology. Allergy to CSs should be suspected in cases of CS-sensitive diseases that respond poorly or not at all to CS treatment, become worse following the use of CSs, or re-occur rapidly after CS withdrawal.

Allergic contact dermatitis from CSs may present as chronic eczema, often with the eruption being more pronounced at the periphery of the treated zone (“edge effect”). Moreover, as there may be a long delay before diagnosis, the clinical presentation can be dominated by other ‘classical’ side effects such as cutaneous atrophy, rosacea and perioral or perinasal dermatitis. In sensitized patients, ocular use of CSs may result in facial or periocular oedema and/or eczema, conjunctivitis, burning, itching and tearing, while inhaled CSs may provoke eczematous eruptions around the orifices (nostrils, nose, lips), with possible loco-regional extension, as well as mucosal reactions, such as stomatitis, nasal congestion and chronic rhinitis. Moreover, bronchospasm and bronchoconstriction as well as systemic reactions have also been observed.

Finally, flare-up reactions at previously affected skin sites and also generalized eruptions following systemic administration of CSs have been reported.

The indisputable value of patch testing

The anti-inflammatory properties of corticosteroids may mask the clinical signs of allergy or render them aspecific, thus rendering the skin-test results difficult to interpret. Testing with corticosteroid-allergy markers in the European baseline series is necessary since both budesonide and tixocortol pivalate detect 89% of the corticosteroid-sensitized patients. However, it is important to test with the particular corticosteroids used as well.

Patch tests remain the most adequate and effective method, with ethanol being the vehicle of choice for most molecules, and with their removal on Day 2 and readings up to 7 days later. The association of intradermal tests allows additional allergy cases to be diagnosed (mainly when ethanolic preparations of the active principles are not available for skin testing), thereby avoiding false-negative skin-test results. Compared to patch tests, ID tests seem easier to read and become positive sooner (at least on D1 or D2), but later readings such as D7 are, in most cases, not useful. Local ID reactions are less intense and shorter. However, there is an important risk of atrophy, particularly with potent corticosteroids and when in suspensions, hence this is a contraindication for routine use. Prick tests are of minor diagnostic value for diagnosing CSs delayed allergic hypersensitivity, though no side effects were noted.

The central role of halogenation and C16-methyl substitution and reappraisal of the ABCD classification

Sensitized patients frequently (85%) test positively to several corticosteroids. Although the existence of cross-reaction phenomena has been demonstrated by positive skin tests to synthetic corticosteroids to which a patient could never have been exposed (simply because they were not available at the time), simultaneous or subsequent sensitization can never be entirely ruled out.

In 1989, Coopman classified corticosteroids (CSs) into 4 reacting groups A, B, C and D in function of clinical and structural characteristics. In 1995, Lepoittevin supported this classification and the central role of constituents of the D-ring by means of conformational analysis of the observed cross-reactions.

Later on, Matura observing the particular behaviour of certain constituents of Group D CS esters, proposed a further subdivision into 2 subgroups, the stable D1 and labile D2 esters.
NEW INSIGHTS ABOUT DELAYED ALLERGIC HYPERSENSITIVITY TO CORTICOSTEROIDS

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In addition to the C_{16}/C_{17} substitutions, Wilkinson \textsuperscript{28} considered that the A-ring was a second reactive centre and that halogenation of the CS structure (C_{6} and/or C_{9}) was of critical importance in their cross-sensitivity pattern.

More recent data indicate that a distinction needs to be made between C_{16-}methylated and non-methylated molecules, the latter of which selectively bind with arginine to form stable cyclic adducts and induce more often sensitization than the former.\textsuperscript{29} Indeed, positive patch-test reactions are, with statistical evidence, much more frequently observed to corticosteroid molecules without C_{16-}methyl substitution in the D ring and not halogenated in most cases, Groups A (esterified or not) and D2, than to those that are halogenated and have a methyl group at C_{16}, Groups C and D1.\textsuperscript{30}

C_{16-}methyl substitution interferes with the protein binding and halogenation of the corticosteroid molecules plays an important role in their stabilization, which seems to protect them from sensitization properties.

Based on patch-test results and molecular modelling of CS, we were recently able to simplify this classification of CSs into 3 different groups \textsuperscript{31}.

**Table I.—Corticosteroids classification.**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>(\text{C}_{16})-methyl substitution</th>
<th>(\text{C}<em>{16}/\text{C}</em>{17}) cis ketal diol structure</th>
<th>(\text{C}_{16})-methyl substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No (\text{C}_{16})-methyl substitution</td>
<td>No halogenation (in most cases)</td>
<td>No halogenation (in most cases except\textsuperscript{4})</td>
</tr>
<tr>
<td>2</td>
<td>(\text{C}_{16})-methyl substitution</td>
<td>Halogenation (in most cases except\textsuperscript{4})</td>
<td>Halogenation (except\textsuperscript{4})</td>
</tr>
<tr>
<td>3</td>
<td>(\text{C}_{16})-methyl substitution</td>
<td>Halogenation (except\textsuperscript{4})</td>
<td>Halogenation (except\textsuperscript{4})</td>
</tr>
</tbody>
</table>

Indicative structure:

- **Group 1:**
  - Budesonide
  - Cloprednol
  - Cortisone acetate
  - Dichlorisone acetate
  - Difluprednate
  - Fluorometholone
  - Fluprednisolone acetate
  - Hydrocortisone
  - Hydrocortisone aceponate
  - Hydrocortisone acetate
  - Hydrocortisone 17-butyrate
  - Hydrocortisone 21-butyrate
  - Hydrocortisone hemisuccinate
  - Isoluprednol acetate
  - Maziapredone
  - Medrysone
  - Methylprednisolone aceponate
  - Methylprednisolone acetate
  - Methylprednisolone hemisuccinate
  - Prednicarbate
  - Prednisolone
  - Prednisolone caproate
  - Prednisolone pivalate
  - Prednisolone sodium metasulphobenzoate
  - Prednisolone succinate
  - Prednisone
  - Triocortol pivalate
  - Triamcinolone

- **Group 2:**
  - Amcinonide
  - Budesonide (R-isomer)*
  - Desonide*
  - Fluchloronide
  - Flumoxonide
  - Flumisolide
  - Fluocinolone acetonide
  - Fluocinolone
  - Fludrocortisone acetate
  - Fluprednisolone acetate
  - Fluprednisolone diacetate
  - Fluprednisolone hexacetonide

- **Group 3:**
  - Alclomethasone dipropionate
  - Beclomethasone dipropionate
  - Betamethasone
  - Betamethasone 17-valerate
  - Betamethasone dipropionate
  - Betamethasone sodium phosphate
  - Cloflasol propionate
  - Cloficasone butyrate
  - Cortivazol*
  - Desoxymethasone
  - Dexamethasone
  - Dexamethasone acetate
  - Dexamethasone sodium phosphate
  - Diflucortolone valerate
  - Diflorasone diacetate
  - Flumethasone pivalate
  - Fluocortin butyl
  - Fluocortolone
  - Fluocortolone caprylate
  - Fluocortolone pivalate
  - Fluprednidene acetate
  - Halomethasone
  - Meprednisone*
  - Fluticasone propionate
  - Mometasone furoate

\textsuperscript{*} may exceptionally only cross react with the acetonides
2: the halogenated molecules with a C_{16}/C_{17} cis ketal/diol structure (acetonide Group B); and Group 3: the halogenated and C_{16}-methylated molecules (Group C and D1) that only rarely produce allergy (Table I). This represents a simplification compared to previous classifications.\(^{25-27}\) However, some patients may also react exclusively to budesonide (R isomer, 32) along with molecules from the acetonide group. Indeed, budesonide is a particular molecule with its acetal function being an equal mixture of two isomers (R and S), hence its resemblance to both Group 1 and Group 2 molecules.\(^{26, 32}\)

Moreover, two sub-groups of corticosteroid-sensitized patients with probably different areas of immune recognition have been identified: Profile 1 patients, who react to molecules from one unique group, Group 1 for whom electrostatic fields (molecular charge) seem important; and Profile 2 patients who may react to the entire spectrum of CSs, Group 1 and Group 2 and/or Group 3 for whom steric fields (molecular structure) are determinant, and who probably present a global recognition of the CS skeleton.

For Profile 1 patients, replacement agents can be chosen within Group 2 and Group 3, since they only react to Group 1.

For Profile 2 patients, a classification, despite being valuable for orienting the search of a replacement molecule, cannot replace systematic, individualized evaluation of their sensitization/tolerance profile. The use of a calcineurin inhibitor, i.e., topical tacrolimus or pimecrolimus may also be an option.

Less is known about the classification and cross-reactivity pattern of the less common delayed reactions following systemic administration of CSs, although this might be the same as with topical use.\(^{33}\)

**Gruppo 1:** molecole non metilato, il più delle volte non-allogenato (Gruppo A, D2 e budesonide) che producano la maggior parte delle reazioni allergiche; **Gruppo 2:** le molecole allogenate con una struttura C16/C17 cis chetale/diolo (acetonide Gruppo B); e **Gruppo 3:** le molecole allogenate e C16-metilate (Gruppo C e D1) che soltanto raramente producano reazioni allergiche.

**Parole chiave:** Dermatite da contatto - Reazioni incrociate - Ipersensibilità.

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Atopic dermatitis (AD) management in an Italian pediatric clinic


**Aim.** Atopic dermatitis (AD) is a common, chronic relapsing inflammatory skin disease characterized by dry skin and variable pruritus sometimes associated with allergic disease in other organs as asthma and rhinoconjunctivitis. AD affects deeply the Quality of Life, thus can be extremely disabling and may cause psychological problems for both affected children and their families.

**Methods.** In order to investigate the estimated prevalence of the disease and the beliefs of the Italian pediatricians, a group of 437 Italian family pediatricians covering a population of almost 380000 children participated in a study based on a questionnaire of 38 items.

**Results.** According to answers of the participants, the incidence of AD has been estimated around 10% of the population and food allergy is believed to be the trigger of the acute phase of the disease in infants. As a second opinion, dermatologists are consulted more frequently than allergologists. Conclusion. The use of emollients is advised in general whilst topical corticosteroids treatment is prescribed only in selected cases; more than 50% of pediatricians do not prescribe topical calcineurin inhibitors.

**Key words:** Dermatitis, atopic - Prevalence - Pediatrics - Child.

Atopic Dermatitis (AD) is a widespread common skin disease with a frequency peak in infants. Even though the last decades have seen a growth in the number of important epidemiological surveys, the study of the incidence of the disease is complicated by the fact that AD is typically characterized by alternate aggravation and remission periods. Consequentially lifetime incidence measures are to be preferred over incidental or punctual measures. From a general analysis of the recent literature, in western countries, lifetime AD incidence is around 20% in patients from 0 to 14 years of age, with a slight predominance in females.1,3

The ISAAC study 1, 2 showed that, over a one-year period, AD incidence varied from less that 2% in Iran and Albania to over 16% in Japan, Sweden, and urban areas of the African Continent. In general, the highest values were found in Northern Europe, Australia, and Japan, whereas the lowest values were found in Eastern Europe and Asia. Furthermore, in majority of the considered countries, the highest values were found in urban as opposed to rural areas.

Few epidemiological studies were available in Italy. The ISAAC study considered children from 14 different Italian cities. Out of a total of 20815 patients ranging from 6 to 7 years of age, the periodic incidence (1 year) was estimated at 5.8%, where acute AD repre-
sented 0.1% of the total. Within the same study, incidence in a sample group of 26477 patients aged from 13 to 14 years, was 5.7% and acute AD was around 0.4% of the children.

In a second study, estimated DA incidence in a sample group of 1369 nine-year old children in 7 Italian cities was 5.8% (95% CI=45-7.1%) with values of 5.7% (95% CI=4.0-7.3%) in males and 6.0% (95% CI=4.1-7.8%) in females. The findings from these two studies are comparable and indicate that in Italy about one child on 20 children suffers from AD, but only 1-4 in 1,000 patients present acute AD.

A third Italian study aimed to verify the incidence of AD in 1402 children in a pre-school age (3-5 year old) cohort. For this purpose, a group of day nursery children was evaluated by mean of the ISAAC questionnaire whilst the atopic status was evaluated through the use of prick tests. According to the researchers, the incidence of AD was 15.4%.

In a last study, carried out in 2009, 3179 children (1618 males and 1516 females) were examined and AD was diagnosed in 224 cases (7.0%). In addition the study revealed the high frequency of the association with bronchial asthma (RR=4.5-95% CI), psoriasis (RR 5.5-95% CI=3.0-10.1) and vitiligo (RR 16.1-95% CI=6.5-39.5).

In 2008 a group of the Italian pediatricians belonging to the FIMP Dermatological Network “photographed” the AD situation from a Family Pediatrician’s point of view. For this objective, an ad-hoc scientific commission (Prof. C. Gelmetti, Dr. R. Bonfanti, Dr. M. Ferrara, Dr. M. Russomando, Dr. G. Ruggiero) elaborated a questionnaire aimed to verify the perception and the management of AD in the outpatient’s clinics in Italy. The results of this study are presented and discussed in this article.

### Materials and methods

The questionnaire (Table I) was composed of a series of multiple choice questions. One of the authors (GR) gathered and statistically elaborated the resulting data (software EPI INFO CDC vers.55.1); the second author (CG) wrote the present study.

The questionnaire was anonymous, filled out by the doctor on the spot during National or local conferences and without any specific preparation or the help of educational material (traditional or electronic).

Data were gathered by the Regional Coordinators of the FIMP Dermatological Network and hence sent to the National Coordinator (GR). This method was chosen to assess what the family pediatricians know and do, as well to test the awareness of the scientific knowledge regarding AD and the perception of this disease within the family pediatrician’s environment.

A total of 437 family pediatricians (FP) took part in this study out of a total of 6011 FPs registered members of FIMP (7,27%). FIMP’s registered FP’s represent 88% of FPs in Italy. The FP’s that participated in the study came from 16 out of the 20 Italian Regions (Figure 1).

According to the average number of patients per doctor (i.e. around 864 children per pediatrician), the total pediatric population can be calculated around 380000 patients. A percentage of 85.1% of the participating FP’s had one or more decades of professional activity (respectively: 43.9% had 10-20 years and 41.2% had 20-30 years of experience after board certification).

### Discussion

The rapid increase of AD incidence observed over the last 30-50 years and the consequent considerable social impact of the disease in terms of are two arguments that can catch pediatricians’ attention. Moreover, the association of AD with other diseases such...
From the data obtained, the following should be highlighted:

1. The percentage of patients affected by AD is estimated to be around 10%; AD is considered mainly (87.8% of FP’s) triggered by environmental and genetic factors.

2. About half of the FP’s does not know the classic (i.e., Hanifin and Rajka and UK working group) diagnostic criteria of AD (48.5%). AD diagnostic criteria published by Bonifazi are the most well known.

3. The majority (68%) of the AD patients seen by FPs are affected by a mild form of AD.

4. More than half (57.9%) of FPs know SCORAD index but only 34% of those who know it use SCORAD in their practice.

5. The greater part of FP’s believe that severe AD in babies is mainly triggered by food allergens (22.2%), environmental allergens (29.8%), environmental factors with non allergic mechanisms (23%).

6. Laboratory work-up is carried out in cases in which allergies are suspected (66.5% of FPs) even if 8.8% of FPs never carry out additional screening and 8.3% of FPs always advice supplementary tests regardless of symptoms. Prick tests and specific serum IgE are the most prescribed tests both in first and second instance; 65.2% of FPs prescribe only one test in the first instance (68.5% in the second).

7. Specialist advice is requested only in selected cases. The dermatologist is requested far more than the allergist.

8. The vast majority (94.1%) of FPs give hygienic and sanitary advice and 86.2% give advice on how to apply topical products; only 20.4% give a personal demonstration of the methods of application.

9. The vast majority (85.8%) of FPs advices the use of emollients and prescribes topical corticosteroids only for selected cases (83.9%) of moderate and/or severe forms and only for a short term.

10. Topical calcineurin inhibitors (tacrolimus and pimecrolimus) are used for AD forms that steroid resistant, however most (56.7%) FPs do not use them.

11. Oral antihistamines are only used in selected cases (75.6%).

12. In cases of impetigination, the preferred antibiotics are oral amoxiclavulanate or macrolides and, topical fusidic acid, mupirocin and gentamicine.

13. In breast feeding babies suffering from AD it is advised to continue breast feeding whilst for babies using artificial milk, in selected cases, special milk is advised, especially hydrolyzed cow’s milk.
14. Complementary and alternative medicine is never advised by most FPs (77.9%). When those therapies are advised, homeopathy and herbal therapy are preferred (19.5%).

15. Only 27% of FPs believes they have a good level of AD awareness. Ninety-six% believe that an in-depth course on AD would be useful.

Almost (49.99%) half of the FPs who participated in the study came from the Northern Italian Regions (218/437), 14.64% came from the Central Regions (64/437), and 35.46% from the Southern Regions and from the Big Islands (Sicily and Sardinia).

Some considerations can be made: the first is that the evaluation of AD incidence in this big sample is in accordance with the scientific data available before the beginning study,1-4 and also with the date that published in the meantime.5 Curiously, half of the FPs is not aware of the classic AD diagnostic criteria and that, amongst those they are aware, the most well known are those described by Bonifazi (Professor Ernesto Bonifazi is, among the Italian Pediatric Dermatologists, one of most respected; Bonifazi’s criteria are less used internationally).

The opinion concerning the etiopathogenesis of AD which contemporaneously focuses both genetic and environmental factors is also coherent with the general opinion of the experts. The opinion that severe AD in babies is mainly triggered by food allergens is still a matter of discussion, especially after the data published in the recent literature. It is encouraging to see that laboratory set-up is usually carried out only in cases of suspected allergy even though there is an 8.3% of FPs that always asks for additional tests. It is also reassuring to note that specialist consultation is requested only in selected cases and that the external specialist called by the FPs is, more frequently, the dermatologist. This has recently become obvious as the first objective of AD treatment is correct skin care.

The FPs usually advise emollients and prescribes topical corticosteroids only in selected cases, however more than half of the FPs does not yet use topical calcineurin inhibitors.

Conclusions

In accordance with scientific literature, it is a common opinion (70.1%) that babies with AD should continue to be breast-fed; when maternal milk is not available, FPs advise a special milk only in selected cases; 67.4% of FPs make only one therapeutic choice between special milks: hydrolyzed milk (37.6%) is the most common, whilst milks with free amino acids are less frequently used (1.8%). Other “special” milks (e.g. soya =8% and HA [HypoAntigenic] milk =8.8%) are ALSO prescribed but in a limited number of cases. Two foods therapeutic choices are advised in 25.56% of cases, while 9.52% of FPs prefer a wider therapeutic range. The caution towards alternative medicine is also reassuring. Lastly, the FPs own opinion regarding their AD awareness (judged as insufficient by ¾ of the participants) perfectly mirrors the consideration regarding the need of more updated informations on this disease which is global and truly pervasive on children and their families.

The FP is, indeed, the first observer of AD who has the task of adopting a correct management. In addition, the FP has the obligation of being informed and updated on this disease. The data collected by this study encourage us to continue the work of diffusion of the informations on the domestic area throughout meetings giving the correct indications on the etiopathogenesis, diagnosis, and cure of AD which, at present, represents the first pediatric cause for a dermatological visit.

Riassunto

Trattamento della Dermatite Atopica in una popolazione pediatrica italiana

Obiettivo. La Dermatite Atopica (DA) è una malattia infiammatoria cronica della pelle caratterizzata da cute secca e prurito intenso che può essere invalidante e causare problemi psicologici per i bambini e le loro famiglie.

Metodi. A questo riguardo 437 pediatri di famiglia iscritti alla Federazione Italiana Medici Pediatri (FIMP) che seguono una popolazione di circa 380000 bambini hanno partecipato ad uno studio basato su un questionario.

Risultati. La prevalenza della malattia è stata stimata intorno al 10% della popolazione e l’allergia ai cibi è ritenuta la causa di scatenamento delle fasi acute in età infantile. Il dermatologo è consultato più spesso dell’allergologo.

Conclusion. Gli emollienti sono consigliati comunque mentre i corticosteroidi topici solo in casi selezionati; mentre più della metà dei pediatri non prescrive gli inhibitori topici della calcineurina.

Parole chiave: Dermatite atopica - Prevalenza - Pediatria - Bambini.

References

1. Williams HC, Robertson C, Stewart A, Ait-Khaled N, Anabwani G, Anderson R et al. Worldwide variations in the prevalence of symp-


APPENDIX

1) What percentage of your present patients suffer from AD?
   1. 1-5%
   2. 5-10%
   3. 10-20%
   4. >20%

2) What percentage of your patients aged up to 1 year suffer from AD?
   1. 1-5%
   2. 5-10%
   3. 10-20%
   4. >20%

3) What percentage of your patients aged from 1 to 3 years suffer from AD?
   1. 1-5%
   2. 5-10%
   3. 10-20%
   4. >20%

4) What percentage of your patients of 3 years of age suffers from AD?
   1. 1-5%
   2. 5-10%
   3. 10-20%
   4. >20%

5) From an etiopathogenic point of view. AD depends on
   1. Environmental factors
   2. Genetic factors
   3. Interaction between environmental and genetic factors
   4. Other:

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6) Which of these diagnostic criteria do you know? (multiple answer)
1. Williams UK Working Party
2. Bonifazi
3. American Academy of Dermatology
4. Hanifin and Rajka
5. None of these

7) Amongst your AD patients, indicate the percentage of mild, moderate and severe forms
1. Mild: %
2. Moderate: %
3. Severe: %
Total: 100%

8) Do you know SCORAD index
1. Yes:
2. No:

9) If you do, do you use it in daily practice?
1. Yes
2. No

10) In your opinion, moderate to severe AD in children is mainly triggered by:
1. Food allergens
2. Environmental allergens
3. Environmental factors with non allergic mechanism
4. Local bacterial infection
5. Only genetic predisposition

11) In your opinion, AD in children aged from 2 to 3 years is mainly triggered by:
1. Food allergens
2. Environmental allergens
3. Environmental factors with non allergic mechanism
4. Local bacterial infection
5. Only genetic predisposition
12) Do you carry out laboratory set-up?
1. never
2. always
3. in cases of suspected allergy
4. in cases of other associated symptoms

13) Which are the first tests you advise? (multiple answer)
1. immunocap
2. specific IgE
3. skin tests (Prick test)
4. provocation test
5. patch test
6. total IgE
7. Other

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| 1 exam  | 271       | 65.2%    |
| 2 exams | 106       | 25.5%    |
| 3 exams | 32        | 7.7%     |
| 4 + exams | 7 | 1.6%   |
| Total    | 416       |          |

14) Which is the second test you advise? (multiple answer)
1. immunocap
2. specific IgE
3. skin tests (Prick test)
4. provocation test
5. patch test
6. total IgE
7. Other

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<td>7</td>
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<tr>
<td>7</td>
<td>5</td>
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| 1 exam  | 232       | 68.5%    |
| 2 exams | 93        | 27.4%    |
| 3 exams | 12        | 3.5%     |
| 4 + exams | 2 | 0.6%   |
| Total    | 416       |          |

15) Do you ask for a Specialist advice?
1. never
2. always
3. only in selected cases

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</table>

16) Which Specialist do you consult most often?
1. dermatologist
2. allergist
3. psychologist
4. Other

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<th>Frequency</th>
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<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>412</td>
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</tbody>
</table>
17) If you consult more than one Specialist, please indicate which (1 indicates most often and 4 indicates least often)
   1. dermatologist
   2. allergist
   3. psychologist
   4. Other

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<th>Cumulative %</th>
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<td>21</td>
<td>45</td>
<td>14.9%</td>
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18) Do you give sanitary and hygiene advices (cleaning, clothing, etc)?
   1. never
   2. always
   3. only in selected cases

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19) Do you advise on application procedures of topic products for cosmetic or therapeutic use?
   1. never
   2. always
   3. only in selected cases

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<td>Total</td>
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20) Do you demonstrate, personally or with the help of audio visual equipment, how to apply topical products?
   1. never
   2. always
   3. only in selected cases

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21) Do you suggest the use of moisturizing creams / emollients?
   1. never
   2. always
   3. only in selected cases

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22) Do you prescribe topical corticosteroids?
   1. never
   2. always
   3. only in selected cases

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23) When do you prescribe topical corticosteroids?
   1. mild forms
   2. moderate forms
   3. severe forms
   4. never

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24) For how long do you advise use of topical corticosteroids?
1. 1-2 days
2. 3-4 days
3. 5-8 days
4. until symptoms disappear

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</table>

25) Do you use topical calcineurin inhibitors (tacrolimus and pimecrolimus)?
1. never
2. always
3. only in selected cases

<table>
<thead>
<tr>
<th>CALC INHIB</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>237</td>
<td>56.7%</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>1.7%</td>
</tr>
<tr>
<td>3</td>
<td>174</td>
<td>41.6%</td>
</tr>
<tr>
<td>Total</td>
<td>418</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

26) If you do, for which forms do you use tacrolimus?
1. mild forms
2. moderate forms
3. severe forms
4. those that do not respond to topical corticosteroids

<table>
<thead>
<tr>
<th>TACRO USE</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0.6%</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>10.4%</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>31.2%</td>
</tr>
<tr>
<td>4</td>
<td>101</td>
<td>57.8%</td>
</tr>
<tr>
<td>Total</td>
<td>175</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

27) If you do, for which forms do you use pimecrolimus?
1. mild forms
2. moderate forms
3. severe forms
4. those that do not respond to topical corticosteroids

<table>
<thead>
<tr>
<th>PRIMECRO</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>2.4%</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>14.6%</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>35.4%</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>47.6%</td>
</tr>
<tr>
<td>Total</td>
<td>164</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

28) Do you use oral antihistamines in general?
1. never
2. always
3. only in selected cases

<table>
<thead>
<tr>
<th>ANTIHIST</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
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<tr>
<td>2</td>
<td>73</td>
<td>17.0%</td>
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<tr>
<td>3</td>
<td>325</td>
<td>75.6%</td>
</tr>
<tr>
<td>Total</td>
<td>430</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

29) For the impetiginized form of AD, which oral antibiotic do you use?
1. Amoxicillin
2. Amoxiclavulanate
3. Macrolides
4. Cephalosporines
5. Other

<table>
<thead>
<tr>
<th>IMPETIG.</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
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<tr>
<td>2</td>
<td>166</td>
<td>43.6%</td>
</tr>
<tr>
<td>3</td>
<td>164</td>
<td>43.0%</td>
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<td>4</td>
<td>10</td>
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</tr>
<tr>
<td>5</td>
<td>3</td>
<td>0.8%</td>
</tr>
<tr>
<td>Total</td>
<td>381</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

30) For the impetiginized form of AD, which topical antibiotic do you use?
1. Mupirocin
2. Fusidic Acid
3. Macrolides
4. Gentamicin
5. Other

<table>
<thead>
<tr>
<th>IMPETIG.</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
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<td>87</td>
<td>23.3%</td>
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<tr>
<td>3</td>
<td>48</td>
<td>12.9%</td>
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<tr>
<td>4</td>
<td>93</td>
<td>24.9%</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>1.3%</td>
</tr>
<tr>
<td>Total</td>
<td>373</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
31) In a breast feeding baby suffering from AD. you:
1. advise to continue breast feeding
2. suggest special milk
3. suggest a hypoallergenic diet to the mother
4. Other

<table>
<thead>
<tr>
<th>BREAST</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>2</td>
<td>14</td>
<td>3.2%</td>
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<td>3</td>
<td>112</td>
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<td>4</td>
<td>3</td>
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</tr>
<tr>
<td>Total</td>
<td>431</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

32) In a formula feeding baby suffering from AD. you:
1. continue with the same formula
2. suggest special milk
3. advise special milk only in selected cases
4. Other

<table>
<thead>
<tr>
<th>FORM</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>14.7%</td>
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<td>72</td>
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<td>4</td>
<td>5</td>
<td>1.2%</td>
</tr>
<tr>
<td>Total</td>
<td>429</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

33) If you use advice special milk. which one do you suggest (multiple answer)
1. H.A. (HypoAntigenic milk)
2. strong hydrolyzed casein milk
3. strong hydrolyzed serum protein milk
4. soya milk
5. hydrolyzed soya milk
6) hydrolyzed rice milk
7) amino acid synthesis milk
8) goat milk
9) Other

<table>
<thead>
<tr>
<th>MILK</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
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<td>60</td>
<td>24.5%</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>36.7%</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>13.1%</td>
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<td>3</td>
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<td>6</td>
<td>17</td>
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<td>7</td>
<td>7</td>
<td>2.9%</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>0.4%</td>
</tr>
<tr>
<td>Sub total</td>
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</tr>
<tr>
<td>remaining</td>
<td>154</td>
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<tr>
<td>Total</td>
<td>399</td>
<td>100.0%</td>
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</tbody>
</table>

34) Do your AD patients use alternative medicine (homeopathy. herbal medicine. etc)?
1. never
2. always
3. only in selected cases

<table>
<thead>
<tr>
<th>HOMEOP</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>3</td>
<td>189</td>
<td>45.7%</td>
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<tr>
<td>Total</td>
<td>414</td>
<td>100.0%</td>
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</tbody>
</table>

35) Do you personally suggest alternative therapy?
1. never
2. always
3. only in selected cases

<table>
<thead>
<tr>
<th>ALTERNAT</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
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<tr>
<td>3</td>
<td>82</td>
<td>19.5%</td>
</tr>
<tr>
<td>Total</td>
<td>421</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

36) If you suggest alternative medicine. which do you prefer?
1. Homeopathy
2. Herbal medicine
3. Cyto test or DRIA based diet
4. Other

<table>
<thead>
<tr>
<th>TYPE</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>9</td>
<td>7.1%</td>
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<tr>
<td>4</td>
<td>6</td>
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</tr>
<tr>
<td>Total</td>
<td>127</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
37) Do you believe your AD awareness to be:
1. scarce
2. sufficient
3. good
4. very good

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
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<td>116</td>
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<tr>
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<td>4</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>430</td>
</tr>
</tbody>
</table>

38) Do you think an in-depth course on AD would be useful?
1. yes
2. no

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>404</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>17</td>
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<tr>
<td>Total</td>
<td></td>
<td>421</td>
</tr>
</tbody>
</table>
Dermatology Life Quality Index score in vitiligo patients: a pilot study among young Italian males

V. INGORDO 1, S. CAZZANIGA 4, C. GENTILE 2, S. S. IANNAZZONE 3, F. CUSANO 3, L. NALDI 4

Aim. A negative impact on vitiligo patients in terms of quality of life (QoL) has been suggested. The aim of this report was to study the QoL in a sample of Italian vitiligo patients by using the Dermatology Life Quality Index (DLQI) questionnaire.

Methods. A sample of forty seven vitiligo subjects, identified among 34,740 potential conscripts resident in southern Italy underwent the Italian version of the DLQI questionnaire.

Results. The median total DLQI score was 1 (IQR: 2; mean: 1.82). In univariate analysis, DLQI total score was significantly influenced by the clinical course of vitiligo, disease extension over the body, and location on face and/or hands. Multivariate analysis using logistic stepwise regression showed that only the localization on the hands and on the face influenced significantly the mean DLQI.

Conclusion. Our study conducted on a random sample of individuals affected by vitiligo selected from the general young male population in Italy, does not document a large impact of vitiligo on QoL. However, variations exist and the location of lesions on the face and/or hands may impact on QoL. Population-based studies are not affected by selection biases connected with seeking medical care and should be more widely performed.

Key words: Vitiligo - Quality of life - Skin diseases.

Vitiligo is an acquired disorder of pigmentation affecting 0.1-8.8% of the world’s population,1-5 characterized by the development of white patches on the skin, often with a typical symmetrical distribution and progressive extension. Although vitiligo does not cause direct physical impairment, it can produce an important psychosocial burden.6, 7 Patients with vitiligo suffer from poor body image, low self-esteem and experience a high level of disability from their skin disease.8, 9 Many vitiligo patients feel distressed and stigmatized by their condition, especially in relation to social activities.10 Exposing the body causes anxiety and embarrassment, which in more intimate encounters may have a negative effect on sexual relationships.11 In other words, there appear to be an impact of vitiligo on the overall patient quality of life (QoL).12 The aim of this report was to study QoL in a sample of Italian young vitiligo patients by using the Dermatology Life Quality Index (DLQI) questionnaire, which has been successfully employed for the same purpose on subjects with vitiligo in other countries.8, 12-19 The DLQI questionnaire is designed for use in adults (i.e., patients over 16). It is self-explanatory and can be simply handed to the patients without the need for detailed explanations. The questions in DLQI are classified into 6 heading items: symptoms and feelings (questions 1-2), daily activities (questions 3-4), leisure (questions 5-6), and personal relationships (questions 8-9) each item with a maximum score of 6; work and school (question 7), and treatment (question 10) each item with a maximum score.
of 3 (Table I). The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more QoL is impaired. The DLQI questionnaire has been translated in 55 languages and extensively validated. Its use in vitiligo patients has been successfully compared with several scales designed to measure self-esteem (Rosenberg’s scale), perceived stigma (an adaptation of Ginsburg and Link’s psoriasis stigma questionnaire) and personal distress (12-item version of GHQ) and with scales designed to evaluate the psychiatric morbidity (Montgomery and Asberg Depression Rating Scale, Hamilton Anxiety Appreciation Scale).

Patients, materials and methods

Until December 2004, Italian Armed Forces were based mainly on the compulsory national service. The potential conscripts resident in the coastal regions of southern Italy, enlisted for the service in Italian Navy, were called at the age of 18 to the Draft’s Council Medical Unit of the Italian Navy in Taranto to evaluate their psycho-physical fitness to recruitment. They underwent a general clinical examination, with a complete clinical examination of the entire skin surface, blood test and urinalysis, cardiological, ophthalmologic, otorhynolaryngologic examination and psychologic evaluation with psychometric tests. Medical Officers-general practitioners of the Medical Unit referred to Italian Navy Hospital subjects showing particular diseases and who need to be seen by other specialists. All the young men consecutively visited can be considered a representative sample of the general population of same age and sex living in the coastal southern Italy. From January 1998 to April 2004 a dermo-epidemiologic project, named EpiEnlist (EPIdemiology, in ENLISTed Men) project, was conducted by the Department of Dermatology of Italian Navy Hospital under the auspices of the Italian Group for Epidemiological Research in Dermatology (GISED).

All the subjects showing skin lesions evocative of neurofibromatosis (NF), congenital melanocytic nevus (CMN), Becker nevus (BN) and vitiligo were referred by Medical Officers-general practitioners of the Draft’s Council Medical Unit to the Department of Dermatology of Italian Navy Hospital for confirming the diagnosis and recording the data. The main results of the entire project have been published by us in another work. With regard to diagnosis of vitiligo, all the individuals who showed some area of hypopigmentation were referred to Department of Dermatology, where the diagnosis was stated on the basis of medical history and clinical appearance (i.e., achromic areas of the skin with sharp outline). In doubtful cases, examination by Wood’s lamp was performed. The subjects provided also their familial history and the information concerning the previous therapies and the clinical course (progression, regression, stable) of the disease. The main epidemiological data of this sample have been published by us in another work. From October 2001 to April 2004, 60 patients with vitiligo on 34740 subjects were observed, obtaining a prevalence of 0.17% (95% CI: 0.13-0.22). Generalized (53.3%), focal (41.7%) and segmental (5%) vitiligo were the observed clinical forms. No cases of acro-facial and universal vitiligo were recorded. The disease involved a limited area of the skin in most cases: in 80% of subjects only ≤5% of the total body surface was affected. Eighteen subjects (30%) reported a familiarity of the disease. Out of these people, a random sample of 47 people were proposed to fill in the Italian version of the DLQI questionnaire (kind permission was obtained by professor A.Y. Finlay, University of Wales College of Medicine, Cardiff, UK).

Statistical analysis

Continuous variables are presented as means with standard deviations and categorical variables as numbers with percentages and 95% confidence interval. The variables included: age, duration of the disease, age of onset of the disease, clinical course of the disease, extent of affected skin, special sites involved (face, hands and genitalia). DLQI scores were both presented as medians with interquartile ranges and means with standard deviations. Univariate analysis was used to assess differences among demographical and clinical variables for total DLQI score and scores of individual DLQI components. For comparison purpose, continuous variables were categorized using their median or meaningful clinical values (extent of affected skin) as cut-off points. Mann-Whitney U-test was employed to test differences in dichotomous variables, while Kruskal-Wallis test, followed by Tukey-Kramer post-hoc comparison, was used for multiple categorical vari-
TABLE I.—DLQI questionnaire.

<table>
<thead>
<tr>
<th>Heading items</th>
<th>Questions</th>
<th>Answers</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symptoms and feelings</td>
<td>Q1. Over the last week, how itchy, sore, painful or stinging has your skin been?</td>
<td>Very much 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A lot 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A little 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not at all 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q2. Over the last week, how embarrassed or self conscious have you been because of your skin?</td>
<td>Very much 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A lot 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A little 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not at all 0</td>
<td></td>
</tr>
<tr>
<td>2. Daily activities</td>
<td>Q3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?</td>
<td>Very much 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A lot 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A little 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not at all 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q4. Over the last week, how much has your skin influenced the clothes you wear?</td>
<td>Very much 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A lot 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A little 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not at all 0</td>
<td></td>
</tr>
<tr>
<td>3. Leisure</td>
<td>Q5. Over the last week, how much has your skin affected any social or leisure activities?</td>
<td>Very much 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A lot 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A little 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not at all 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q6. Over the last week, how much has your skin made it difficult for you to do any sport?</td>
<td>Very much 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A lot 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A little 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not at all 0</td>
<td></td>
</tr>
<tr>
<td>4. Work and school</td>
<td>Q7. Over the last week, has your skin prevented you from working or studying?</td>
<td>Yes 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If ‘NO’, over the last week how much has your skin been a problem at working and studying?</td>
<td>No 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A lot 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A little 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not at all 0</td>
<td></td>
</tr>
<tr>
<td>5. Personal relationships</td>
<td>Q8. Over the last week, how much has your skin created problems with your partner or any close friends or relatives?</td>
<td>Very much 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A lot 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A little 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not at all 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q9. Over the last week, how much has your skin caused any sexual difficulties?</td>
<td>Very much 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A lot 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A little 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not at all 0</td>
<td></td>
</tr>
<tr>
<td>6. Treatment</td>
<td>Q10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?</td>
<td>Very much 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A lot 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A little 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not at all 0</td>
<td></td>
</tr>
</tbody>
</table>

ables. All variables tested in the univariate analysis with a P value ≤0.1 were included in a multivariate case-control analysis to assess which factors influence the total DLQI score. Investigated factors included: clinical course of the disease, extent of affected skin, involvement of face and hands. In case-control definition the median of total DLQI score was used as threshold in order to have an homogeneous data partition. Case were defined as subjects with a score ≥1 (small to large effect on patient’s
life) and control as subjects with zero score (no impact on patient’s life). Multiple logistic regression with forward stepwise selection was used to identify main risk factors. C-index was used to assess predictive power of the fitted model. Effects of identified factors were calculated as odds ratios with 95% confidence interval. The analysis was carried out using SPSS software, version 17.0 (SPSS, Chicago, IL, USA).

**Results**

Among the 47 patients who compiled the DLQI questionnaire, the mean age was 19 years (SD ± 1.1). The mean age of onset of the disease was 12.3 (SD ± 5.5) years and the mean duration of the condition was 7.7 (SD ± 5.7) years. The mean extent of skin involved was 3% (SD ± 4.2). Face (36.1%; 95% CI: ±13.7), hands (38.2%; 95% CI: ±13.8) and genitalia (70.2%; 95% CI: ±13) were the most frequently involved sites. With respect to clinical course in the last year, vitiligo was stable in 25 (53.1%; 95% CI: ±14.2), progressive in 9 (19.1%; 95% CI: ±11.2), regressive (following therapy or spontaneously) in 13 (27.6%; 95% CI: ±12.7) patients.

**DLQI results**

The median total DLQI score was 1 (IQR: 2; mean: 1.82). The median and mean scores for the individual DLQI components are reported in Table II. The distribution of DLQI scores in the sample is represented in Figure 1. The main component influenced by the disease was “symptoms and feelings”, followed by “personal relationships”, “leisure” and “daily activities”. The components “work and school” and “treatment” were influenced very weakly by vitiligo. Patient’s age, duration of the disease and age of onset did not influence significantly the total DLQI score (Table III). On the contrary, the total DLQI was significantly influenced by the clinical course of vitiligo (Table III). Moreover, in multiple comparison analysis, progression/stability and progression/regression pairs showed a significant association with DLQI (corrected P-value <0.05). The total DLQI score increased significantly when skin involvement was over 5% (Table III).

![Figure 1.—DLQI score.](image)

The value of the median and mean total DLQI along with DLQI scores of the different explored components, evaluated according to the involvement of specific locations (face, genitalia and hands), are reported in Table IV. The overall DLQI scores and the score of specific components, with exception of the heading item “work and school” were significantly higher in subjects in whom the face was affected by the disease. The localization of vitiligo on the hands showed significantly a higher total DLQI score and...
higher partial scores in heading items “symptoms and feelings”, “daily activities” and “personal relationships”.

Multivariate logistic regression analysis of independent contribution of demographic and clinical variables in people with a DLQI total score \(\geq 1\) (N=25) compared to subjects with zero score (N=22), showed that only the localization on the hands (OR: 6.32; 95% CI: 1.35-29.50) and on the face (OR: 5.03; 95% CI: 1.05-24) were significantly associated with some impact of vitiligo on patient’s life (C-index: 0.80; 95% CI: 0.67-0.93).
Discussion

To the best of our knowledge, based on a systematic search regarding studies published from 1994 to 2009, this is the first report evaluating QoL in Italian vitiligo patients by using the DLQI questionnaire. Other studies have been conducted on Italian vitiligo patients by using different methods to investigate QoL.24, 25 The present survey was performed on vitiligo patients randomly selected among all vitiligo young men identified in a representative sample of Italian young male adults undergoing assessment for compulsory service in national Navy. Most of the studies of QoL in vitiligo have been conducted on patients attending a medical intervention12-14, 16, 17, 19 or members of vitiligo associations8, 15 (who were probably highly conscious of the level of disability of their disease) and, in some instances, the persons received the questionnaire by mail8, 12 and stated by themselves the severity of the disease8, 15 pointing to possible selection bias. One limitation of our study is the small sample size and the fact that it was conducted almost ten years ago when army service was compulsory in Italy.

The total mean DLQI in our subjects was surprisingly lower than the mean indexes reported in other studies (Table V). We believe that this finding could be explained both by the fact that we studied a population-based sample including many subjects with a very limited skin involvement and by the male gender of our subjects. In fact, according to most surveys, women affected by vitiligo show a DLQI score significantly higher than male patients12, 14, 16, 17, 19 and the severity/extent of the disease significantly correlated with the DLQI score8, 12, 14, 15, 17, 19. In the few instances where no correlation was documented the average skin involvement in the sample was quite high.13 In our sample, the total DLQI score was significantly higher in people showing vitiligo involvement >5% of skin surface.

Some authors pointed out a significantly higher DLQI in young vitiligo patients8, 13, but this observation was not confirmed by others.12, 14, 17 Since our study was restricted to younger people we cannot

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>N° patients</th>
<th>Setting</th>
<th>Mean DLQI of patients (SD)</th>
<th>N. controls</th>
<th>Mean DLQI of controls (SD)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kent and Al-Abadie, 1996</td>
<td>614</td>
<td>Members of Vitiligo Society; postal survey</td>
<td>4.82 (4.84)</td>
<td>nd</td>
<td>//</td>
<td>//</td>
</tr>
<tr>
<td>Parsad et al., India, 2003</td>
<td>150</td>
<td>Patients referred to a Department of Dermatology</td>
<td>10.67 (4.56)</td>
<td>nd</td>
<td>//</td>
<td>//</td>
</tr>
<tr>
<td>Aghaei et al., 2004, Iran</td>
<td>70</td>
<td>Patients referred to a Department of Dermatology</td>
<td>7.05 (5.13)</td>
<td>nd</td>
<td>//</td>
<td>//</td>
</tr>
<tr>
<td>Ongenae et al. 2005, Belgium</td>
<td>119</td>
<td>Patients referred to a Department of Dermatology; postal survey</td>
<td>4.95</td>
<td>162 patients with psoriasis</td>
<td>6.26</td>
<td>P=0.01</td>
</tr>
<tr>
<td>Ongenae et al., 2005, Belgium</td>
<td>78</td>
<td>Patients attending a meeting organized by a Vitiligo association</td>
<td>6.9 (5.6)</td>
<td>nd</td>
<td>//</td>
<td>//</td>
</tr>
<tr>
<td>Mechri et al., 2006, Tunisie</td>
<td>60</td>
<td>Patients referred to a Department of Dermatology</td>
<td>9.4 (17.1)</td>
<td>60 patients with other skin diseases</td>
<td>2.5 (1.0)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>van Geel et al., 2006, Belgium</td>
<td>20</td>
<td>Patients referred to a Department of Dermatology attending treatment by transplantation of epidermal grafts</td>
<td>6.95 (4.13)</td>
<td>nd</td>
<td>//</td>
<td>/</td>
</tr>
<tr>
<td>Belhadjali et al., 2007, Tunisie</td>
<td>60</td>
<td>Patients referred to a Department of Dermatology</td>
<td>9.4 (4.1)</td>
<td>60 patients with other skin diseases</td>
<td>2.1 (1.0)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Al Robae, 2007, Saudi Arabia</td>
<td>109</td>
<td>Patients referred to a Department of Dermatology</td>
<td>14.72 (5.17)</td>
<td>nd</td>
<td>//</td>
<td>//</td>
</tr>
<tr>
<td>Present study</td>
<td>47</td>
<td>Vitiligo subjects randomly selected among a sample representative of general population</td>
<td>1.82 (2.95)</td>
<td>nd</td>
<td>//</td>
<td>//</td>
</tr>
</tbody>
</table>

nd: not done.
draw any conclusion on such an aspect, but we can only note the overall low value of DLQI score in our vitiligo sample.

According to our data, the length of the disease (i.e., the age of onset: infancy/childhood vs. adolescence/adult age) was not statistically related to the mean DLQI score. Among the studies which analyzed this variable, only the report of Parsad et al. showed differences in DLQI score according to the length of the disease, on the contrary other authors were in agreement with us.8,17

In the present study the clinical course of the disease (progression vs. regression/stability) correlated significantly with the total DLQI score. Belhadjali et al. did not observe any influence of the aforesaid variable on the DLQI score in their sample. On the contrary van Geel et al. and Parsad et al. showed a significant decrease of overall DLQI in their patients after a successful therapy.

When DLQI score was considered with respect to the visibility of the affected sites or to involvement of special sites, the observations of published studies are inconsistent. According to Ongenae et al., the overall DLQI score correlated with localization to face, trunk and feet, but did not correlate with localization to hands. On the contrary the visibility of the sites involved, grouped together, significantly correlated with higher DLQI score. The same author, in another study, showed that the DLQI score was significantly correlated with the total severity score and with self-assessed severity of the disease in different localizations, indicating that visibility was not a major determinant of DLQI score. That was not observed for involvement of face/head/neck, which seemed to highly impair the QoL, independently of the disease severity.15 On the contrary, Belhadjali et al. did not observe any significant difference in DLQI score between patients with vitiligo involving covered and uncovered skin, nor in patients in which face and genitalia were respectively involved/uninvolved.17 According to our data, the involvement of face and hands significantly correlated with total DLQI score, but the involvement of genitalia did not correlate with it. This observation was reinforced by logistic stepwise regression analysis, which showed that localization of vitiligo on the face and/or on the hands was the only variable to determine any worsening of QoL when reciprocal control for other variables was obtained.

In conclusion, QoL does not seem to be significantly impaired in Italian young men affected by vitiligo when identified from the general population. In our sample, multivariate analysis shows that the only variable to significantly influence DLQI is the involvement of such socially important areas as face and hands. Larger studies conducted on population-based samples are needed to confirm our findings possibly involving primary care physicians.26

Riassunto

Punteggio del Dermatology Life Quality Index in pazienti affetti da vitiligine: uno studio pilota tra uomini adulti in Italia

Obiettivo. È stato suggerito che la vitiligine possa avere un impatto negativo sulla qualità della vita dei pazienti. Lo scopo di questo studio è stato quello di studiare la qualità della vita in un gruppo di pazienti italiani affetti da vitiligine impiegando il questionario Dermatology Life Quality Index (DLQI).

Metodi. La versione italiana del questionario DLQI è stata somministrata ad un campione di 47 soggetti affetti da vitiligine, selezionati tra 34.740 giovani sottoposti alla visita di leva, residenti nell’Italia meridionale.

Risultati. Lo score totale mediano è risultato 1 (IQR: 2; medio: 1,82). Lo score totale è stato influenzato significativamente dall’evoluzione clinica della vitiligine, dall’estensione della malattia sulla cute, e dalla localizzazione sulla faccia e/o sulle mani. L’analisi multivariata, eseguita usando il metodo della regressione logistica per gradi, ha dimostrato che solo la localizzazione sulle mani e sul volto influenzava significativamente il DLQI medio.


Parole chiave: Vitiligine - Qualità della vita - Malattie cutanee.

References

results from the pilot phase of the PraKtis study: self-reported diagnoses of selected skin diseases in a representative sample of the Italian population. Dermatology 2004;208:38-42.
Evaluation of incidental thyroid nodules in patients with primary melanoma

P. A. FANTI 1, E. DIKA 1, R. BALESTRI 1, G. RECH 1, S. BELLAVISTA 1, E. BALDI 2, H. I. MAIBACH 3, A. PATRIZI 1

Aim. Literature data have suggested an increase of incidental thyroid nodules in patients with malignancies, including melanoma.

Methods. The ultrasound findings of 168 consecutive melanoma patients were revisited in order to evaluate the presence of incidental thyroid nodules and the results were compared with clinical features, Breslow thickness and the rate of malignancy of incidental thyroid nodules.

Results. We observed that: 1) incidental thyroid nodules are more frequent in patients affected by melanoma (60.6%) than in the healthy population; 2) no statistically significant difference were found in thyroid involvement on the basis of gender and age; 3) incidental thyroid nodules frequency is increased in patients with thinner melanoma and this increase is more evident if we consider melanoma in situ and female patients; 4) it was not detected malignant incidental thyroid nodules.

Conclusion. The data revealed a high frequency of incidental thyroid nodules in patients with melanoma, suggesting that it is necessary to study this association in a larger group of patients, also including age/gender matched controls.

Key words: Thyroid nodule - Melanoma - Surgical procedures, operative - Thyroid neoplasms.

Thyroid nodules are common and frequently benign. The reported frequency of nodular thyroid disease depends on the studied population and the methods used in detecting nodules. Nodule incidence, that increases with age, is more frequent in women and in subjects with iodine deficiency. Data have shown an increased incidence after radiation exposure. The mean frequency of incidental thyroid nodules (ITN) reported is 2-6% with palpation and 19-67% with ultrasound examination (US).

In 2007 Wilhelm et al, reported an increased rate of malignancy of ITN in patients with other primary malignancies, including malignant melanoma (2 out of 41 patients with malignancies).

The present study, has taken into consideration: 1) frequency of ITN in melanoma patients detected by ultrasound examination; 2) statistical correlation between US findings of thyroid nodules, demographic data of patients, clinical features and Breslow thickness of melanoma; 3) risk of malignancy of the nodules.

Materials and methods

The study included 185 consecutive patients undergoing MM excision between the 1st of January 2007 and the 10th of December 2009 in the Dermato-Oncological Surgery Service of our Department. Pa-
tients with a known thyroid disease or with a previous malignancy were excluded from the study.

Written informed consent was obtained from all patients.

All patients after primary MM excision underwent US neck examination, as a part of their disease surveillance. The US examination was performed using the Esaote Mylab™ 25 Ultrasound unit (Esaote Milano ITALIA) in order to detect possible lymphnodal recurrences of this region.

All US examinations reports involving head and neck, were revisited in order to evaluate the presence of ITN in these patients.

Age, race and gender of patients, upper or lower body location and MM Breslow thickness were evaluated. Upper body location included head, neck, upper extremities and over-diaphragmatic portion of the trunk; lower body location included under-diaphragmatic portion of the trunk, genital area and lower extremities.

In order to perform statistical analysis patients were grouped as follows: 1) according to the age, into 4 groups, respecting our population’s quartiles of age: younger: <47, aged: ≥47 and <60, aged: ≥60 and <71 and finally ≥71; according to MM Breslow thickness, into 3 groups: in situ (MIS), Breslow thickness <0.7 mm and ≥0.7 mm.

Blood tests to assess the functioning of the thyroid and/or endocrinological consultations were performed in all patients.

Statistical analysis

Data were analysed with SPSS 17.0® (version 17.0; SPSS Inc,Chicago, IL, USA); a 1st type error ≤0.05 was accepted.

Non-parametric tests were performed for comparison because measures were not in a normal distribution (Mann Witney U test); Fisher test, Pearson χ², Odd ratio corrected following Mantel Haenszel were performed for categorical and ordinal data.

Results

Out of the 192 patients undergoing melanoma excision, 24 were excluded because of previously diagnosed thyroid disease (12), a prior thyroidectomy (5 cases), or previous melanoma excisions (7 patients). A total of 168 patients successfully completed the whole examination and their main characteristics are summarized in Table I.

All patients were Caucasian. They consisted of 80 men and 88 women, aged from 25 to 88 years (with average age of 60 years); 43 patients were younger than 47 years, 47 were between 47 years and 60 years, 39 were between 60yrs and 71 years, and 39 older than 71 years (interquartile range (IQR): 47-71 years). Comparison between groups of different age showed no statistically significant difference in IQR, revealing an acceptable distribution of patients (Table II).

The characteristics of patients and their MM are summarized in Table II.

In our population, upper body MMs were more frequent in men (58/80=72.5%) than in women (50/88=56.8), who often show lower body MM, and the difference is statistically significant at Fisher exact test with P<0.04 (Table II).

MMs of major Breslow thickness (>0.7 mm) were more frequent in men than in women. MIS were de-

| Table I.—Description of demographic and clinical characteristics of the sample of 168 consecutive melanomas. |
|---|---|---|---|---|---|---|---|
| | Age<47 yrs | 47yrs>=Age<60yrs | 60yrs>=Age<71yrs | Age>=71yrs |
| | Males | Females | Males | Females | Males | Females | Males | Females |
| Gender (80 males and 88 females) | | | | | | | | |
| MIS (N.=26) | 0 | 4 | 3 | 3 | 1 | 4 | 4 | 7 |
| Breslow thickness | | | | | | | | |
| <0,7mm. (N.=76) | 10 | 11 | 10 | 15 | 5 | 11 | 8 | 6 |
| >=0,7mm (N.=66) | 8 | 10 | 7 | 9 | 16 | 2 | 8 | 6 |
| Thyroid involvement | | | | | | | | |
| Present (N.=100) | 9 | 15 | 15 | 11 | 14 | 14 | 10 | 12 |
| Absent (N.=68) | 9 | 10 | 5 | 16 | 8 | 3 | 10 | 7 |
tected with a higher incidence in women (P<0.04).
ITN were diagnosed in 100 patients (60.6% CI 95%=53.21-67.99%) on ultrasound examination and 3 types of thyroid nodules were detected on the basis of US findings: type 1 - cystic, type 2 - mixed (cystic and solid portion) and type 3 - solid. Most patients had multiple thyroid nodules.

No statistically significant difference was revealed regarding ITN distribution while considering gender and age of patients and of localization of MM (upper body – lower body) (Table III).

In order to avoid the influence of confounding factors, an odd ratio stratified for age, gender, localization and presence of thyroid involvement was performed, following Mantel Haenszel.

Statistical analysis showed an increased risk of ITN in MIS vs. “invasive” melanomas (OR_MH=14.777 (CI 95%: 2.837-76.979), with P<0.001) (Tables III, IV). Comparing the presence of ITN in males with MM thinner than 0.7 mm vs. MM≥0.7 mm the difference was not statistically significant. In females, on the contrary, patients with melanoma <0.7 mm had a 4 times higher risk of thyroid involvement ORMH=4.135 (CI 95%: 1.237-13.428) (P<0.02: statistically significant). (Table IV, Figure 1).

Blood tests assessing thyroid functioning as well as an endocrinological check-up were prescribed in all cases with ITN. No abnormalities were reported in blood tests. On the basis of the decision of the endocrinologist a follow-up, including further examinations, was carried out in some patients, involving ultrasound examination and blood test once in a year. Moreover, in 23 patients a fine-needle aspiration biopsy (FNAB) was requested either by the endocrinologist or the radiologist. In these patients histological examination showed primary thyroid adenomas and was negative for primary thyroid carcinoma or metastatic disease.

**Discussion**

Incidental thyroid nodules can be discovered during many radiographic imaging tests since pa-

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**Table II.**—Description of the studied sample: demographic data, breslow thickness of melanoma, thyroid involvement.

<table>
<thead>
<tr>
<th></th>
<th>Males N=80</th>
<th>Females N=88</th>
<th>Statistic tests</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50th P</td>
<td>62</td>
<td>54.5</td>
<td>Mann-Witney</td>
<td>P=0.192</td>
</tr>
<tr>
<td>IQR</td>
<td>48-71.75</td>
<td>47-70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper body</td>
<td>58</td>
<td>50</td>
<td>Fisher exact test</td>
<td>P&lt;0.04</td>
</tr>
<tr>
<td>Lower body</td>
<td>22</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIS</td>
<td>8</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breslow thickness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.7</td>
<td>33</td>
<td>43</td>
<td>Pearson (c² = 6,979)</td>
<td>P&lt;0.04</td>
</tr>
<tr>
<td>≥0.7</td>
<td>39</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>48</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid involvement</td>
<td>32</td>
<td>36</td>
<td>Fisher exact test</td>
<td>P=1</td>
</tr>
</tbody>
</table>

**Table III.**—Thyroid involvement in the studied population.

<table>
<thead>
<tr>
<th></th>
<th>Thyroid involvement N=100</th>
<th>No thyroid involvement N=68</th>
<th>Statistical tests</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Males female</td>
<td>48</td>
<td>32</td>
<td>Fisher exact test</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>52</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>50th P</td>
<td>61</td>
<td>54.5</td>
<td>Mann-Witney z=-0.874</td>
</tr>
<tr>
<td>IQR</td>
<td>48-71</td>
<td>47-71.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper trunk</td>
<td>67</td>
<td>41</td>
<td>Fisher exact test</td>
<td>0.414 NSS</td>
</tr>
<tr>
<td>Lower trunk</td>
<td>33</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIS</td>
<td>24</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breslow thickness</td>
<td>&lt;0.7</td>
<td>45</td>
<td>31</td>
<td>Pearson c²=15.919</td>
</tr>
<tr>
<td>≥0.7</td>
<td>31</td>
<td>35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NSS: Non statistically significant.
Patients with primary malignancies routinely undergo many of these tests as a part of their disease surveillance.

The prevalence of ITN in the general population differs from an ultrasonography study to the other (10% to 67%).

The higher frequency reported by Ezzat et al. that indicates a 67% of ITN among the studied population is not significant, because of the unequal distribution of patients (with a prevalence of females that represent the 84% of the studied population).

Autopsy series indicate that nearly 50% of 1000 subjects undergoing routine consecutive postmortem examination without palpable abnormalities, show thyroid nodules on sectioning of the gland.

Ultrasonographic studies have found a thyroid nodule prevalence of 27% among normal subjects in a non-goiter-endemic area of Finland and only 19% in Belgium.

A study of the population carried out in Germany, which is a country previously iodine-deficient and currently borderline-iodine-sufficient country, detected thyroid nodules by US in 20% of the population aged 20-79 years.

Wiest et al. compared the detection of thyroid nodules by physical examination and high-resolution ul-

### Table IV. Correlation between ITN, gender and Breslow thickness.

<table>
<thead>
<tr>
<th>Thyroid involvement</th>
<th>Not involved</th>
<th>Involved</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIS</td>
<td>Gender</td>
<td>f N. 2</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>11.1%</td>
<td>88.9%</td>
</tr>
<tr>
<td></td>
<td>m N. 0</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>0.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Total N. 2</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>7.7%</td>
<td>92.3%</td>
</tr>
<tr>
<td>B.Th. &lt;0.7</td>
<td>Gender</td>
<td>f N. 16</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>37.2%</td>
<td>62.8%</td>
</tr>
<tr>
<td></td>
<td>m N. 15</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>45.5%</td>
<td>54.5%</td>
</tr>
<tr>
<td></td>
<td>Total N. 31</td>
<td>45</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>40.8%</td>
<td>59.2%</td>
</tr>
<tr>
<td>B.Th. ≥0.7</td>
<td>Gender</td>
<td>f N. 18</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>66.7%</td>
<td>33.3%</td>
</tr>
<tr>
<td></td>
<td>m N. 17</td>
<td>22</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>43.6%</td>
<td>56.4%</td>
</tr>
<tr>
<td></td>
<td>Total N. 35</td>
<td>31</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>53.0%</td>
<td>47.0%</td>
</tr>
</tbody>
</table>

B.Th.: Breslow thickness.

Figure 1. Comparison between thyroid involvement and Breslow thickness, in men and women.
trasonography using small groups of blinded, experienced physician examiners working with a sample of 2441 persons from Estonia, most of whom were Chernobyl nuclear reactor clean-up workers. Nodules were found in 249 (10.2%) subjects by high-resolution ultrasonography.24

As far as the Italian population is concerned, a study conducted on 704 consecutive patients (400 women, 304 men) without thyroid diseases and in an area with a low iodine intake, reported a frequency of ITN of 33.1%.25

As an additional point of reference, it was also examined the data of the general incidence of thyroid nodules (TN) among a group of patients evaluated specifically for thyroid abnormalities by an Italian no-profit oncologic association (Associazione Nazionale Tumori, ANT). One hundred clinically healthy subjects (50 men and 50 women), from Bologna province, underwent thyroid US examination and blood tests. The clinician of the association reported that the incidence of TN was 44% (44/100), 54% in women (27/50) and 34% in men (17/34) (unpublished data).

Considering the literature and the forementioned data, the present study is the first to report the frequency of ITN specifically in MM patients, although detection of ITN has been recently described in patients with other malignancies.1 In fact a previous study exists on ITN detection during routine surveillance of other primary cancers, and the authors report the presence of ITN in two patients with malignant melanoma.17

Our study differs due to the fact that we specifically examined a population of patients with primary MM on which it was also found a newly discovered ITN during routine surveillance screening.

Our data reveal a relatively high frequency of ITN in these patients (60.6%).

Moreover, if the US examination of our patients would have been performed in order to specifically evaluate TN, the incidence could have been higher than the previously reported.

This percentage is distributed equally among all patients, regardless of gender and age, in contrast with the data on general population (literature data report that ITN incidence increases with age and is higher in women).1

The average age of our patients with and without ITN is, as a matter of fact similar (Fisher exact test with P=0.38) and the difference between males and females with thyroid involvement is not statistically significant (Fisher exact test with P=1) (Table III).

An even more interesting observation (Table IV) was that an increased thickness of MM was associated with an inversely decreasing rate of ITN (from 92.3% of ITN in patients with MIS to 47.0% of ITN in patients with MM Breslow ≥0.7 mm).

This decreased incidence is even more evident considering only women, dropping from 88.9% of ITN in MIS to 33% in women with MM Breslow ≥0.7 mm. The result related to few men with MIS (8 patients) does not permit the same evaluation in this gender.

According to the collected data, we conclude that:
1) ITN are more frequent in patients affected by MM than in the healthy population as it is impossible to find any Italian study reporting a percentage of ITN similar to that of this study (60.6%).
2) No statistically significant difference were found in thyroid involvement on the basis of gender and age, in contrast to literature;
3) ITN frequency is increased in patients with non-invasive (thinner) melanoma (MIS and MM<7 mm) and this increase is more evident if we consider MIS (24/100 – 24% patients with ITN vs. 2/68-2.94% with MIS without ITN) and female patients.
4) It was not detected malignant ITN (FNAB results) while the risk of malignancy reported ranges from 1.5% to 17% in incidentally detected lesions.15-17, 25-29

The interpretation of these data is not simple and many questions can be raised.

First of all, it is unknown whether there is a correlation between the development of thyroid nodules and the development of an oncologic disease, since ITN are described to have a higher frequency among patients with malignancies.

While considering our population it is hard to establish whether ITN had preceded or followed MM initiation, as these nodules were detected only after melanoma excision.

The crucial point is to understand whether melanoma is more common in people with TN or TN are more frequent in melanoma patients. Furthermore, if a hypothesis can be brought about, despite the limited number of patients included here, could these thyroid nodules be possibly developed as a response against MM?

Is this a response that represents a defence against
the progression of MM, considering that ITN have been detected more frequently in patients with non-invasive MM? And finally, the co-presence of ITN and melanoma be perceived as a favourable prognostic factor regarding melanoma progression and ITN risk of malignancy?

Conclusions

This future project includes a confrontation of the frequency of ITN between a controlled group (matched for age and sex, followed by our outpatient clinic for multiple moles) and melanoma patients.

Parole chiave: Tiroide, nodulo - Melanoma - Trattamento chirurgico - Tiroide, tumori.

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Methyl-aminolevulinate photodynamic therapy for the treatment of actinic cheilitis: a retrospective evaluation of 29 patients

D. FAI 1, I. ROMANO 1, N. CASSANO 2, G. A. VENA 2

Aim. Multiple treatment modalities have been proposed for actinic cheilitis (AC), and topical photodynamic therapy (PDT) has recently been included among these modalities. We report our experience with PDT using methyl-aminolevulinate (MAL) in AC.

Methods. We performed a retrospective analysis of 29 patients who had undergone MAL-PDT for treatment of AC: 4 patients received one single session and 25 patients two consecutive weekly sessions.

Results. At 3 months, 21 patients (72%) obtained a complete clinical response, which was sustained over a follow-up period of 6-36 months (mean, 20 months) in 20 patients. Cosmetic outcome was generally rated as good or very good. Transient local adverse events related to the procedure were common and mild to moderate in the majority of cases.

Conclusion. Our preliminary experience suggests that MAL-PDT may be considered a valid modality for the treatment of AC, although long-term follow-up studies in large patient series are required to obtain precise data about clinical and histological recurrences.

Key words: Photochemotherapy - Methyl 5-aminolevulinate - Actinic cheilitis.

Topical photodynamic therapy (PDT) is a therapeutic procedure based on the application to the skin of a photosensitizer which is subsequently activated by light energy, thus producing a photodynamic reaction that is cytotoxic and vasculotoxic. 1, 2 PDT has become an established treatment modality for actinic keratosis and nonmelanoma skin cancers, thanks to the minimal invasiveness of the procedure, and the ability to achieve high response rate and favourable cosmetic outcome. 3, 4 Preliminary reports have proposed PDT as a new therapeutic approach to actinic cheilitis (AC). 5-10

We describe the cumulative results obtained in a series of patients with AC treated with PDT using methyl-aminolevulinate (MAL), the methyl ester of the porphyrin precursor 5-aminolevulinic acid.

Materials and methods

We performed a retrospective chart review involving patients with AC who had undergone treatment with MAL-PDT in a hospital outpatient setting. The patient series consisted of 29 subjects, 20 males and 9 females, with a mean age of 71.5 years (range, 53-88 years). AC was diagnosed clinically in all cases, with histological confirmation required in 6 cases. None of the patients presented any known contraindication to the use of PDT. Ten patients had never used any treatment for their AC in the past, whereas 19 patients had previously been treated with other therapeutic modalities (cryosurgery, topical 5-fluouracil and/or imiquimod cream) without any sub-
substantial benefit, and such treatments were interrupted at least two months before the baseline evaluation. An informed consent was obtained prior to PDT treatment. Scales and crusts, when present, were gently removed. Subsequently, a thick layer (approximately 1 mm) of MAL 160 mg/g cream (Mevix®, Galderma Italy) was applied for 2-3 hours. Thereafter, the skin was exposed to red light (Aktilite CL 128, PhotoCure ASA, Oslo, Norway) at a fluence of 37 J/cm². As concerns the application time of the cream, it lasted 3 hours in the first 3 patients but was then reduced to 2 hours in order to improve the tolerability. All subjects were instructed to apply local antiseptics and topical preparations containing antibiotics and corticosteroids for 5-7 days after the therapeutic procedure.

Patients were evaluated one week after the first MAL-PDT session, when a second session was performed as needed. In the post-treatment phase, patients were assessed monthly during the initial 3 months and every 3 months thereafter.

Information on safety and tolerability of MAL-PDT treatment was also collected.

Results

Of the 29 patients examined, 25 patients underwent two consecutive weekly MAL-PDT sessions, whereas only one session was performed in 4 patients. At 3 months, complete remission of AC was achieved in 21 patients (72%), a partial response (with a moderate to good improvement) was observed in 4 subjects, whereas 3 patients did not have any noticeable clinical change and a patient presented even an evident enlargement of AC lesions as compared to baseline. Most patients who were partial responders or non-responders received alternative treatment modalities.

Among patients with an initial complete response, 20 of them remained disease-free over a follow-up period of 6 to 36 months (mean, 20 months), while a patient showed signs of clinical recurrence of AC 30 months after treatment.

Regardless of clinical outcome, cosmetic results were rated as good to excellent in 28 patients (97%). Only a patient developed scarring within the treated area.

The most frequent adverse events were transient and related to the procedure. Erythema was observed in 24 patients, edema in 19 patients, and erosions or ulcerative lesions in 16 patients. In patients in whom the time of MAL cream application lasted 3 hours, oedema and blistering were particularly intense. Twenty-six patients complained of pain or burning sensation during the procedure. Such symptoms were graded as mild and tolerable in 11 cases, moderate (requiring irradiation period to be split) in 9 cases, and severe (requiring temporary discontinuation of illumination, application of cold dressings and air cooling) in 6 patients.

Discussion

AC is a common premalignant condition which can progress into invasive squamous cell carcinoma. Effective treatment is mandatory in order to minimise the risk of malignant transformation. Multiple treatment methods have been reported for AC, including cryosurgery, electrosurgery, carbon dioxide laser ablation, 5-fluorouracil, imiquimod or scalpel vermilionectomy, which are aimed at inducing destruction/removal of the damaged epithelium.

PDT has been proposed as a therapeutic intervention for AC, as suggested by case reports and open-label studies, which have however considered different treatment protocols and photosensitizers, including 5-aminolevulinic acid (ALA), MAL and methylaminopentanoate. The largest study population evaluated until recently is that described by Sotiriou et al in 2010, consisting of 38 patients with AC who received two ALA-PDT sessions at 2-week interval. These authors noted a complete clinical response at 3 months in 68% of cases, being this rate almost similar to our results, whereas at 18 months the clinical recurrence and histological recurrence rates reported by the Greek colleagues were 15.4% and 34.6%, respectively.

In our preliminary experience, the cosmetic outcome was very favourable and the recurrence rate appeared to be particularly low, with only a patient presenting with signs of recurrence among complete responders examined over an average follow-up period of 20 months.

Local transient reactions due to the procedure occurred in the majority of our patients. These reactions were mild to moderate in many cases. The development of severe pain, oedema and blistering in the initial 3 patients in whom MAL cream was applied for
3 hours prior to the illumination led us to modify our treatment protocol, changing the application time of the cream to 2 hours, with an overall improvement of the tolerability profile of the procedure.

Conclusions

Our study have several limitations, including the retrospective design, the small patient sample, the short follow-up period, and the absence of histological assessment of response. Nevertheless, awaiting more precise information from long-term follow-up experiences in large patient populations and taking into account that treatment procedure and protocols require optimization, our preliminary results suggest that MAL-PDT may be considered a new valid therapeutic approach to AC, showing an excellent cosmetic outcome and a sustained clinical response in most patients.

References

Add-on diagnostic tool for allergic contact dermatitis: the strip patch test

S. HESSAM, P. ALTMEYER, H. DICKEL

The “conventional” patch test (PT) is considered to be the “gold standard” in diagnosing allergic contact dermatitis. However, the method of patch testing has repeatedly been criticized for its limited diagnostic accuracy and it is therefore by no means uniformly accepted as a reliable test method. Basic idea of the “strip” patch test (SPT), a modification by repeated tape stripping prior to patch testing, is to increase the quantity of allergen reaching the deeper epidermal cell layers and, thus, to increase the test sensitivity. The SPT according to our proposed standardized protocol is promising to improve diagnosis of allergic contact dermatitis which is demonstrated exemplarily in the field of occupational contact dermatitis.

Key words: Dermatitis, allergic contact - Patch tests - Diagnosis.

The “conventional” patch test (PT), as introduced by Jadassohn in 1895, is commonly considered to be the “gold standard” in diagnosing allergic contact dermatitis. Even though its global sensitivity and specificity is assumed to be between 70% and 80%, standard indices of diagnostic accuracy for individual patch test substances turned out to be considerably lower. Against this background, it stands to reason that diagnostic accuracy and reliability of the PT is discussed quite controversially.

Patch test results can be false negative, even if the patient has a sensitization. To date, the magnitude of this problem is only marginally discussed in the literature. However, it is for quite some time assumed that false-negative results in patch testing are more common than generally believed. A patch test reaction may remain not only negative, but also undetected. In this context it is interesting to note that despite absence of a morphologically visible skin reaction immunohistological investigations of negative patch test sites have shown cellular traffic comparable to a positive skin reaction, i.e., with an increase of monocytes and T cells and a decrease of antigen presenting cells. On account of these findings, negative patch test results are no proof of the absence of immunosensitivity in a patient.

Allergic contact dermatitis depends considerably on the ability of the allergen to permeate the epidermal barrier, i.e., to penetrate in the vital epidermis. Thus, the quantity of allergen reaching the deeper epidermal cell layers is rather crucial than the amount of allergen on the skin surface. However, the elicitation of allergic contact dermatitis depends not only on the penetration of the allergen in the epidermis. The epidermis is composed of a physical, a biochemical and an immunological barrier. First, the stratum corneum represents the physical barrier against percutaneous penetration of allergens. Percutaneous penetration is depending on various influencing factors such as repetitive allergen contact to the skin, skin friction, skin maceration, and micro traumata of the skin. Second, according to today’s knowledge of the mechanisms of allergic
contact dermatitis, elicitation requires some type of irritative, non-antigen-specific pro-inflammatory stimulus preceding antigen-specific effector cell activation.\textsuperscript{19} For example, mechanical removal of the upper layers of the stratum corneum by tape stripping not only causes harm to the physical skin barrier and facilitates percutaneous penetration of allergens,\textsuperscript{20} but also induces an immunological stimulus in the form of subclinical inflammation by upregulation of non-antigen-specific pro-inflammatory cytokines (\textit{e.g.}, TNF-\textalpha{}), adhesion molecules and growth factors.\textsuperscript{21} Additionally, it was found that Langerhans' cells in tape stripped skin showed increased epidermal cell density and stimulatory activity in terms of maturation, respectively.\textsuperscript{22, 23}

Hence, skin barrier disruption and immunological stimulus seem to be both essential, too, for eliciting a positive patch test reaction.

### The strip patch test

Various modifications of the PT have been described in the past.\textsuperscript{24} Fundamental intention was always to increase the patch test sensitivity and thus to enhance diagnostic accuracy and reliability of the patch test results. Among these modifications, the “strip” patch test (SPT), inaugurated by Spier and Natzel in 1953,\textsuperscript{25} still enjoys a use as supplemental tool in the diagnosis of allergic contact dermatitis.\textsuperscript{26} Basic idea behind this modification of patch testing was to increase the quantity of allergen reaching the deeper epidermal cell layers and, hence, to lower elicitation thresholds for patch test substances in a sensitized patient. This was primarily achieved by reduction of the stratum corneum at the test site on the back by repeated tape stripping prior to patch testing.\textsuperscript{27} However, it was Spier who himself realized early on that there may be additional stimuli explaining an increased responsiveness of the epidermis to patch test substances.\textsuperscript{28}

#### Previous application in clinical practice

Since its inauguration until today, a standardized procedure for the SPT was missing, which not only has made it difficult to implement widely the SPT in clinical practice, but also complicated comparability as well as reproducibility of the test results.

Extensive literature search revealed the use of the SPT primarily in the diagnosis of allergic contact dermatitis to systemically and topically applied drugs, metal salts and aeroallergens (Table I).\textsuperscript{29-55} Drugs are normally characterized by a poor permea-

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**Table I.—Fields of application of the non-uniformly performed strip patch test.**

<table>
<thead>
<tr>
<th>Author (and co-author/s)</th>
<th>Test substance</th>
<th>Adhesive tape</th>
<th>N. of tape strips</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruynzeel-Koomen et al.\textsuperscript{41}</td>
<td>Aeroallergens</td>
<td>NS</td>
<td>15</td>
</tr>
<tr>
<td>Buckley et al.\textsuperscript{15}</td>
<td>Aeroallergens</td>
<td>Sellotape\textsuperscript{0}</td>
<td>12</td>
</tr>
<tr>
<td>Langeveld-Wildschut et al.\textsuperscript{35}</td>
<td>Aeroallergens</td>
<td>Transpor\textsuperscript{0} hypoallergenic tape</td>
<td>10 or 20</td>
</tr>
<tr>
<td>Oldhoff et al.\textsuperscript{42}</td>
<td>Aeroallergens</td>
<td>Transpor\textsuperscript{0} hypoallergenic tape</td>
<td>10</td>
</tr>
<tr>
<td>van Voorst Vader et al.\textsuperscript{43}</td>
<td>Aeroallergens</td>
<td>Transelasta adhesive plastic tape</td>
<td>8 or 15</td>
</tr>
<tr>
<td>Bahmer\textsuperscript{44}</td>
<td>Formaldehyde</td>
<td>NS</td>
<td>down to the stratum lucidum</td>
</tr>
<tr>
<td>Veien et al.\textsuperscript{45}</td>
<td>Metal salts</td>
<td>Nopi\textsuperscript{0}</td>
<td>6</td>
</tr>
<tr>
<td>Fernandes et al.\textsuperscript{46}</td>
<td>European standard series</td>
<td>Micropore\textsuperscript{0}</td>
<td>2</td>
</tr>
<tr>
<td>Frosch et al.\textsuperscript{47}</td>
<td>Ophthalmics</td>
<td>NS</td>
<td>calculated individually for each patient</td>
</tr>
<tr>
<td>Koch et al.\textsuperscript{48}</td>
<td>Ophthalmics</td>
<td>as proposed by Frosch et al.\textsuperscript{47}</td>
<td>10</td>
</tr>
<tr>
<td>Akita et al.\textsuperscript{49}</td>
<td>Ophthalmics</td>
<td>Micropore\textsuperscript{0}</td>
<td>10</td>
</tr>
<tr>
<td>Maucher et al.\textsuperscript{28}</td>
<td>Ophthalmics / dental materials</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Bircher\textsuperscript{50}</td>
<td>Ophthalmics/systemic drugs</td>
<td>Scotch Tape\textsuperscript{0}</td>
<td>10</td>
</tr>
<tr>
<td>Trautmann\textsuperscript{51}</td>
<td>Drugs with mucosal contact</td>
<td>Tesafilm\textsuperscript{0}</td>
<td>10</td>
</tr>
<tr>
<td>Lückerath et al.\textsuperscript{52}</td>
<td>Systemic drugs</td>
<td>NS</td>
<td>30</td>
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<tr>
<td>Ozkaya-Bayazit et al.\textsuperscript{53}</td>
<td>Systemic drugs</td>
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<tr>
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<td>Heparins</td>
<td>As proposed by Oldhoff et al.\textsuperscript{42}</td>
<td>NS</td>
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<tr>
<td>White\textsuperscript{55}</td>
<td>Photopatch test substances</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: not specified
tion of the stratum corneum or a lower percutaneous penetration at the patch test area than on the site of clinical exposure, respectively. For example, in line with other authors, Corazza et al. pointed out that the PT with ophthalmic products is often unsuccessful. Differential diagnosis of allergic contact dermatitis to metal salts (e.g., nickel sulfate, potassium dichromate, and cobalt chloride) represents another important application field. Tape stripping prior to patch testing results in a facilitated permeation of the stratum corneum of these primarily lipophobic substances. Finally, the SPT was repeatedly mentioned in the diagnosis of delayed hypersensitivity reactions to inhalant allergens (aeroallergens) in patients with atopic dermatitis. By reduction of the stratum corneum and by influencing the immunological epidermal barrier at the patch test area the SPT may simulate lesional skin of patients with atopic dermatitis more accurately than the PT on untreated skin.

The standardized strip patch test

In a multicenter pilot study we recently proposed a first protocol for uniformly performing the SPT.

Protocol

According to the proposed protocol (Table II), the patient first receives tape strips on the intact, non-inflamed skin at one upper side of the back until the skin surface starts to glisten (Figure 1A), i.e., shows three small glistening spots indicating that the stratum lucidum (simple-to-judge visual endpoint) has been reached. The individual number of tape strips to the stratum lucidum is then multiplied by the tape-specific correction factor \( cf = 11/26 \approx 0.42 \).

The calculated number of tape strips is finally performed on the untreated patch test area (Figure 1B, C). After that, patch test substances are applied for 24 hours (Figure 1D) and reading of skin reactions is performed in the conventional way of patch testing.

Test sensitivity

The increased test sensitivity of the standardized SPT compared to the PT was exemplarily confirmed in serial dilution tests with nickel sulfate (1.0%, 0.5%, 0.1%, 0.05%, and 0.005% in distilled water) and potassium dichromate (0.1%, 0.05%, 0.01%, 0.005%, and 0.0005% in distilled water). Use of the standardized SPT allowed a median reduction of the necessary test concentration for eliciting a skin reaction to nickel sulfate by a factor of 10 and to potassium dichromate by a factor of 5, respectively. Particularly with regard to declining concentrations of the patch test substances, the superiority of standardized SPT versus PT became evident.

Furthermore, the reproducibility rates of the pre-existing sensitizations to nickel sulfate and potassium dichromate were considerably higher by standardized SPT compared to PT. With the serial dilution test in the nickel-sensitive subjects, we detected 94% of the sensitizations by standardized SPT versus 63% by PT and in the dichromate-sensitive subjects,
respectively, 82% of the sensitizations by standardized SPT versus 47% by PT.

**Diagnostic accuracy**

In a multicenter validation study we found that the standardized SPT showed a vastly better sensitivity than the PT in detecting “truly” sensitized patients to nickel sulfate and potassium dichromate, respectively, with only marginal compromises in terms of specificity. Differences between sensitivities of standardized SPT and PT were 16.4% (95% CI, 8.7-24.1%) for nickel sulfate and 25.0% (95% CI, 8.9-41.0%) for potassium dichromate, both favoring standardized SPT. In contrast, the necessarily resulting advantage of the PT in terms of specificities was only minor: 3.3% (95% CI, 1.7-5.0%) for nickel sulfate and 2.9% (95% CI, 1.5-4.3%) for potassium dichromate. Hence, even though not error-free, the standardized SPT balances in a much better way the primary clinical aim of reducing the numbers of false negatives and the risk of increasing the number of false positives which may result in superior management of patients and improved patient-important outcomes.

**Influence on epidermal barriers**

In further investigations we could show that not only the physical epidermal barrier but also the immunological epidermal barrier is influenced by tape stripping according to our proposed protocol for standardized SPT (Table II). Study data suggest...
that the defined reduction of stratum corneum of 31±9% by good interrater agreement in association with the upregulation of epidermal mRNA expression levels including TNF-α, Hsp90, Hsp70, IL-33, and IL-8 may be in large part responsible for the considerably increased test sensitivity of standard-
ized SPT versus PT.38, 39 Evidently, standardized tape stripping of the skin prior to patch testing not only facilitates the percutaneous penetration of patch test substances and, thus, increases the bioavailability of patch test substances in the vital epidermis, but also enhances skin immunoreactivity to patch test substances. As a consequence, the standardized SPT has the potential to detect delayed-type sensitizations in patients with a negative PT.

However, it can be hardly estimated how much the observed stratum corneum reduction or changes in epidermal cell immunology contribute to the enhanced test sensitivity of the standardized SPT. The pathophysiological significance of these findings needs to be further scrutinized.

Conclusions

The standardized SPT proved to be clinically safe and particularly accurate for obtaining additional information on a patient’s delayed-type sensitization status and supporting diagnosis of allergic contact dermatitis. Thus, the standardized SPT may play a decisive role and its more time-consuming procedure should be no impediment to implementing this method in routine allergy testing.

Proposed application in clinical practice

As a direct consequence of the above mentioned study results, the standardized SPT may be recommended as a promising diagnostic tool for allergic contact dermatitis beyond the PT. So far, its usage in routine allergy testing can be recommended:24 1) if PT fails to reproduce a preexisting delayed-type sensitization; 2) if PT remains negative or question-
able despite continued suspicion of allergic contact dermatitis or delayed-type hypersensitivity, respec-
tively; 3) in case of patch testing substances with poor permeation of the stratum corneum or with a low concentration; 4) if percutaneous penetration of the substance on the patch test area is lower than on the site of clinical exposure; and 5) if repeated tape stripping should simulate lesional or sensitive skin on the intact patch test area.

From all points of view, the standardized SPT may particularly enhance the diagnosis of allergic contact dermatitis in occupational dermatology.

Exemplary practical application in occupational dermatology

Exposure conditions at the workplace, possibly irritat-
ing and/or sensitizing, are inadequately imitated by the PT leading to false-negative results. As long ago as 1931 Sulzberger and Wise wrote that there is repeated skin contact to working materials during work process.17 Additionally, physico-chemical abrasion of the skin leads to an enhanced percutaneous penetration of working materials and to an increased responsiveness of the skin.18

The standardized SPT may help to imitate several of these occupational exposure conditions more adequately than the PT. Thus, the elicitation threshold for work-related test substances is lowered and even weak sensitizations can be detected. We recently demonstrated, for example, the case of a 57-year-old former heavy-current electrical worker with low-grade sensitization to nickel sulfate that was only detected twice by strip patch testing.40 This result had a significant impact on legal and insurance aspects resulting in a pension entitlement according to no. 5101 of the German ordinance on industrial disease.

Riassunto

Strumento diagnostico aggiuntivo per la dermatite allergica da contatto: lo strip patch test

Il patch test (PT) “convenzionale” è considerato lo standard di riferimento nella diagnosi della dermatite allergica da contatto. Tuttavia, il metodo del patch test è stato ripetutamente criticato per la sua limitata precisione diagnostica e non è quindi accettato uniformemente come metodo di test affidabile. L’idea alla base dello “strip” patch test (SPT), una modifica apportata tramite la tecnica del tape stripping ripetitivo prima del patch test, è quella di aumentare la quantità di allergene che raggiunge gli strati più profondi delle cellule epidermiche, aumentando così la sensibilità del test. L’SPT, in accordo al protocollo standardizzato da noi proposto, promette di migliorare la diagnosi della dermatite allergica da contatto, come dimostrato in maniera esemplare nel settore della dermatite da contatto occupazionale.

Parole chiave: Dermatite allergica da contatto - Test allergologici - Diagnosi.
ADD-ON DIAGNOSTIC TOOL FOR ALLERGIC CONTACT DERMATITIS

HESSAM

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ADD-ON DIAGNOSTIC TOOL FOR ALLERGIC CONTACT DERMATITIS

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The diagnosis of human phthiriasis (often referred to as the “crab” or the “pubic louse”) can be more difficult than other types of pediculosis (Pediculus corporis and Pediculus capitis) because this insect has a smaller body of 1.2x0.8 mm, may be lighter in color, not as mobile and therefore harder to see to the naked eye. Can dermoscopy aid to perform a better analysis of the skin? The clinical experience developed in two patients gives an affirmative answer, moreover adding useful information of insect and its eggs already known to entomologists but never used in dermatological diagnosis. The identification in vivo can distinguish Phthirus pubis from other skin signs while the conical shape of the operculum and the wide fixing sleeve of egg to hair, tells what species of louse is infesting, even if the insect is unavailable or nits are elsewhere from the pubic area. Entodermoscopy, provided that dermatologists have some knowledge of entomology, therefore promises advantages over standard microscopic examination.

**Key words:** Dermoscopy - Pediculus - Phthirus.

Phthirus pubis can be more difficult to diagnose clinically than the other forms of pediculosis, not only because being smaller it is more difficult to identify visually, but also because its flattened body can be only slightly pigmented.

In this context the utility of dermatoscope can be hypothesized not only for visual magnification but also because the observation would be locally facilitated as P. pubis does not tend to dart about or hide as happens with the other two louse species. Diagnosis of phthiriasis could also benefit from dermoscopy when the parasite is found on other parts of the body, such as the trunk or armpit hairs, or on more unusual areas such as the eyelashes and scalp hair.

Since the literature on the topic of infestation in these areas does not use universal terminology and as diagnosis is not so rare, this paper proposes the use of Phthiriasis capitis, Phthiriasis oculi, Phthiriasis axillae, Phthiriasis corporis according to the affected body parts, using the term Phthiriasis pubis only when the parasite primarily is mainly confined to the pubic-perineal region. A similar classification has already been formulated in the past. This more detailed topographically-based attribution would also seem to be a more suitable way of describing clinical cases of primitive extrapubic locations, given that the historical nomenclature might not correspond to the affected area when it is different from pubis.

Two types of dermatoscope were employed, exploiting the different characteristics of each one. The observations were performed with a technique previously known as “dry dermoscopy” i.e. not requiring the use of a glass plate and liquid film interface. This set-up is the only one that respects the vitality of the parasite, leaving the host micro habitat intact. The same area can therefore be examined repeatedly without causing any undue local changes.

**CASE REPORTS**

**Human phthiriasis.**

Can dermoscopy really help dermatologists? Entodermoscopy: a new dermatological discipline on the edge of entomology

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A Delta 20 dermatoscope (Heine) manually connected to a Minolta G530 digital camera (5mpx) was used only to produce unpolarized led light images, while the Dermlite Pro II dermatoscope (3 Gens, LLC) fixed to a Sony W70 (7mpx) with an adapter, was primarily used to obtain polarized led light images. The former produces images emphasizing shape and texture, whilst the latter highlights in greater detail the vital internal components of the bug and eggs.

With regard to devices, entodermoscopy requires a specific dermatoscope dedicated to parasite study, capable of using different lighting sources and reaching magnifications far above 10x [see instrumental specifications on www.entodermoscopy.net; In fact, most of the photos in this paper are magnified about 30 times, by using the optical zoom, which on these cameras can magnify 3x. Multiplying the two factors of enlargement (dermatoscope and zoom) thus gives a “theoretical” magnification of thirty times. Pictures examined in full-frame format are even more enlightening. Depending on the megapixel resolution of the sensor, when the image is not reduced by the screen dimension, it can be enlarged further to show even greater detail.

An instrument designed specifically for searches such as these (entodermoscope) would eliminate some current drawbacks, thus making the study of ectoparasitosis simpler, more efficient and more reproducible in situ.

**Clinical series**

**Case 1.** A 61-year-old man experiencing itching in the inguinal-abdominal region was treated for a significant time with various moisturizing products, antiseptic soaps, cortisones or antibiotic creams, but decided to consult a specialist when the symptoms persisted.

During objective examination, the subject exhibited an excellent general and local state of hygiene, being a professional; with the naked eye, he showed no signs of macroscopic elements of interest (such as maculae ceruleae or excoriations), except for very rare dark spots on the pubic skin strongly suggestive of pediculosis (Figure 1).

Under the dermatoscope, most of his skin and annexes appeared normal but when focusing on the rare punctiform lesions, the characteristic triangular body of *Phthirus pubis* could be easily identified, clinging with its claws onto the surrounding hair (Figure 2). What appeared to the naked eye as indefinite dark spots, showed itself through dermoscopy to be made up really of red fecal granules clustered close to the caudal section and the bug’s pigmented claws (Figure 2).

Despite observing the parasite for a considerable length of time, it made no attempt to escape and made no sudden movements of its limbs. On switching to polarized light, the digestive tract of the parasite (previously not visible) could clearly be seen because the red color of the blood inside and its lively peristaltic activity (Figure 3).
bular towards the proximal part of the hair shaft (Figure 7). This wider conformation can be photographed on pubis with more technical difficulties than crab nits on scalp hair.

On searching for other diagnostical signs, only a very few number of nits were found on pubic hair, some with operculum, others without. The operculum of the proximal nits (i.e. those unhatched, closer to the skin) exhibited a characteristic conoid shape (Figure 4) thus distinguishing them from the nits of *P. capitis*, which have a dome-shaped operculum. These two different shapes are known enough to dermatologist but they are available only when lice eggs are analyzed under optical microscope.

Another microstructural egg feature, never used for dermatological diagnosis but already described microscopically by P.A. Buxton in 1947, and reported by Howard V. Weems Jr. in 1980, regards segment attached to the hair shaft. This special portion of the nit that I like to call “fixing sleeve” assumes considerable evolutionary and therapeutic importance. In fact it enables the egg to be exposed to the right degree of heat allowing proper embryo development and it imposes the use of a fine-toothed comb to mechanically remove the eggs. Rather than to believe that the egg is simply glued onto the hair shaft, the nit has really to be imagined fixed firmly onto a tubular structure (fixing sleeve) surrounding and probably tightening the shaft to create the strong adhesion we know to hair. Based on my photographic experience, commonly sleeve of *P. capitis* appears as a tubule of even caliber, the same length or longer than the egg shell (Figure 6).

By contrast in this patient fixing sleeve of *P. pubis* appears as a shorter sheath which increases in thickness towards the basal pole of the egg then becoming more tubular towards the proximal part of the hair shaft (Figure 7).
decided to consult a dermatologist, not for a diagnosis (a diffused pubic phthiriasis already correctly diagnosed by another colleague) but rather to ensure that her treatment had been successful. The patient was not only worried for her health but, even more so, for her relationships with work colleagues and pupils. When she was visited, therapy had already been performed, and on her own unauthorized initiative repeated several times with different pediculicides; nevertheless, the itching did not entirely disappear and the search for new bugs became a full-time occupation for the woman. All these psychological pressures resulted in a severe lack of sleep and a growing anxiety-compulsive disorder.

The dermatoscopic observation began in the pubic region, which the patient had already completely shaved at the onset of the illness, continuing in the ocular region and finally the scalp being infestation widespread all over the body.

The pubic skin looked normal, almost entirely hairless with protruding hair stems only, and of course no direct macroscopic sign of parasites or eggs. On the other hand, real evidence of past infestation by *P. pubis* was irrefutably confirmed by numerous nits on eyelashes, easily identifiable despite the black mascara on the patient’s eyes. No parasite was detectable *in situ* and no local therapy was refered. Most of the nits were lacking operculum and black in colour as if the mascara had got through the vacated opening. However, there were also some black nits that were still closed, with a typically conoid operculum (Figure 8).

**Case 2.** A 38-year-old woman, a primary school teacher, decided to consult a dermatologist, not for a diagnosis (a diffused pubic phthiriasis already correctly diagnosed by another colleague) but rather to ensure that her treatment had been successful. The patient was not only worried for her health but, even more so, for her relationships with work colleagues and pupils. When she was visited, therapy had already been performed, and on her own unauthorized initiative repeated several times with different pediculicides; nevertheless, the itching did not entirely disappear and the search for new bugs became a full-time occupation for the woman. All these psychological pressures resulted in a severe lack of sleep and a growing anxiety-compulsive disorder.

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Here, the fixing sleeve again exhibited in both operculum cases a thickening close to the basal part of the egg as found in clinical case 1. This conformation found on the head, and not only on the pubis (Figures 4-7), confirms the hypothesis that it is a constant characteristic of the bug, expressed independently from its location.

Given the several cycles of therapy (pluritherapy) with different drugs (polytherapy) which the patient had undergone, also here it was not possible to find directly any insects on the scalp or surrounding skin.

After the examination, the patient was reassured that the care she received had been successful, which was the main reason for her consultation.

But despite her relief because therapy success, on subsequent visits she still reported significant emotional distress, requiring low dose of Pimozide (2 mg) for 10 days.

At the end of therapy, the patient showed good control of the fears that heavily compromised her working life and relationships for several weeks.

**Discussion**

Considerations about lice and nits are addressed below in separate sections.

**Dermatoscopic markers of mobile forms (insects)**

*P. pubis* in these two cases shows a good ability to adapt to different temperature, humidity and light microenvironments, apparently without changing its behavior. In dermatoscopy, it was identified directly only in patients 1 but not in patient 2, because she had already been successfully treated, although some symptoms could suggest a persistence of the disease as the woman believed, having fallen into a delusion of parasitosis.

In the first clinical case, previous visits failed to recognize with naked eye any kind of parasite on pubis, resulting unsuitable treatments of patient. Diagnostic delay may occur when an infestation, kept to a very low level because of scrupulous personal hygiene, is supported by a parasite population limited to very few individuals. Such a situation is insufficient for immediate identification unless the doctor has already experienced this peculiar clinical eventuality.

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The dermatoscope proves useful for identifying those forms of itchy dermatitis resistant to common therapies, whose cause is really a pediculosis below the diagnostic threshold, which would otherwise be misdiagnosed.
The dermoscopic markers that best define *Phthirus* are its short, triangular and little colored body, brown claws, red-globular internal digestive tract with its peristaltic activity under polarized light (Figures 2, 3).

In the second case, entodermoscopy was unusually used to confirm eradication of the infestation, fairly inevitable given the multiple therapies, the trichotomy over almost the entire body and the interruption of any further potentially contagious contact.

More specifically, it was a useful tool for the patient because in her particular emotional state (delusion), she demanded a careful instrumental verification that treatment had been successful. In patients with symptoms suggesting active infestation, dermoscopic examination proves its utility for excluding factors which could wrongly indicate failure of treatment.

**Dermatoscopic markers of fixed forms (nits)**

In cases 1 and 2, eggs were found respectively in course of infestation and as delayed testimony where trichotomy was impossible to carry out (hair and eyelashes). Removal of hairs in fact prevents any direct or indirect diagnosis with existing equipment.

In both patients, the conoidal shape of the operculum confirmed that the parasite was really crab louse, being this attribute specific for *Phthirus*, especially favoring differential diagnosis on the scalp where nits of *P. capitis* are statistically more common. The images in this paper clearly describe this microstructure, which entomologists have already well documented using optical microscopy, but which is, in dermatological world, very uncommon to see in vivo and in situ through the dermatoscope (Figures 4-7).

But also a second unexpected indicator can be documented through dermoscope. It regards the fixing sleeve which could be able to distinguish nits of *Phthirus* even when they have lost the specific operculum and the anatomic site is not typical (i.e. head).

According to personally consulted sources, this item seems to have never been documented in dermoscopy before this study. The fixing sleeve of *P. capitis* is generally a tubular case to which much of the nit is attached, usually leaving the proximal pole of the egg detached from the hair shaft (Figure 6) or however well distinguishable from it (Figure 5). By contrast, the fixing sleeve of *P. pubis* in these observations appears to widen as it nears the egg, to “incorporate” and partially hiding its proximal pole (Figures 4-10). One can also have impression to watch in side projection a kind of “sail” or “truncated cone”, between egg and the hair shaft. This morphology has been documented consistently in different patients (cases 1-2) and at different sites (pubis, head) demonstrating that it is not influenced by the anatomic site in which *P. pubis* is located.

**Conclusions**

Dermoscope in the guise of an “entodermoscope” can provide useful additional information for both direct diagnosis and differential diagnosis. Entodermoscopy is a young and evolving application of traditional dermatoscope that can, now with some technical restrictions, explain those fuzzy red marks perceptible to the naked eye (made up of pigmented claws, external faecal pellets and blood within the gut), that always dermatologists have unknowingly used in macroscopic clinical diagnosis of *Phthiriasis*.

It also allows to identify *in situ* and *in vivo* certain microstructural differences between nits species (i.e. operculum and fixing sleeve) which are otherwise inaccessible to the naked eye. These items are useful for knowing the infesting kind of *Pediculus* even in its absence, when nits have already hatched (i.e. free of specific operculum) and they are in atypical locations, without interrupt ordinary visit anyway because optical microscope use.

In addition to still images, dynamic studies of the parasite can also be carried out by filming the parasites with a digital camera (clip available on homepage of www.entodermoscopy.net). Dynamic information has to be considered an indispensable complement in the search for specific markers of infestations.

All such observations, preferably obtained from a specific dermoscope designed “ex novo”, create the groundwork for a better *in situ* and *in vivo* understanding of complex host-parasite relationship which could in future better define new pathways for diagnosis and therapeutic strategies.

**Riassunto**

**Pediculosi ed entodermoscopia**

La diagnosi ad occhio nudo dello *Phthirus pubis* può comportare qualche difficoltà rispetto alle altre forme di
pediculosi (*Pediculus corporis* e *Pediculus capitis*) a causa delle sue piccole dimensioni 1,2x0,8 mm, per la sua scarsa colorazione ma anche perché può rimanere fermo abbastanza a lungo da non richiamare l’attenzione dello sguardo.

Data queste premesse può l’ausilio del dermatoscopio ritornerne in qualche modo vantaggioso? L’esperienza sviluppata in due casi clinici “limiti” sembra dare una risposta positiva grazie all’aggiunta di informazioni specifiche sull’insetto e sulle uova note agli entomologi ma non correntemente impiegate nella diagnosi clinica dei dermatologi.

Con il dermatoscopio l’identificazione del *Phthirus pubis* può avvenire *in vivo ed in situ* per mezzo di due attributi specifici della lendine rappresentati dalla forma conoidale dell’opercolo e dall’ampio manicotto di fissaggio della stessa al pelo.

Tali aspetti permettono all’operatore di risalire all’identificazione dell’insetto non più reperibile o le uova si trovano in sedi diverse dal pube. L’entodermoscopia (*la dermoscopia ad indirizzo entomologico*) quindi sembra promettere vantaggi importanti rispetto all’osservazione al microscopio ottico in termini di immediatezza dell’analisi in corso di visita ma anche in termini di specificità a condizione che il dermatologo abbia qualche conoscenza di entomologia sul parassita.

**Parole chiave:** Dermoscopia - Pediculus - Phthirus.

**References**

8. Buxton PA. The louse. An account of the lice which infest man, their medical importance and control. 2ndEd. Edward Arnold & Co. London viii+164; 1974
Papular-purpuric “gloves and socks” syndrome (PPGSS), first described by Harms et al. in 1990,1 is an acute dermatosis characterized by a papular-purpuric edematous rash in a distinct “gloves and socks” distribution. It clinically presents with a painful, pruritic edema and a purpuric erythema rapidly evolving in petechias limited to the palms, soles and dorsal areas of the hands and feet. Cutaneous lesions are often accompanied by fever, asthenia and lymphadenopathies. Less frequently, elbows, knees, external genitalia and oral mucosa may be involved, showing enanthema and painful multiple erosions. The disease is self-limited with a short course and a benign prognosis in most cases: the exanthema usually resolves within 1 to 2 weeks under symptomatic treatment. More than half of the reported cases have implicated parvovirus B19 (B19V) as the causative agent,2 but other viruses (including Human Herpes Virus 6, Coxackie A and B, measles, rubella Virus, Hepatitis B, CMV, EBV) should also be involved.2-4 In addition, drugs such as trimethoprim/sulfametaxol or chemotherapics have been found to induce PPGSS.5 We describe a case of PPGSS with a serologically proven B19V infection in a 42-year-old Italian kindergarten teacher suffering from acute bacterial pharyngitis.

Case report

A 42-year old kindergarten teacher was admitted to our department with a 5-day history of painful burning red-purple papules, associated with purpuric erythema, local-
ized on the palmo-plantar surface and on the dorsal areas of the feet and hands. A well-defined symmetric limit was evident at the wrists and ankles (Figure 1). Similar but non itching, non purpuric, erythematous lesions were recognized on the chest, neck, cheeks, chin and nose. Enanthema, lymphadenopathy, liver and spleen enlargement as well as signs of meningeal irritation, were not evident. The patient also revealed a 3-day history of pharyngitis, anorexia, myalgia, arthralgia and joint pain associated with intermittent fever (up to 39 °C). She denied having taken any medications and was not aware of any allergies. There was no history of blood transfusion, foreign travel, insect bites, tick exposures, or outdoor activities. Blood chemistry revealed an elevated erythrocyte sedimentation rate and C-reactive protein while the leukocyte count was decreased (with neutrophils raised to 73.4% and lymphocytes reduced to 15.7%). A crioglobulin study showed the presence of crioglobulin type III, a criofibrinogen and crioimmunofixation (IgA, IgG, IgM) test revealed polyclonal IgG and IgM. On admission, immunoglobulin M and immunoglobulin G antibodies by enzyme-linked immunosorbent assay (ELISA) to parvovirus B19 were negative, but after five days the IgM dropped to 17 E/ml (N.<10). Serology for CMV, EBV, HIV1, HIV2, HBV, HCV, HSV1, HSV2, Coxsackie viruses, and rickettsiosis were negative. A pharynx swab culture showed staphylococcus pyogenes. Histological examination showed dermal-ipodermal inflammation with evidence of leukocytoclastic vasculitis principally interesting the small venules. On these bases a PPGSS was suspected. Considering the positivity of the swabs, our patient was treated with antibiotic therapy (amoxicillin + clavulanic acid 1 gram twice a day) for 10 days. The cutaneous rash resolved after 2 weeks.

**Discussion and conclusions**

Since 1991, when IgM antibodies anti-B19 were first detected in the serum of a patient with PPGS, the association between PPGSS and B19V has been widely reported but serological or DNA evidence of B19 has been documented so far only in about 50 cases of PPGSS. In fact, B19V cannot be grown in conventional cell cultures. Its diagnosis is not always easy and is primarily based on the detection of specific antibodies by enzyme-linked immunosorbent assay or on the detection of viral DNA by dot blot hybridization or PCR. Our case confirms the association of PPGSS with B19V, demonstrated by seroconversion. A peculiarity of our case was the presence of the associated symptoms including pharyngitis, anorexia, myalgia, arthralgia and joint pain associated with intermittent fever. Adults with B19V infection are generally asymptomatic or have mild, nonspecific, cold-like symptoms. We hypothesize that the immune response related to the pharyngitis may have
contributed to the appearance of the viral syndrome and to the important cutaneous manifestations.

Although the pathogenetic mechanism underlying the mucocutaneous manifestations of PPGSS is still unclear, most of the current hypotheses refer to a vascular reaction to an antigenic stimulus. Studies based on direct immunofluorescence investigations demonstrated C3, and immunoglobulin deposits in dermal vessels, and/or a cytotoxic reaction to virally infected cells. In our patient, the multiple antigenic stimuli may have contributed to the rise of significant cutaneous lesions and the vasculitis may be related to the presence of cryoglobulin type III and cryofibrinogen.

In conclusion, we reported our case to support that PPGSS is an immunomediated disease and that B19V morbidity varies with the immunologic and hematologic status of the host. B19V infection should be always considered in the initial workup of any patient presenting with a petechial/purpuric eruption of unclear origin in particular in patients in close contact with children, as in our case, or in the immunosuppressed. Considering that a patient with B19V infection might still be infectious at the time of the diagnosis with significant implications for susceptible contacts, all patients with palmo-plantar petechial and purpuric eruption should be considered PPGSS carriers until the contrary has been demonstrated. The main differential diagnoses of PPGSS include necrotizing vasculitis, Henoch-Schönlein purpura, giant-cell arteritis, hepatitis and myocarditis, early stage of vasculitis, multiform erythema, Kawasaki disease in the initial phase, idiopathic palmo-plantar hidradenitis, hand-foot-mouth syndrome, Giannotti-Crosti syndrome and acral erythema during chemotherapy.

**Riassunto**

*Sindrome papulo-purpurica “guanti e calzini”*

La sindrome “Guanti e Calzini” è una dermatosi acuta delle estremità caratterizzata da un rash eritemato edematoso, con elementi papulari e purpurici, che si interrompe tipicamente in corrispondenza di polsi e caviglie. Le lesioni cutanee sono sovente accompagnate da febbre, astenia e linfonodopatie. Il parvovirus B19 (B19V) è l’agente etiologico più frequente, anche se altri virus o farmaci, come i sulfamidici, sono stati chiamati in causa. Riportiamo il caso di una maestra di asilo di 42 anni con Sindrome Guanti e Calzini associata ad infezione da B19V e faringite batterica.

**Parole chiave:** Parvovirus B19, umano - Saggio immunoassorbente legato all’enzima - Malattie cutanee.

**References**

Localized reactive erythemas of different types in a family

G. L. CAPELLA

“Reactive erythemas” is an umbrella term grouping several different conditions, all of which have in common the fact of being stereotypical inflammatory clinical patterns of the skin in response to disparate infectious, immune, or toxic factors. Typically, such eruptions are symmetrical or disseminated. The here reported cases are different. An elderly man underwent recurrent infections of an epidermoid cyst, accompanied by a typical erythema annulare centrifugum near the infectious focus. His grandson, aged ten months, presented with an infectious conjunctivitis, during the resolution of which two small annular lesions, compatible with annular erythema of infancy, appeared on the face. A man aged 42, respectively son and father of the two former patients, presented with an erythema multiforme target lesion proximally to an infected wound. There were no detectable predisposing factors in all cases. Familial cases of reactive erythemas have been reported. However, such limited distributions have not yet been described.

**KEY WORDS:** Erythema - Erythema multiforme - Causality.

Several dermatological reactive patterns in response to a wide array of immune, infectious, or chemical triggers are recognised, which, albeit quite morphologically and clinically different, arise in similar etiological settings. Examples include certain subsets of urticaria and vasculitis; erythema nodosum; erythema multiforme (EM); erythema annulare centrifugum (EAC) and its “microlesional” variants (erythema microgyratum perstans or erythema simplex gyratum, which were kept distinct in the former literature); and erythema gyratum not otherwise specified. In the past, several authors endeavoured to group some of these hypersensitivity reactions together. It could be argued that, given their morphoclinical heterogeneity, the analogy between such entities is merely nominal (i.e., the term “erythema” followed by a specification). However, because of their evident aetiopathogenic affinity, it has come natural to gather these conditions in the maybe provisional, yet well defined category of “reactive erythemas” (REs).

Annular erythema of infancy (AEI) seems not to be associated with definite triggering factors. However, it is suspected to represent the manifestation of similar hypersensitivity mechanisms. Accordingly, in this paper AEI will be tracked back to the RE group as well.

All REs usually involve several cutaneous districts, often in a symmetrical fashion, or even the whole tegument. The here described familial cases of REs are unusual in this regard, because they presented in a topographical restricted fashion, close to a focal infection.

**Clinical series**

**Case 1.**—In 1997, a man aged 72 consulted because of recurrent infections of an epidermoid cyst of the right shoulder with a typical EAC near the infectious focus (Fig.-
EAC flared up in coincidence with each infectious episode, and cleared up after proper antibiotic treatment (oral clarithromycin, 250 mg bid, topical sodium fusidate). A brisk suppurative recurrence eventually brought about the destruction of the cyst and the disappearance of EAC.

Case 2.—In autumn 2005, two faint, small, annular erythematous lesions appeared on the superior left eyelid and the forehead of a 10-month-old toddler, just after the resolution of a bilateral infectious conjunctivitis treated with tobramycin eyedrops (Figure 2). The clinical picture was compatible with AEI (see below, Discussion). Extemporaneous scotch-test: no dermatophytes or yeasts on microscopic examination. After one week of centrifugal progression (maximum diameter attained 1.5 cm), spontaneous resolution took place within 15 days. This boy was the grandson of patient n° 1.

Case 3.—A 42-year-old man, son and father of patients n° 1 and 2, respectively. In summer 2006, 5 days after the superinfection of an accidental cut wound of the right hand, treated with topical sodium fusidate cream, an isolate EM target lesion appeared proximally to the wound (Figure 3). Spontaneous resolution was typical, with detachment of the central vesicle and re-epithelialization within three weeks (Figure 3 A-D).

In all cases, proper laboratory investigations, including ASLO, autoimmunity and tumour markers, thyroid hormones, coprocultures, cold agglutinins, HBV, HCV, CMV, parvovirus B19, and rubella serology as required, yielded negative results. Extemporaneous patch-tests with sodium fusidate or tobramycin were negative as well. No patients either presented evidence of arthropod assaults elsewhere on the skin, or took relevant drugs. Patients n° 1, 2 did not further develop pityriasis rosea, infectious or drug-related exanthemas, or rheumatic fever. Patient n° 3 did not suffer from clinically evident herpes simplex or infections of the respiratory tract. No recurrences of the REs were observed any more (follow-up of 14, 6, and 5 years, respectively).

Discussion

The outbreak of different REs in distinct members of the same kinship is strikingly curious, but probably coincidental. Indeed, familial cases of EAC and
Erythema gyratum perstans have been observed. However, the peculiar limited topographical distribution of the REs here described is quite unusual and, to the best knowledge of the author, unreported. In a previously published case of erythema gyratum, the infection was focal (odontogenic), but the skin eruption showed a tendency to spread, as usual. Most REs are known to associate - among others - to an extended array of bacterial infections, even focal ones. Albeit bacteriological investigations were not performed, clinical evidence and response to specific therapy pointed to a staphylococcal aetiology in all of the 3 cases. It could be argued that two patients (N. 2, 3) had applied topical drugs before their RE appeared. However, leaving aside the fact patch tests with the involved chemicals were negative, such an objection does not offer an answer to the conundrum posed by the strict localisation of the eruptions. Indeed, either EM or EAC can be triggered by several chemicals as well. Notwithstanding, a merely local pattern of appearance, close to the contact site of the putative offending drug or allergen, has not yet been described as well: in the only reported case of “contact EAC” to nickel and cobalt, skin lesions were widespread. No ordinary cases of either EM or EAC induced by topical application of sodium fusidate or tobramycin have been described to date. Anyway, in the localised REs here reported, the course of the skin lesions strictly paralleled that of the infection and/or the period of application of the topical medication, and their duration was very short as compared with the typically long-lasting, even multiyear persistence characterising such conditions. These considerations turn out to be further circumstantial confirmations of a putative causal link between a focal trigger and a consequent localised RE.

Patient n° 2 posed special problems as to diagnostic classification. Clinical differential diagnosis of AEI has been thoroughly dealt with by Peterson and Jarratt. The duration and the annular shape of each lesion, the absence of scaling and of fungi on microscopic examination, all pointed to the diagnosis of a localised, microlesional variant of AEI. It should be underscored that the diagnostic work-up of EAC of the adult also applies to AEI. Such an operative attitude is dictated by the overt affinity existing between these REs. Clearly, the apparently benign clinical course prompted to avoid invasive diagnostic procedures in a toddler, as purported elsewhere.

In the here described cases, the physiopathological process which would develop on systemic grounds in ordinary cases of REs related to infections, autoimmune diseases, neoplasms, or drugs, seemed to have taken place in a limited fashion instead, just near a localised infection. The physiopathological process which would develop on systemic grounds in ordinary cases of REs, seemed here to have taken place in a limited fashion. The observed cases apparently extend the variety of skin eruptions which can be tracked back to the concept of “contiguous inflammation of the skin.” From a merely speculative viewpoint, taking classical induction of tissue injury by immune complexes as a conceptual frame, it could be advanced that, whereas in common cases of REs critical concentrations of the responsible reactant would be reached throughout extended portions of the skin or even in the whole integument, in localised REs such concentrations would be reached only at a fixed critical distance from the focal trigger, somewhere along a diffusion gradient of the reactant itself. If we consider that EAC and AEI rings are extended lesions, unlike “punctiform” EM target ones, such a model could be complicated by the speculation that diffusive concentration microfluctuations on the edge of the critical distance could lead to an anisotropic surface development of the lesion. This would explain why annular elements were not exactly pivoted on the infectious foci. The author recognises that his interpretations are merely theoretical, and questionable. Notwithstanding, the surprising aspects of the clinical pictures he observed, along with their familial clustering, arouse curiosity, and should elicit a renewed interest in the understudied topic of RE pathogenesis.

Riassunto

Eritemi reattivi localizzati di differente tipologia in una famiglia

“Eritemi reattivi” è un termine generico che indica cumulativamente diverse condizioni, accomunate dal fatto di costituire modalità stereotipe ad espressione cutanea di reazioni inflamatorie in risposta a svariati fattori infettivi, disimmunitari o tossici. Tipicamente, queste eruzioni si manifestano in regioni tegumentarie simmetriche, o sono disseminate. I casi qui descritti sono differenti al riguardo. Un uomo di 73 anni accusava ripetuti episodi di sovrinfestazione di una cisti epidermoide, accompagnati da un tipico eritema anulare centripeto a ridosso del focolaio infettivo.
Suo nipote, dell’età di dieci mesi, durante la risoluzione di una congiuntivite infettiva presentò due piccole lesioni anulari del volto, compatibili con la diagnosi di eritema anulare dell’infanzia. Un quarantaduenne, rispettivamente figlio e padre dei due pazienti precedenti, manifestò un eritema polimorfo unilesionale prossimalmente ad una ferita infetta di una mano. Non si rilevarono altri fattori predisponenti in nessuno dei tre casi. Sono stati descritti casi familiari di eritemi reattivi, ma del medesimo tipo e non caratterizzati dalla distribuzione limitata perifocale riscontrabile nella presente casistica.

Parole chiave: Eritema - Eritema multiforme - Causalità.

References

Dear Editor,

A 46-year-old woman, with no past medical history, presented to our Department of Dermatology with an abrupt eruption localised to her arms. On physical examination, erythematous vesico-bullous plaques of the upper limbs (Figure 1) together with painful and violaceous infiltrated plaques and nodules of the lower limbs (Figure 2) were noted. There were no palpable lymphadenopathies, nor associated systemic symptoms. The patient was afebrile. On examination, a concomitant painful and purulent gingival pocket was noted in her mouth. No oral swab was performed as the patient had just started antibiotics.

A punch biopsy of one lesion of her right arm was performed showing marked oedema of the papilla-ry dermis with flattening of the rete ridges (Figure 3). A dense perivascular mainly neutrophilic but also lymphocytic infiltrate was present; some neutrophils showed bilobated nuclei. Vasodilation and endothelial swelling were noted, with no evidence of vasculitis (Figure 4). The findings appeared consistent with Sweet’s syndrome.

Laboratory showed mild leukocytosis (11000/mm³), with marked neutrophilia (86%), and elevated markers of inflammation (ESR: 89 mm/1st hour; C-reactive protein: 11.7 mg/L); renal function, liver function and electrophoresis of seroproteins were in the normal range. Positive anti-nuclear antibodies (titer 1:160), with homogeneous pattern and negative anti-extractable nuclear antigens antibodies were found. Chest X-ray was normal.

Cutaneous and parodontal lesions resolved dramatically within one week of oral Amoxicillin-Clavulanate (2 g/day for 7 days), Paracetamol (1 g/day) and rest. A diagnosis of Sweet’s syndrome with Sweet’s panniculitis was made.

Sweet’s panniculitis is rare and idiopathic. It presents as neutrophilic panniculitis, usually from secondary spread-
ing of dermal neutrophils into the subcutaneous fat.² Only in rare cases, it can present as isolated panniculitis, with neutrophils invading the subcutis alone.³ It can present as lobular or, less frequently, septal or mixed panniculitis. Like classical Sweet’s syndrome, it can be associated with malignant hemopathies.³

As reported in the literature, Sweet’s syndrome can be associated with infections, such as Yersinia enterocolitica, Mycoplasma pneumoniae, Mycobacterium tuberculosis, atypical mycobacteria and HIV infection. In our case, the cutaneous eruption rapidly followed the oral infection. The dramatic response to antibiotics leads to the diagnosis of Sweet’s syndrome associated with parodontal infection, or post-infectious Sweet’s syndrome. As stated previously, an oral swab was not performed because the patient had just started antibiotics.

In the differential diagnosis, even if rare, we considered the association of Sweet’s syndrome and erythema nodosum.⁴⁵ Both are reactive dermatoses, which can be post-infectious in origin and may be treated with the same drugs (i.e., corticosteroids, potassium iodide).

We excluded the last diagnosis because of the multiplicity of lower legs lesions and their rapid healing with no hecchimotic halos: erythema nodosum usually presents with fewer lesions, which last longer and heal with typical hecchimotic macules. Histopathologically, Sweet’s panniculitis differs from erythema nodosum as the former presents as neutrophilic, mainly lobular panniculitis, while the latter is characterized by a granulomatous inflammation, with a mostly septal panniculitis.

Early lesions of erythema nodosum can contain neutrophils, but more often lymphocytes and histiocytes with giant cells are present. Since we did not perform a deeper confirmatory biopsy we are unable to discuss histopathological differential diagnosis in our case.

In conclusion, we describe a rare case of Sweet’s syndrome and panniculitis, after parodontal infection. We would like to underline the importance of recognizing this entity, for its abrupt onset and possible associated disorders. Misdiagnosis of Sweet’s panniculitis can lead to unnecessary investigations and inappropriate treatment.

References


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Erythema annulare centrifugum: a “deep type” figurate eruption

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Dear Editor,

Erythema annulare centrifugum (EAC) is an uncommon inflammatory skin disease with unknown etiology, nowadays considered a clinical reaction pattern and not a specific clinico-histologic entity, clinically characterized by slowly peripherally enlarging annular, arcuate or polycyclic erythematous lesions, preferentially affecting the trunk, buttocks, thighs and legs.1, 2 The lesions have a tendency for spontaneous resolution and exacerbations over a period of several months or years. Patients are usually asymptomatic, except for mild pruritus.

We report a 48-year-old woman presenting with a 5-months history of annular pruritic eruptions on her extremities. Cutaneous examination revealed large, well-defined annular and polycyclic erythematous plaques located on the buttocks, thighs and lower legs (Figure 1).

The lesions had firm, slightly raised borders with no signs of scaling. Review of systems as well as the family history were unremarkable. Routine laboratory investigations were within normal limits. Tests for anti-nuclear antibodies, Borrelia burgdorferi serology and carcino-embryonic antigen were negative. Cultures showed no evidence of fungi. A biopsy specimen was obtained from the active border of a lesion on the back surface of the right leg. Microscopic examination revealed a dense perivascular and periadnexal lymphocytic infiltrate in the superficial and reticular dermis with numerous eosinophils and absence of epidermal involvement (Figure 2). Periodic acid-Schiff (PAS) staining was negative. Clinico-pathologic findings were consistent with the diagnosis of EAC, “deep type”. The patient was successfully treated with systemic corticosteroids (methylprednisolone, 4 mg/day) in association with twice-daily application of methylprednisolone aceponate 0.1% cream, with complete regression of cutaneous lesions within 4 weeks. After a follow-up period of 12 months, no recurrence of cutaneous lesions has been observed.

EAC was first described by Jean Darier in 1916,3 and classified in 1978 by Ackerman in a deep and a superficial variant.4 The deep variant of EAC clinically appears with a firm, indurated border, devoid of scales, and is rarely associated with pruritus. Histopathologically, the deep type shows a moderately dense perivascular lymphocytic infiltration with a “sleeve-like” arrangement in the upper and deep dermis, with lack of epidermal involvement. The superficial form clinically presents with an indistinct border with a delicate rim of scale on the inner margin of the advancing edge of erythema and pruritus. In addition to a mild superficial perivascular lymphocytic infiltrate, frequent epidermal changes including focal spongiosis, parakeratosis, edema of the papillary dermis and epidermal hyperplasia are common histopathologic features observed in the superficial type. In both variants the infiltrating cells are mostly lymphocytes, but histiocytes, eosinophils and rarely neutrophils can be observed.1, 2 Whether the superficial and deep types of EAC are variants of the same entity or unrelated conditions is still controversial. Based on clinical and histopathologic differences between the superficial and deep type of EAC, several authors indeed support the clear-cut separation of these two entities.4

Clinical differential diagnoses of EAC include a large spectrum of cutaneous diseases presenting with annular lesions such as granuloma annulare, urticaria, tinea corporis, erythema migrans, discoid and subacute lupus erythematosus and cutaneous lymphomas (mycosis fungoides and B-cell lymphoma).1, 4 Annular elements can be also found in the urticarial stage of bullous pemphigoid and pemphigus vulgaris, lichen planus, sarcoidosis, syphilis, erythema multiforme, pityriasis rosea and psoriasis. In the case described here, the clinical aspect of the lesions was suggestive of granuloma annulare, subacute lupus erythematosus and cutaneous B-cell lymphoma. Histopathologic differential diagnoses of EAC include tumid lupus erythematosus, Jessner’s lymphocytic infiltration and early stage of polymorphic light eruption when the superficial and deep perivascular infiltrate is composed entirely of lymphocytes.4 However, a marked edema of the papillary dermis is usually observed in polymorphic light eruption and mucin in the reticular dermis in tumid discoid lupus erythematosus. Additional differential diagnoses such as drug eruption, urticaria and bullous pemphigoid (urticarial stage) should be considered in cases characterized by numerous eosinophils. In our case, clinico-pathologic features of the figurate eruption were consistent with the diagnosis of the deep form of EAC.

The pathogenesis of EAC is not fully understood. EAC is thought to represent a hypersensitivity reaction triggered by infections due to bacteria, virus, fungi, mycobacteria or parasites, medications, autoimmune diseases, hormonal influences, pregnancy and malignant neoplasms.6, 8 However, most cases remain unexplained. Clinical and laboratory findings may be helpful to prove a causal relationship between EAC and an associated disease and the eruption often resolves after successful treatment of the underlying disease. No causal relationship could be proved in our patient.

EAC tends to be persistent over several months to a few years, waxing and waning in severity, but some cases eventually regress spontaneously. No routinely effective therapy is currently available unless a triggering factor can be identified and eliminated. Systemic and topical corticosteroids usually suppress EAC, as observed in our patient, but recurrence is common when these drugs are stopped. Oral antihistamines may be helpful for pruritus. Use of antibiot-
ics and antifungal medications as well as topical vitamin D analogues in combination with 311 nm ultraviolet B narrow band phototherapy has been successfully reported in sporadic cases.9, 10

References

LETTERS TO THE EDITOR

Pilomatrixoma, a misdiagnosed lesion: two pediatric case reports

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Dear Editor,

Pilomatrixoma is a benign cutaneous tumour arisen from hair follicle matrix cells and common under 20 years of age and in the sixth decade of life, but frequently misdiagnosed. We describe here two atypical pediatric cases of pilomatrixoma, with an early onset and unusual characteristics at the physical and instrumental examination.

Case 1.—A newborn girl developed a nodule on the right supraorbital region and was brought to us after seven months. Physical examination showed a clearly delimited, solid and protuberant red nodule, 11.7 mm in diameter, surrounded by an erythematous halo (Figure 1). Ultrasonography showed in the soft tissue an oval slightly inhomogeneous, mainly hypoechoic lesion delimited by an hyperechoic rim with some vascular spots. This picture suggested vascular malformation. After one month the nodule became twice and we required a surgical excision. Histological examination was compatible with pilomatrixoma: a well delimited subepidermal nodular lesion with proliferation of basophilic cells (without atypias), anucleated eosinophilic cells (shadow cells) and areas of variable keratinisation.

Case 2.—A six-month-old boy consulted us for a nodule on the right mandibular region present since two months. Physical examination showed a red-bluish nodule, about 10 mm in diameter, not fixed to underlying tissue, with some telangiectasias and an hard consistence (Figure 2). Ultrasonography showed: echogenic lesion with hyperecogen rim and rich peripheric vascularization. Magnetic resonance imaging (MRI) revealed: round
formation (about 15 mm in diameter) in soft tissue, with hypointense signal in T1-weighted images (T1W1) and hyperintense signal (fluid type) in T2-weighted images (T2W2); it had a multiple lobular aspect due to internal septa, and regular margins with cleavage plane; contrast medium administration produced peripheric rim enhancement and a weak intralesional contrast enhancement. According to radiologists MRI was compatible with cystic lymphatic dysplasia and a very small vascular component was associated. After one month after the first dermatological consultation, the lesion increased (as reported with MRI), became more protuberant and red colored, with an angiomatous aspect. It was surgically excised; macroscopically it seemed a calcifying and well-delimited dermal nodule and histologic examination confirmed the diagnosis of pilomatrixoma.

Generally pilomatrixomas present as single lesions in the head and maxillofacial zone and less frequently in limbs and trunk. In the early period pilomatrixomas are usually cystic and consist of uniform basaloïd cells lining the cystic cavity, ghost cells (dead cells without nucleus) and keratin. Late lesions are characterized by ghost cells, keratin debris, secondary multinucleate giant cells, dystrophic calcification and sometimes bone formation.

Often clinical diagnosis is difficult. Lesions that may be considered in the differential diagnosis with typical pilomatrixoma are: epidermal cysts, calcified lymph nodes, calcified hematomas, foreign body granulomas, osteomas of the skin, dermoid cysts, parotid gland tumors and atheromas. Unlike dermoid and epidermal cysts, pilomatrixomas are mobile and may present with irregular nodules.

In our cases lesion appeared very early and presented as non-tender nodule with a red-bluish discoloration that may be due to growth of blood vessels into the overlying skin or to hemorrhage. This angiomatous aspect may mislead clinicians to hemangioma and vascular malformation. Hemangioma onset generally occurs earlier than pilomatrixoma: at birth in one third of patients and after the birth (in the first weeks until one year) in the remaining two thirds. Head and neck are the most frequent localization of both lesions. Generally hemangioma is softer and compressible on the palpation and growth is faster than pilomatrixoma, but is followed by a slow regression in the childhood, while spontaneous regression has never been observed in the latter lesion. Also vascular malformations do not regress but grow commensurate with the child.

In the literature there are few report of pilomatrixoma that have been misdiagnosed as hemangiomas. Some of these were histologically classified as lymphangieciatic type for the presence of vascular spaces between the tumor and the epidermis and atrophic epidermis. In patient 1 the rapid growth of the lesion is unusual and may be mistaken with a malignant feature, although it is very unlikely.

In both cases we could not make a certain diagnosis on the basis of instrumental investigations. The ultrasonographic image of fully or partial calcified pilomatrixoma is: a completely echogenic mass (or with inner echogenic foci), with peripheral hypoechoic rim or with strong posterior or acoustic shadowing in the subcutaneous layer, suggestive of calcifications.

In the first and in second case the lesions were hypoechoic and anechoic, respectively, with peripheral hyperechoic rim and without posterior shadowing. The lesion presented vascular spots in the first patient and a rich peripheric vascularization in the other, resembling a vascular malformation. Also in four cases of a recent ultrasound study of pilomatrixoma vascular signals are reported, usually peripheric and only rarely intra-lesional. Generally calcifications and sign of inflammation occur late and probably in these patients vascularization or vascular spot may be related to inflammation. Hypoechoic ultrasonic pattern is present also in vascular malformation. Recently Solivetti et al. have reported new ultrasound pattern of pilomatrixoma with three new types that have never been described. These may be recognized with the use of high-frequency probes.

MRI is considered inconclusive, in fact in the Lim series only 60% of pilomatrixoma were correctly diagnosed. As in our case, MRI may reveal internal reticulations and patchy areas on T2-weighted images and contrast-enhanced T1-weighted images, corresponding to edematous stroma. According to the new ultrasound classification and on the basis of MRI and ultrasonographic images, in this case pilomatrixoma may belong to type 3 (pseudo-cystic lesion), one of the new pattern. This ultrasound pattern may be mistaken with sebaceous cyst and more cases are needed to confirm the real incidence of all new types reported.

Instrumental investigations may be added to physical examination in order to view the depth of the lesion and the surrounding structures, but sometimes they are not enough for a certain diagnosis. In these cases surgical excision and histological examination are needed and helpful to distinguish pilomatrixoma with angiomatous aspect from other childhood lesions like hemangioma and vascular malformations.

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Talon Noir: utility of dermoscopy for differential diagnosis with respect to other acral skin growths

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Dear Editor,

Black heel (calcaneal petechiae) is a self-limited, asymptomatic, trauma-induced darkening of the posterior or posterolateral aspect of the heel that occurs primarily in young adult athletes. It is characterized by speckled bluish-black areas of macular pigmentation occurring at the border of the heel slightly above the hyperkeratotic edge of the plantar surface.1 A similar lesion termed black palm (tache noir) has been described on the thenar eminence in weightlifters, gymnasts, golfers, tennis players, and mountain climbers. Although this manifestation is benign and self-limiting, it may cause apprehension in patients and general practitioners due to confusion with pigmented skin lesions such as malignant melanoma. This often explains the anxiety with which these young patients seek medical advice, often accompanied by equally worried parents.

The most important goal in such cases is to differentiate black heel (calcaneal petechiae) from melanoma or other skin lesions, such as angiomatoid growths and common warts. Usually no specific workup is necessary to diagnose black heel. The diagnosis is generally clinical and can be aided by paring down the lesion with a surgical blade. Melanocytic lesions will not lose their pigmentation with paring, while black heel may clear completely after the stratum corneum is removed. Patients may be contrary to this marginally invasive operation, due to unjustified fear of a plantar nevus turning malignant or of profuse bleeding by angiomas and plantar warts.

Epiluminescence techniques, such as dermoscopy and video macroscopy, can be used to aid differential diagnosis of pathological conditions and/or growths with respect black heel. Dermoscopy is a noninvasive technique that allows visualization of structures that cannot be detected by clinical examination. If performed by experts, it increases diagnostic accuracy for pigmented skin lesions, especially for malignant melanoma.2 Dermoscopic differential diagnosis of melanoma and dysplastic nevi or other melanocytic lesions is complex and requires the opinion of a dermatologist. On the other hand, differential diagnosis of melanocytic pigmented lesions and lesions of vascular (such as calcaneal petechiae) or other origin (such as common warts) is simple by dermoscopy. Black heel appears as grouped globular or punctate haemorrhages, often arranged in a linear pattern (Figure 1).3 On the other hand, viral warts are keratinocytic lesions with lobular structure (like frog spawn), sometimes with a central thrombosed capillary in each lobule; normal dermatoglyphics are interrupted and some have papilliform structure. Regarding pigmented skin lesions (PSL), three specific pigment patterns are considered normal in benign melanocytic naevi of plantar skin: parallel furrows, lattice-like pattern and fibrillar pattern.4 In each, the pigment is located in the plantar dermatoglyphic furrows. The patterns arise as a reflection of normal vertical (parallel furrow) or slanting melanin columns in the stratum corneum. Finally, malignant melanoma exhibits different patterns on the palmar and plantar surfaces with respect to other skin areas. Saida and workers reported asymmetry and irregular (variegated) color as a common feature (Figure 2). Pigmentation of ma-
Lignant melanoma is often accentuated on dermatoglyphic ridges, not in the furrows as in benign lesions.\(^5\)

In conclusion, in cases of black heel, urgent referrals are common from general practitioners or specialists in sports medicine wishing to exclude warts, nevi or even melanoma. Patients may be very anxious about this condition. Since dermoscopy makes diagnosis simple and precise, general practitioners and specialists in sports medicine could benefit from at least basic training in this technique.

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