Allergic contact dermatitis is a T cell mediated, antigen-specific inflammatory reaction of the skin due to repeated epidermal exposure to antigens. Immunologically it is divided into 2 phases, induction and elicitation phase. During the first phase which is clinically silent, naïve T cells are activated and differentiate into antigen-specific memory T cells. During the elicitation phase, after recontact with the same antigen, memory T cells are activated and exert direct and indirect cytotoxic effects towards cells of the skin. In this review we summarize immunological mechanisms leading to allergic contact dermatitis.

KEY WORDS: Allergic contact dermatitis - Contact hypersensitivity - Contact allergy - Perforin - Cell mediated cytotoxicity.

Contact dermatitis is an inflammatory reaction of the skin caused by direct contact with external agents. Primary skin lesions include erythematous macules, papules and vesicles. Secondary lesions such as weeping and crusting may occur. Patients typically suffer from pruritus or a burning sensation. Occupational contact dermatitis is a matter of great public health concern, contributing to high direct and indirect personal and public costs. Contact dermatitis is usually classified into irritant (ICD) and allergic contact dermatitis (ACD). While ICD is considered an inflammation of the skin resulting from direct cytotoxic effects of irritant chemical or physical agents, ACD is an immune-mediated response and typically represents a type IV delayed hypersensitivity reaction as classified by Coombs and Gell. With a prevalence of 20-30% in the general population it is a very common disease. Diagnosis is primarily based on the skin appearance and a history of exposure to an allergen. To prove sensitisation the patch test introduced more than 100 years ago by Jadassohn is still the gold standard.1

During the past years significant advances have been made in our understanding of the cellular and molecular mechanisms that are involved in the initiation, elicitation and resolution of cutaneous immune responses. In this review we shall focus on immunological pathomechanisms of ACD.

Histological and immunohistochemical characteristics of allergic contact dermatitis

Histologically ACD is a superficial inflammation of the skin with epidermal and dermal changes characterized by exocytosis and an extracellular oedema (spongiosis) in the epidermal cell layer which eventually may lead to the formation of intraepidermal vesicles.2 Immunohistochemical analysis show a massive T cell infiltrate, dominated by CD4+ T cells.
(CD4/CD8 T cell ratio 2:1) in the dermis and the epidermis. Most of these T cells (>95%) express an αβ T cell receptor. Natural killer (NK) cells and dendritic cells (DCs) are also found in considerable numbers (>10% of infiltrating cells). Interestingly, high numbers of cytotoxic T cells expressing perforin and granzyme B are found in the epidermis. Electron microscopic analysis in sensitized individuals show an extracellular oedema of the epidermis starting about 3 h after painting the antigen on the skin. Some hours later lymphocytes and DCs start to migrate to the epidermis.5

**Immunological pathomechanisms of allergic contact dermatitis**

ACD represents a T cell-mediated inflammatory response of the skin to low-molecular weight chemicals termed haptenes. ACD is pathophysiologically divided into 2 phases, namely an induction phase and an elicitation phase. During the induction phase, haptenes penetrate the skin and are then attached to amino acid residues on proteins. Such hapten-protein conjugates are then internalized by resident antigen-presenting cells, i.e., Langerhans cells (LCs) and dermal dendritic cells (DDC). During migration to the regional lymph nodes, these DCs are thought to undergo further maturation, which enables optimal presentation of these haptenes to naive T cells. This process leads to clonal expansion of hapten-specific memory T cells with different phenotypes (e.g., CD4+, CD8+), cytokine profiles (e.g., type 1 cytokines: IFN-γ, TNF-α), and type 2 cytokines: IL-4, IL-5, IL-13) and functions (e.g., cytotoxic T cells, T regulatory cells). Upon re-exposure of a sensitized individual to the corresponding hapten, a cutaneous inflammatory immune response termed as the elicitation phase of ACD can be induced by hapten-specific effector memory T cells recruited to the skin. The detailed mechanisms and characteristic of the cells involved in the induction and elicitation phase of ACD are discussed in the following.

**Induction phase**

The induction phase, also called the phase of sensitisation, is clinically silent. DCs and T cells are the main cell types involved in this phase (Figure 1).

**Role of dendritic cells in the induction phase**

DCs are antigen-presenting cells with the ability to induce primary immune responses. They represent the link between innate and adaptive immune system and their functional and phenotypic properties profoundly determine the outcome of an immune response.7 DCs comprise a morphologically, phenotypically and functionally heterogeneous cell population. Depending on lineage markers, two different subsets of DCs have been described, plasmacytoid (pDC, CD123+, BDCA2+) and myeloid DCs (mDC, CD11c+). Both, pDC and mDC are believed to derive from CD34 positive precursor cells in the bone marrow. Whereas pDC are mainly found circulating in the blood, mDC are predominantly situated in the peripheral tissues.

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immunostimulatory DCs. This process includes the up-regulation of co-stimulatory molecules and the enhanced delivery of hapten bound to the MHC peptide complex onto the cell surface. This process includes the up-regulation of co-stimulatory molecules and the enhanced delivery of hapten bound to the MHC peptide complex onto the cell surface. Furthermore, they also lose their endocytic capacity, so that only antigen captured at the site of inflammation is processed. In the lymph node LCs home to and localize within the T cell rich paracortical regions where different subsets of hapten-specific T cells are induced.

Recent data using mice deficient in LCs unexpectedly showed a slightly impaired contact hypersensitivity compared to control animals. Furthermore, mice constitutively and durable deficient for LCs even demonstrated an enhanced contact hypertensitivity. These results show that the antigen-presenting function of LCs may be taken over by other cell types. Furthermore, they suggest that LCs may play a role in the down-regulation of immune responses and in the generation of tolerance.

**Sensitization of T cells**

During contact hypersensitivity several different T cell subsets are stimulated. The factors responsible
for this highly complex activation pattern are still unknown. It is believed that several different mechanisms are responsible for this activation such as different DCs subpopulations, the affinity of the hapten-bound MHC-peptide complex to the T cell receptor, the cytokine milieu and the presence of danger signals. Initial observations suggested that mDC have intrinsic capacity to polarize naïve T cells toward a T-helper (Th)1 phenotype and pDC toward a Th2 phenotype. However, these reports have been challenged by findings that after viral challenge pDC may also induce a strong Th1 response. It is, however, clear that DCs by secreting certain cytokines (i.e., Type I IFN, IL-4, IL-10, IL-12) and chemokines (MIP-2) ultimately may determine the polarization of T cells. Interestingly, recent reports have indicated an increased expression of IL-1β, IL-6, IL-12 and IL-18 in mouse DCs following exposure to dinitrofluorobenzene (DNFB). Both IL-12 and IL-18 are known to play a central role in polarizing naïve T cells towards memory effector T cells with a type 1 cytokine profile. Furthermore, analysis of blood-derived DCs using microarray technology have shown that one of the most up-regulated genes after dinitrobenzene sulfonic acid (DNBS) treatment was IL-8. The up-regulation of IL-8 mRNA and protein expression was also described in DCs after exposure to the contact allergen DNCB or nickel chloride.

In recent years detection of pathogen associated molecular pattern (PAMP) receptors on DCs has provided further interesting data regarding polarization of T cells. PAMP receptors recognize conserved molecular structures of pathogens. Toll like receptors (TLR) are the best studied PAMP receptors. mDC and pDC express different sets of TLR (mDC: TLR1-9, pDC: TLR1, 6, 7 and 9) enabling them to react to different sets of PAMPS. After ligand recognition TLR trigger maturation and migration of DCs and induce distinct patterns of cytokines resulting in different Th1/Th2 polarization. dsRNA has been shown to induce the release of type 1 IFNs, leading to the development of Th1 effector cells. Conversely, the stimulation of DCs with a Schistosoma mansoni egg extract promoted the maturation of Th2 effector T cells. Interestingly, low molecular weight compound, i.e. imiquimod have also been reported to activate TLR. Although the role of TLR in contact hypersensitivity reactions still remains unknown, activation of these receptors may influence the induction of skin sensitization. Taken together, it is likely that during contact sensitization various danger signals (infectious agents, cellular components released by chemical and physical injury, cytokines like TNFα, IL-1β) lead to activation of DCs and subsequent influence the development of functionally different subpopulations of T cells. In this context, it is also interesting that hapten-induced additional toxic effect to the epidermis have a higher potential to induce an ACD.

The central event during the induction phase of ACD is the activation and clonal expansion of antigen-specific memory T cells in the draining lymph nodes. Thereby, different functional T cell subsets can be generated e.g. Th1/Th2 as well as T cytotoxic (Tc1) and Tc2 cells. The immunological events during the phase of sensitization were mainly studied in experimental animals where T cells from the draining lymph node may easily be obtained after painting of contact allergens to the skin. Repeated application of formaldehyde and DNCB lead to the generation of lymph node cells producing type 1 cytokines such as IFN-γ, but only low levels of the type 2 cytokines (IL-4, IL-10). Interestingly, the type 2 cytokines were produced by CD4 T cells (Th2 cells) with no evidence for the induction of type 2 CD8 T cells (Tc2 cells). Further reports have also shown the generation of IFN-γ-producing effector CD8+ Tc1 cells and IL-4/IL-10 producing CD4+ Th2 cells. In addition, Martin et al. have reported the predominant induction of a high frequency of allergen-specific CD8+Tc1 cells in association with the murin immune response to the contact sensitizer trinitrophenyl (TNP).

One major paradigm in immunology is that exogenous antigens as haptons are presented on MHC class II molecules and, therefore, stimulate CD4+ T cells. However, increasing evidence indicates that hapten specific CD8 T cells are the main effector cells in ACD. In the last few years, it has become evident that DCs are able to present exogenous antigens on MHC class I molecules. This process, also called cross presentation/cross priming, allows the induction of specific CD8+ T cells to exogenous antigens. In vitro generated LCs have been shown to be able to cross present peptide antigens to T cells. Whether cross priming during the generation of hapten specific T cells occurs has not been studied so far. However, highly reactive haptons such as TNP may lead to direct covalent modification of peptides associated with MHC class I and II molecules on the surface of DCs and, thereby, may induce both CD4+ as well as CD8+ T cell activation.
Recent research suggest that the events during T cell priming may lead to the generation of distinct populations of antigen-specific memory T cells with different homing (e.g., cutaneous lymphocyte antigen, CLA), adhesion (e.g., L-selectin, CD62L) and chemokines receptors (e.g., CCR7). In the peripheral tissues effector memory T cells (CCR7-CD62L+) are thought to migrate to inflamed peripheral tissue and display immediate effector functions upon antigen contact, whereas central memory T cells (CCR7+CD62L+) that home to T cell areas of secondary lymphoid organs, have little or no effector functions, but quickly proliferate and differentiate to effector cells in response to antigen. The targeting of effector memory T cells to the skin is controlled by surface expression of the skin-homing molecule CLA and certain chemokine receptors, i.e., CCR4 and CCR10, on the T cells and E-selectin expression on the endothelial cells in the skin. CLA+ memory T cells also express the integrins CD11a/CD18 (αLβ2, LFA-1) and CD49d/CD29 (α4β1) that bind to ICAM-1 and VCAM-1 which are up-regulated during skin inflammation on the endothelial cells. Interestingly, recent homing and chemokine receptor coexpression studies suggest that the CLA+/CCR10+ memory CD4+ T cell population contains members that have access to both secondary lymphoid organ and skin compartments; and, therefore, can act as both central and effector memory T cells. The precise factors leading to the development of hapten-specific skin-homing or central memory subsets of T cells is still poorly understood and remains to be elucidated in future studies.

**Induction of regulatory T cells**

The induction phase of an ACD is also highly influenced by inhibitory mechanisms of the immune system. It has been shown that CD4+CD25+ regulatory T cells (T reg) may inhibit contact hypersensitivity through a Fas ligand dependent mechanism and ultraviolet irradiation induces T reg that are able to suppress the effector phase of an ACD. Furthermore, about 20% of peripheral T cells from nonallergic donors may release high amount of IL-10 but not IFN-γ or IL-4. These IL-10 producing T reg were highly effective in blocking the maturation of DCs and inhibited their capacity to present antigens to T cells. More recently also CD4+ T reg able to suppress contact hypersensitivity independent from cytokine production have been described. Evidence exists that these cells modulate antigen response by direct cell-to-cell contact.

**Elicitation phase**

After recontact with the same chemical allergen, hapten-specific memory T cells are quickly recruited from the blood to the skin (Figure 2). They recognize antigens (haptens or metal ions bound to proteins) presented on MHC molecules. These T cells were shown to be able to destroy skin cells either by direct cytolysis or by indirect mechanisms such as cytokine release or activation of cells of the innate immune system. This process leads to a cutaneous inflammatory response that clinicians call eczema.

**Involvement of dendritic cells and keratinocytes in the elicitation phase**

LCs and keratinocytes are likely to be the first cells in contact with antigen applied to the skin. During the elicitation phase the distribution of DCs is profoundly altered compared to normal skin (Figure 3). In diseased skin CD1a positive cells are found more frequently in the dermis slightly less frequent in the epidermis, indicating that during the inflammatory reaction LCs migrate out of the epidermis. As shown in Figure 3 expression of the mannose receptor (CD206) which is expressed mainly by DCs is highly upregulated in the elicitation phase of an ACD indicating that DCs are crucial during the inflammatory reaction in ACD. However, the complete depletion of LCs in mice using a diphtheria toxin receptor-based system to achieve inducible ablation slightly reduced the extent of a contact hypersensitivity reaction and the depletion of resident LCs with topical steroids after sensitization has been reported to results in an increased response. Interestingly, recent reports have indeed shown that not only LCs but also mature pDC are able to induce a hapten-specific immune response indicating that these cells may act as prominent amplifiers of the adaptive immune response in ACD.

In addition to DCs, keratinocytes may also have a decisive role in the elicitation of ACD. Under normal circumstances keratinocytes express MHC class I molecules, but no class II molecules. After stimulation they may, however, express MHC class II molecules, act as nonprofessional helper APC and activate CD4+ and CD8+ effector T cells. After exposure to contact
allergens keratinocytes up-regulate cytokines (IL-12, IL-1α, GM-CSF) and chemokines (MCP-1, RANTES, IP-10, MIG, Gro-alpha) and thus provide various signals, which may further activate neighbouring DCs. Concomitant chemical and physical trauma, ultraviolet B irradiation or infectious agents may perpetuate the inflammatory response by further inducing the production of proinflammatory cytokines and chemokines, which subsequently lead to upregulation of selectins and integrins on endothelial cells. In concert with chemokines (e.g. CTAC/CCL27) these molecules enhance the recruitment of CLA+, CCR4+, CCR10+ memory T cells to the site of antigen application.46

**Effector T cell mechanisms**

Although it is well established that T cells are intimately involved in the pathogenesis of ACD,22, 57 there have been major controversies on the precise roles of CD4+ and CD8+ T cells in the elicitation of the inflammatory response. In contrast to classical delayed-type hypersensitivity reaction, which are mediated primarily by MHC class II restricted CD4 T cells, the T cell response to haptens in ACD appears to be more complex. Many reports indicate that cytotoxic CD8 T cells (Tc1) are particularly important in eliciting cutaneous inflammation.22, 39, 58, 59 Interestingly, experiments from CD4 and CD8 knockout animals con-
ducted by Wang et al. indicate that both CD4 and CD8 T cell subsets are required for full development of contact hypersensitivity. Thus, it appears that at least in some instances CD4+ T cells can function as effector cells, while a subset of CD4+ T cells, which may correspond to the recently described CD4+ CD25+ regulatory T cell population are endowed with down-regulatory functions.

One of the main feature of ACD is the exocytosis of T cells and the generation of epidermal cell damage. Recent research has revealed that T cell-mediated cytotoxicity towards hapten-modified target cells, i.e. keratinocytes critically contributes to the development of epidermal cell damage. Generally, two different pathways of T cell-mediated cytotoxicity have been described. Firstly, after direct cell contact and antigen activation cytotoxic T cells release the content of their granules, mainly perforin and granzymes. Perforin polymerizes after secretion leading to the formation of a channel in the cell membrane through which granzymes and other constituent of the granules penetrate into the target cell leading to lysis. Second-
ly, cytotoxicity may also be mediated through death receptors, e.g., via FAS/FAS ligand interactions. Interestingly, both cytolysic mechanisms seem to be required for the full development of cutaneous inflammation in ACD. The contribution of antigen specific cytotoxic T cells in ACD has been studied in experimental animal models using mice deficient in both perforin and FAS/FAS ligand pathways. Although animals lacking both pathways were able to generate hapten-specific CD8+ T cells, they were unable to mount chronic hypersensitivity reactions. Studies with skin from patients with ACD showed that infiltrating T lymphocytes express cytotoxic molecules like perforin and granzyme B at a high frequency. These cells are particularly located in the epidermis where signs of keratinocyte cell damage is present (Figure 4). These data suggest that T cell mediated cytolysis by perforin and granzymes is a central mechanism for antigen-specific tissue damage in ACD. In addition FAS/FASL induced killing has also been described to be involved in generation of keratinocyte damage in ACD. However, FAS/FASL induced cell death may mainly be important in the regulation of the immune response, whereas the main mechanism of direct cytotoxicity seems to be perforin dependent.

In addition to these direct cytolysic effects T cells also produce cytokines and chemokines which act as pro inflammatory effector molecules in ACD. IFN-γ, TNF-α, IL-12 and IL-17 produced by DCs and infiltrating T cells also induce keratinocytes to produce cytokines (IL-1, TNF-α, IL-8 and IL-12) and chemokines (IP-10, Mig, I-TAC, ligand for
CXCR3). These mechanisms have a strong potential to amplify the inflammatory reaction leading to tissue damage.

Resolution of the inflammation

To limit excessive tissue damage and to terminate the inflammation during ACD regulatory mechanisms are essential. Over the last years substantial progress was made in the analysis of cellular and molecular mechanisms involved in this process. T cells were described to modulate the immune response by the release of IL-10. In humans nickel reactive CD4 T cells were found in blood and skin of patients suffering from ACD which are able to produce high levels of IL-10, low levels of IFN-γ and no IL-4. These CD4+CD25+ T reg are able to block, through an IL-10 dependent mechanism, the maturation of DCs including IL-12 release, thus impairing their capacity to activate T cells. Infiltrating the inflamed skin of an ACD these T reg may have a role in limiting the extent of tissue disruption. This process may lead to the exhaustion of the immune response and termination of the inflammation. Future research, in particular combination of gene profiling using microarray analysis as well as proteomic analysis will hopefully give us a more comprehensive picture of the inflammatory mechanisms involved in ACD.

Riassunto

La dermatite allergica da contatto: rassegna dei meccanismi immunologici


Bullous pemphigoid, an autoimmune blistering disease with protean clinical manifestations. Review of recent advances from the bench to the bedside

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Bullous pemphigoid (BP) is the most frequent autoimmune subepidermal blistering disease and affects predominantly the elderly. It is associated with autoantibodies directed against the BP antigen 180 (BP180 or BPAG2) and the BP antigen 230 (BP230 or BPAG1), two hemidesmosomal components that promote dermo-epidermal cohesion. The clinical features of BP are extremely protean. While its diagnosis is easily considered in the presence of a pruritic eruption with widespread blistering, atypical variants or early stages of BP with either localized or generalized, excoriated, eczematous, vesicular or urticated lesions may constitute a clinical pitfall. In these cases, diagnosis of BP uniquely relies on the findings of the immunofluorescence microscopy studies as well as on the characterization of targeted antigens. Recently, in addition to the identification of clinical criteria useful for the diagnosis of BP and further improvement of the standard immunopathological investigations, enzyme-linked immunosorbent assays (ELISA) utilizing recombinant proteins of BP180 and BP230 have been developed, that allow the rapid characterization of circulating anti-BP180 and anti-BP230 antibodies with high specificity and sensitivity. These tests represent useful diagnostic tools, but their value for the management and follow-up of affected patients remains to be determined.

Key Words: Bullous pemphigoid, diagnosis - Bullous pemphigoid, drug therapy - ELISA.

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Bullous pemphigoid (BP) is the most frequent autoimmune subepidermal blistering disease. In the past few years our understanding of this disease has considerably increased. Much has been learned about the autoantigens involved, their distribution and function in the skin and mucosae as well as the underlying immune response mediating tissue injury and subepidermal blister formation.1-8

BP typically affects people age 65 and over. The annual incidence has been estimated to be at least 6-7 new cases per million population. The risk to develop the disease in patients older than 90 years of age appears to be approximately 300-fold higher than for those of 60 years or younger.9 Nevertheless, this blistering disease can also occur in infancy and childhood.

The aim of this article is to review the clinical presentations of BP and to critically evaluate the immunological tests required and useful for the diagnosis of this disease. Furthermore, recent advances in our insights into the physiopathology of BP will be emphasized. Finally, some practical points important for clinical management and therapy will be discussed.
The diagnosis of BP is easily considered in the presence of a generalized bullous eruption.\textsuperscript{6-8} In the full-blown bullous stage, vesicles and bullae arising on apparently normal or erythematous skin together with urticarial and infiltrated papules and plaques are characteristically observed (Figure 1). The blisters are usually tense, up to 1-3 cm in diameter, with a clear exudate, and may persist for several days, leaving eroded and crusted areas. The lesions are frequently distributed symmetrically and predominate on the flexural aspects of the limbs, lower trunk, and abdomen. Sometimes, an annular or figurate pattern is observed. In the intertriginous spaces, vegetating plaques may develop. Healing may leave postinflammatory changes, such as hyper and hypopigmentation and, more rarely, milia. Involvement of the oral cavity is observed in only up to 10\% to 20\% of cases. The mucosae of eyes, nose, pharynx, esophagus and ano-genital areas are only rarely affected.

Nevertheless, physicians first see the majority of BP patients when no obvious blisters are present. At this stage, BP may constitute a pitfall even for experienced dermatologists. In this nonbullous stage of the disease, manifestations are nonspecific, with pruritus, of variable severity, accompanied or not by excoriated, eczematous, papular and/or urticarial lesions. The features can thus mimic the entire spectrum of inflammatory conditions. Importantly, this unspecific presentation may persist for several months or even remain the only signs of the disease (Figure 2).

**Atypical variants of bullous pemphigoid**

In a subset of patients with BP, skin manifestations are sometimes peculiar and striking because of either their extent, their localization or the type of the lesions.\textsuperscript{10} BP can remain occasionally localized, such as around stomas (Figures 2, 3), on irradiated areas or confined to a paralyzed limb.\textsuperscript{11-13} Involvement limited to the pretibial area (pretibial pemphigoid),\textsuperscript{14, 15} to the palmo-plantar region with features mimicking dyshidrosiform eczema (dyshidrosiform pemphigoid)\textsuperscript{16, 17} or, finally, to the vulvar region (vulvar pemphigoid)\textsuperscript{18} has been reported. The latter presentation is typically observed in young girls. It is characterized by recurrent blisters and erosions of the genital area that may result in scarring and atrophic changes.

Several generalized variants of BP have also been reported. In certain patients, BP closely resemble dermatitis herpetiformis with multiple grouped small tense vesicles showing a symmetrical distribution (vesicular pemphigoid).\textsuperscript{19-21} Patients have sometimes intertriginous vegetating plaques exhibiting clinical resemblance to pemphigus vegetans (pemphigoid vegetans).\textsuperscript{22} In some instances, the inflammatory lesions are constituted by strong pigmented macules and only later on bullous lesions develop (pigmented BP).\textsuperscript{23} Pemphigoid nodularis is another misleading variant.\textsuperscript{24, 25} Most reported cases are elderly women showing excoriated nodules and papules predominantly distributed on lower and upper extremities and shoulders (Figures 2, 3). Blisters may precede or follow the development of nodular lesions and arise either at sites...
of nodular lesions or on uninvolved skin. Erythrodermic BP is an unusual variant characterized by an erythroderma and blistering. Some patients with exfoliative erythroderma without obvious blistering have been reported, in whom diagnosis relied solely on the results of the immunopathological findings (Figure 2). Single cases of extensive erosive BP have also been described. Affected patients present large eroded areas of skin without pruritus, blisters or urticarial inflammatory lesions. BP has been reported in association with other distinct dermatoses, such as psoriasis vulgaris or pustular psoriasis. An other rare variant of BP is lichen planus pemphigoides, which is associated with features of both lichen planus and BP. It is characterized by the presence of lichen planus lesions with vesicles and bullae arising on both involved and uninvolved skin. Light microscopy studies of papular lesions demonstrate features typical for lichen planus, while biopsies obtained from bullous lesions reveal a subepidermal blister usually suggestive of BP. Patients with lichen planus pemphigoides present with some peculiar common features, including a peak incidence of occurrence in the fifth decade, a predilection for an involvement of the distal extremities, and a relatively benign course. Finally, although no large series are available, in which diagnosis was firmly established, BP also occurs in children (childhood BP) (Figure 4). Features appear to be similar to those observed in the elderly, although frequent involvement of mucosae and palmo-plantar regions has been suggested.

It is obvious that only dermatologists can afford to have so different names for the same disease! Is there a justification for the distinction of so different variants? In most cases, the answer to this question is no. In fact, there is no evidence indicating that these variants represent distinct entities. Moreover, patients with
BP frequently show a mixture of various features: dyshidrosiform, vesicular, vegetating, papular or nodular lesions may coexist. Finally, the predominating type of lesions can change in the course of the disease or under therapy. Nevertheless, it is likely that some clinical features, such as mucosal involvement or tendency to scarring, reflect a distinct autoantibody profile to BP180 and BP230.

Associated diseases and drug-induced bullous pemphigoid

The trend towards an increased risk of malignancy in BP appeared to be marginal. In most patients the association of malignant diseases with BP is fortuitous and related to their old age. A case-control study did not find any increased risk for autoimmune disorders in BP. The anecdotal occurrence of BP in patients with inflammatory bowel diseases, rheumatoid arthritis, Hashimoto’s thyroiditis, dermatomyositis, lupus erythematosus, or autoimmune thrombocytopenia probably reflect a genetically determined susceptibility to develop autoimmune diseases. In some patients, BP appears to be triggered by trauma, burns, radiotherapy, or ultraviolet irradiation.

BP has also been found in association with psoriasis and lichen planus as well as with neurological disorders, such as multiple sclerosis, Shy-Drager syndrome or amyotrophic lateral sclerosis. The significance of these associations remains unclear. However, it should be noted that neuronal variants of BP230 are strongly expressed in the central and peripheral nervous systems. Finally, in certain patients, systemic medications appear to trigger or induce BP. A case-control study assessing the drugs used on a long-term basis prior to onset of the disease found that two classes of drugs, aldosterone antagonists and neuroleptics, were used more frequently by BP patients than by control subjects. The list of implicated drugs is long: diuretics (e.g. furosemide and bumetanide), analgesics (e.g. phenacetin), D-penicillamine, antibiotics (e.g. amoxicillin and ciprofloxacin), potassium iodide, gold, and captopril. Relapse and exacerbation of BP lesions following drug reintroduction has been described in some cases (e.g. with furosemide), but in other instances both diagnosis of BP and the imputability of the drug were poorly documented.

Physiopathology of bullous pemphigoid: recent advances

The autoimmune etiology of BP appears now clearly established. Affected patients have autoantibodies and autoreactive T cells that target well characterized self-antigens expressed in the basement membrane zone of skin and mucosa. In vitro models with human skin and in vivo animal models of the disease have provided strong evidence for the pathogen-
Bullous pemphigoid, an autoimmune blistering disease with protean clinical manifestations

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The role of autoantibodies; furthermore, in gestational pemphigoid, a disease closely related to BP occurring during pregnancy, the transplacental transfer of autoantibodies from the mother into the neonate can cause a transient bullous eruption; finally, the disease occurs in association with distinct HLA genotypes and responds to immunosuppressive therapy.53

A model has been proposed, in which autoantibodies to the extracellular domain of BP180 are pathogenically critical for the initiation of the disease, whereas development of antibodies against antigenic determinants on the intracellular domain of BP180 and on BP230 represents a secondary event. Although this model needs to be confirmed by experimental data in humans, preliminary findings in a mouse model of BP indicate that antibodies to the NC16A region develop indeed in the early phase of the disease and are followed by the appearance of antibodies reactive with additional antigenic sites on BP180.54 A prospective multicenter study is currently characterizing the sequential dynamic of the immune response to BP180 and BP230 in the various phases of the disease in a large cohort of patients with BP.55 In brief, the advances can be summarized as follows:

— BP is associated with a humoral immune response directed against two molecules, the BP antigen 180 (BP180, BPAG2 or type XVII collagen), and the BP antigen 230 (BP230, or BPAG1-e);3-6, 40 BP180 and BP230 are components of hemidesmosomes, adhesion complexes promoting epithelial-stromal adhesion in stratified and other complex epithelia, such as the skin and mucous membranes. BP180 is a transmembrane molecule with a collagenous extracellular domain serving as cell surface receptor, whereas BP230 is a cytoplasmic protein belonging to the plakin family of proteins and is implicated in the organization of the keratin filament network.41

— Patients’ autoantibodies predominantly recognize antigenic reactive sites located on the membrane proximal region of the extracellular domain of BP180 (NC16A subdomain) and the COOH-terminal region of BP230. Nevertheless, there are additional antigenic reactive sites spread over the entire extracellular and intracellular domain of BP180 and BP230 molecule.42-48

— Binding of autoantibodies to BP180 and BP230 results in a cascade of events: complement activation, recruitment of inflammatory cells (mainly neutrophils and eosinophils) and liberation of various chemokines and proteases, such as matrix metalloproteinase -9 and neutrophil elastase.51, 52, 56, 57 These proteinases degrade various extracellular matrix proteins as well as BP180. Infiltrating eosinophils are implicated in tissue damage by releasing proteases and proinflammatory mediators, such as IL-5 and eotaxin. Autoantibodies to BP180 can also amplify the inflammatory response, by directly stimulating keratinocytes to express various cytokines, such as IL-6 and IL-8.58

— BP patients have autoreactive CD4+ T cell responses directed against BP180 and BP230, which are likely to critically regulate B cell function and hence, autoantibody production.59, 60 Noteworthy, these autoreactive T cells appear to recognize epitopes contained in the same immunodominant regions recognized by circulating autoantibodies. Autoreactive T cell response are restricted by certain HLA class II alleles, such as the HLA-DQB1*0301, that are prevalent in BP.53, 59, 60

Diagnosis of bullous pemphigoid: clinical and immunopathological criteria

Diagnosis of BP is based on a combination of criteria encompassing:

1. Clinical features, which may be either typical (blistering eruption) or compatible. A recent study has found that in patients with a subepidermal blistering disorder associated with linear deposits of IgG and/or C3 along the epidermal basement membrane the presence of 3 of 4 clinical criteria indicates to a diagnosis of BP with a high sensitivity and specificity: a) absence of skin atrophy; b) absence of mucosal involvement; c) absence of head and neck involvement and; and d) age greater than 70 years.61, 62 These criteria have a prognostic positive value over 95%.  

2. Histological findings demonstrating characteristically subepidermal blister formation with an inflammatory infiltrate rich in eosinophils (Figure 5). Nevertheless, in many cases, findings are nonspecific or even misleading. Finally,

3. Positive immunopathological studies, which provide the most critical informations for the diagnosis of BP and allow its differentiation from the vast group of subepidermal blistering disorders. The latter include linear IgA bullous dermatosis, epidermolysis bullosa acquisita (EBA), gestational pemphigoid, and cica-
tricial pemphigoid and may mimic BP with overlapping clinical and immunopathological features. In a majority of cases, direct and indirect immunofluorescence studies are sufficient for an appropriate and correct classification of BP. In other instances, the peculiar clinical setting (e.g., pregnancy for gestational pemphigoid) or the presence of distinct clinical features (such as predominant mucosal involvement with tendency to scarring for the diagnosis of cicatricial pemphigoid) facilitates the proper classification.

The following points should be emphasized:
— In patients with either atypical presentations or in the early nonbullous stage of the disease, correct classification and diagnosis of BP rely on immunopathological findings.
— Although no studies are available providing a validated and cost-effective approach for the work up of patients at risk for BP, we routinely perform direct and indirect immunofluorescence studies in elderly patients with chronic pruritic skin disorders, either localized or generalized, for which history, clinical examination and standard laboratory studies do not find any obvious underlying cause, including a drug-related side effect. It is yet unclear whether testing utilizing the commercially available BP180-ELISA can be used as a first screening to identify patients with BP or at risk for developing the disease.
— A number of elderly patients with itchy skin eruptions, in whom direct immunofluorescence microscopy findings are initially negative, later on develop full-blown BP. It is hoped that a better knowledge of the profile of the humoral immune response to BP180 and BP230 in the various phase of the disease and the characterization of markers associated with early disease will help clinicians to identify patients at risk for BP to promptly start appropriate treatment.63, 64

Immunopathological studies and tools for diagnosis of bullous pemphigoid

1. Direct immunofluorescence studies, which have to be performed (and sometimes repeated) on perilesional, uninvolved skin, discloses in invariably all patients the presence of fine, linear, continuous deposits of IgG and/or C3, and more rarely, of other Ig classes along the epidermal basement membrane (Figure 5). Testing of autologous patient’s skin after treatment with 1 M NaCl might be helpful in the distinction of BP from other autoimmune blistering disorders by demonstrating immune deposits located at the epidermal or at both epidermal and dermal sides of the split.65 The computer-aided fluorescence overlay antigen mapping (FOAM) technique enables to determine precisely the localization of deposits immunoreactants.66 Notably, a recent study indicates that the analy-
sis of the distribution pattern of the immunoreactants along the basement membrane zone easily allows the distinction of BP from EBA. While in the former the immunofluorescence staining has a so-called "n-serrated pattern", in the latter an "u-serrated pattern" is observed. Important prerequisites for the assessment of these distinct fluorescence patterns are: 1) availability of tissue sections of good quality with little background; and 2) a microscope with at least a ≥40 X objective that allows generation of digitalized images. Finally, a recent study has provided evidence that the use of a 0.9% NaCl solution as a transport medium for skin biopsy specimens subject to direct immunofluorescence microscopy studies increases the sensitivity of the technique. However, processing needs to be carried out within 24-48 h.

2. Indirect immunofluorescence studies. In 60% to 80% of patients, circulating antibasement membrane autoantibodies of the IgG, and less frequently, of the IgA and IgE class, are detectable. These autoantibodies bind to the epidermal side or, less frequently, to both the epidermal and dermal side of saline separated normal human skin. Finally, the use of either skin samples or keratinocyte cell lines that are deficient in specific basement membrane proteins, such as BP180 or type VII collagen, may constitute in selected circumstances a simple tool to determine the specificity of patients' autoantibodies.

3. Immunelectron microscopy studies. Their practical utility is limited because they are technically demanding, time-consuming and expensive. Nevertheless, in the absence of circulating autoantibodies precise localization of immune deposits may be required for proper diagnosis and distinction from EBA.

4. Immunochemical methods, such as immunoblot and immunoprecipitation studies of keratinocyte extracts show in 60% up to 100% of patients' sera the presence of IgG autoantibodies binding to a 180 kDa and 230 kDa protein, corresponding to BP180 and BP230, respectively. Patients' sera frequently contain also specific IgA and IgE autoantibodies. Recombinant forms of BP180 and BP230 produced in bacterial or eukaryotic expression systems (such as baculoviruses or yeast expression systems) have been employed to facilitate the detection of autoantibodies. Nevertheless, the routine use of these techniques has been increasingly abandoned, because of the development of enzyme linked immunosorbent assays (ELISA).

5. ELISA utilizing recombinant proteins containing immunodominant regions of the target antigens, such as the NC16A domain of BP180 and the COOH-terminal region of BP230, allow a rapid search of circulating autoantibodies and have been found to be specific and sensitive (Figure 6). However, a critical analysis of the available data obtained with the commercially available ELISA utilizing a recombinant form of NC16A domain indicates that the overall sensitivity is not significantly higher than that of indirect immunofluorescence microscopy utilizing NaCl-separated skin. The best results with almost 100% sensitivity are obtained when a combination of ELISA utilizing various portions of BP180 (NC16A domain and COOH-terminal region) and BP230 is used. Recent studies from our and other laboratories have provided evidence that serum levels of autoantibodies to BP180 vary in parallel to disease activity. Furthermore, we have found that autoantibodies from BP patients with mucosal involvement target frequently both the NH2- and COOH-terminal regions of the ectodomain of BP180, while presence of a dual IgG1 and IgG4 response against the NH2-ter-
minal region of the ectodomain of BP180 is associated with a more severe phenotype. Although these ELISAs are very helpful for diagnostic purposes, their usefulness for the practical management of patients and for guiding treatment remains unclear.

### Differential diagnosis

Since the clinical manifestations of BP are very heterogeneous and protean, it is obvious that the differential diagnosis can be extremely broad: drug reactions, contact dermatitis, prurigo, fixed urticaria, vasculitis, arthropod reaction or scabies… These disorders can be usually distinguished on the basis of the clinical history and setting, pathologic features and, above all, of the negative immunofluorescence microscopy findings. In the presence of vesicles and frank bullae manifestations of BP may occasionally be reminiscent of pompholyx, bullous drug eruption, pseudoporphyria or porphyria cutanea tarda. The differentiation of BP from the other autoimmune blistering diseases, such as the inflammatory form of EBA, relies on the immunopathological studies, although clinical criteria are also very useful. In children, diagnoses such as bullous impetigo, the group of congenital epidermolysis bullosa, and bullous mastocytosis need, among others, to be considered.

### Prognosis, therapy and practical management

BP is a chronic disease showing spontaneous exacerbations and remissions. The disease is associated with significant morbidity, with impact on the quality of life, because of the presence of severe itch, bullous, eroded and crusted lesions. Although the majority of patients go into remission under treatment, the mortality rate, estimated between 12% to 40% in the majority of patients, shows that the overall morbidity is considerable. Nevertheless, in recent years, thanks to the efforts of French Study Group on Bullous Diseases, the first large scale multicenter controlled studies have been initiated to assess the validity of different therapeutic interventions. One of these trials has demonstrated that potent topical corticosteroids (such as clobetasol propionate) are not only useful in localized or mild forms of BP, but also in generalized forms. Topical potent steroids are even better than oral prednisone in terms of both the rapidity of disease control and survival. Nevertheless, it should be kept in mind that topical steroids can also result in systemic (e.g., diabetes, suppression of the hypothalamic-pituitary-adrenal axis…) and local side effects (e.g., skin atrophy, infections…). Furthermore, the approach with topical therapy over months raises the question of its practical feasibility in elderly patients requiring assistance and who cannot benefit from a regular medical support. Hence, in a number of cases it will be more appropriate to introduce systemic steroids. The latter have been widely utilized in clinical practice and their efficacy have been confirmed in both uncontrolled and controlled studies. However, their side effects profile, as previously underlined, is less favourable compared to topical steroids.

For patients with extensive disease, oral prednisone at the dosage of 0.5 to 1 mg per kg per day usually controls the disease within 1 or 2 weeks. This dose is then progressively tapered over a period of 6 to 9 months.

The use of immunosuppressive drugs, such as azathioprine, chlorambucil, cyclophosphamide, mycophenolate mofetil, and methotrexate, is a matter of debate, since they have not been validated by controlled studies. Some clinicians prefer to introduce them only when corticosteroids alone fail to control the disease, or if the latter are contraindicated. In addition, in certain treatment-resistant cases, pulse corticosteroid therapy, intravenous immunoglobulins, plasmapheresis and extracorporal photophoresis have been utilized.

The choice of the immunosuppressive drugs depends on the profile of their side effects, patient’s overall condition and on the experience of the physician with a given drug. Alternatively, dapsone, the association of nicotinamide and minocycline or tetracycline have been tried with some success.

Finally, in all BP patients, it is important to undertake all measures aimed at preventing the complications of both the cutaneous lesions and of the treatment. Prior starting therapy, we recommend to carry out investigations to exclude potential contraindications for corticosteroid therapy as well as an up-to-date with age-related cancer screening tests recommended for the
general population. The latter should be performed according to the patient’s history, findings of the physical examination and in the presence of atypical presentations, such as onset of the disease in a middle-aged person. Finally, the possibility of a drug trigger should be always considered, since discontinuation of the implicated drug may lead to a rapid improvement.

**Riassunto**

Pemfigoide bolloso, una malattia vescicante autoimmune con manifestazioni cliniche proteiformi. Review dei recenti progressi dalla teoria alla pratica clinica

Il pemfigoide bolloso (bullous pemphigoid, BP) rappresenta la patologia vescicante subepidermica autoimmune più frequente e colpisce principalmente i soggetti anziani. Esso è associato alla produzione di autoanticorpi diretti contro l’antigene BP 180 (BP180 o BPAG2) e contro l’antigene BP 230 (BP230 o BPAg1), due componenti emidessmosomiali che promuovono la coesione dermo-epidermica. Gli aspetti clinici del BP sono estremamente proteiformi. Men-}

**References**

LEBEAU

BULLOUS PEMPHIGOID, AN AUTOIMMUNE BLISTERING DISEASE WITH PROTEIN CLUSTERNING MANIFESTATIONS


BULLOUS PEMPHIGOID, AN AUTOIMMUNE BLISTERING DISEASE WITH PROTEAN CLINICAL MANIFESTATIONS

LEBEAU

66. De Jong MC, Bruins S, Heeres K, Jonkman MF, Nieboer C, Boorsma DM et al. Bullous pemphigoid and epidermolysis bullosa acquisi-
67. Vodegel RM, Jonkman MF, Pas HH, de Jong MC. U-serrated immuno-
68. Vodegel RM, De Jong MC, Meijer HJ, Weytingh MB, Pas HH, Jonkman MF. Enhanced diagnostic immunofluorescence using biops-
69. Gammon WR, Fine JD, Forbes M, Briggaman RA. Immunofluore-
scence on split skin for the detection and differentiation of basement
70. Ishiko A, Shimizu H, Kikuchi A, Ebihara T, Hashimoto T, Nishikawa T. Human autoantibodies against the 230-kD bullous pemphigoid antigen (BPAG1) bind only to the intracellular domain of the hemidesmosome, whereas those against the 180-kD bullous pem-
phigoid antigen (BPAG2) bind along the plasma membrane of the
71. Christophoridis S, Büdinger L, Borradori L, Hunziker T, Merk HF, Hertl M. IgG, IgA and IgE antibodies against the ectodomain of
BP180 in patients with bullous and cicatricial pemphigoid and linear
73. Schmidt E, Obe K, Brocker EB, Zillikens D. Serum levels of autoan-
tibodies to BP180 correlate with disease activity in patients with bul-
77. Horsnot DP, Breneman DL, Rosen GB, Hersh CS, Cardone S, Mutat
Is allergic contact dermatitis a lifelong affliction in man?
A critical review of the literature

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The prognosis of allergic contact dermatitis (ACD) refers to its course over time with and without medical intervention. It takes into account the chances of healing, its effect on the quality of life and employment, and the financial costs for both the individual and the wider community. Notoriously, ACD is a disease with a long-lasting and relapsing course; however, at the moment, the long-term prognosis in the general population is unknown. We reviewed the most important epidemiological studies published between the 1950s and 2005, attempting to quantify the natural history of contact allergy. Recent reports appear to indicate that the prognosis of ACD is better than was previously reported; in particular, after the 1990s, the clearance occurs in up to 70% of patients, with an average between 18% and 40%. Sex and age of onset of contact dermatitis do not appear to influence prognosis; on the contrary, a personal history of cutaneous atopy, duration of symptoms before diagnosis, some types of occupations, as well as the ubiquity of contact allergens, appear to be associated with poor prognosis. Prognosis is better in patients who comply with rules of prevention. Most studies indicate that the prognosis is poorer in patients with irritant contact dermatitis than in those with ACD.

Key words: Allergic contact dermatitis - Irritant contact dermatitis - Prognosis - Patch test - Atopy - Occupational contact dermatitis - Epidemiology - Clearance.

The prognosis of a disease refers to how long it is predicted to last (its natural evolution) with and without medical treatment. In allergic contact dermatitis (ACD), and especially in occupational forms, prognosis will take into account the patient’s chances of healing, the disease’s effects on her/his quality of life and working activities and the financial costs for both the individual and the whole community.

So the more precise the information available on the prognosis of ACD, the more useful it will be to the dermatologist and the regional and national health authorities, for the following purposes:
1. To predict the course of the disease.
2. To calculate the risk of exposure to sensitizers.
3. To plan preventive measures to be adopted over time.
4. To gain medico-legal elements for examining a patient’s right to indemnity in occupational disease.

When considering the evolution of ACD over time, it is essential to consider the question: is contact allergy a lifelong disease in man? In other words, can the natural evolution of ACD be quantified?

In the present work, current data on the prognosis of ACD are analysed and commented.

Review of the literature

Numerous studies focus on the variations of contact sensitisation over time. However, they are dif-
difficult to compare for various reasons. First, there is no standard definition of the concept of healing. In other words, when should ACD patients be considered healed? In the absence of clinical manifestations over a reasonable period of time (several years), or after negative results at patch testing for the substance responsible? In our opinion, the second hypothesis should be the guiding principle when judging healing. Many studies on the prognosis of ACD report improvement or worsening of the dermatitis over time, but the clinico-morphological parameters that should support such a judgment are lacking.

Another reason why the studies are not comparable is the extremely wide variation in the duration of follow-up, from a few months to 10-15 years or more, although the mean time is quite short.

Another serious limitation is that all studies conducted so far have been retrospective and included only selected patients with severe or persistent ACD or those applying for an indemnity for occupational disease. Both these conditions involve repeated patch testing over time. So many patients who did not undergo repeated tests were excluded from the prognostic assessment, likely introducing a selection bias.

**Future prospects**

It is clear from these considerations that standardization of some clinical parameters is urgently needed, as are prospective studies on the evolution of ACD. However, a prospective study of the whole contact dermatitis population would obviously be very difficult to achieve. It would require the periodical recall (every 1-2 years) of all patients for a long time (throughout life) to repeat the patch tests. Even if they were to be recalled, how many patients would be willing to undergo such controls? Moreover, such tests would be extremely costly for both the individual and the public health service system.

For a prospective study in this particular field of skin diseases, it would also be difficult to find control subjects for comparison. For all these reasons, the behaviour of contact allergy in the general population is, and will likely remain, partly unknown.

**The prognosis of allergic contact dermatitis today**

Analyses of retrospective studies have allowed us to acquire useful data on the current situation as regards the prognosis of ACD. For this purpose, the more comparable studies have been analysed, as well as the larger ones in terms of patient series and follow-up times.

**Trend over time**

Healing has been observed in 8-77% of ACD patients over a follow-up period from 1 to more than 10 years.\(^1\)-\(^15\) In particular, epidemiological studies conducted up to the 1980s seem to indicate poor prognosis, as healing occurred in only 8-33% of cases.\(^1\)-\(^11\) Instead, those conducted after 1990 seem to show a clear improvement in prognosis, where healing can occur in up to 70% of patients.\(^12\)-\(^16\)

This progressive improvement is likely due to a series of factors. First, standardization of diagnostic procedures has had an important role, together with improvement in identifying irritant and sensitising contactants, which has made patch tests one of the most precise and reproducible *in vivo* methods currently available. Finally, advances in health education have taught patients to pay greater attention to the causes of contact dermatitis and to adopt possible prevention measures in both the working and the leisure time environment, thus contributing to a higher index of healing of the disease.

**Influence of time of diagnosis**

The prognosis of contact dermatitis seems to be worse in proportion to the length of time elapsing before the diagnosis is made.\(^17\)-\(^21\) Apart from the delay in instituting preventive measures, this is likely due to immunological reasons, because it is clear that the longer the allergic condition has lasted, the more evident the failure of the regulation mechanisms, and, therefore, the probability that the phenomenon will be difficult to control.

**Influence of age and sex**

The studies investigating this aspect do not seem to show that the age of onset of the dermatitis has an influence on its prognosis.\(^4\),\(^11\),\(^12\),\(^15\),\(^21\)-\(^23\) Nor have significant prognostic differences been reported among patients in different age groups.\(^15\)

Moreover, most studies indicate no significant sex-related difference in the prognosis of either occupational or non occupational ACD. However, some
authors have observed a statistically more favourable prognosis of occupational ACD in men than in women. This tendency to a greater persistence of ACD in the working environment in women may, in our view, be only apparent and, in practice, be due to concomitant contact irritation of the hands due to “wet” working conditions at work and at home.

In brief, the prognosis of occupational and non occupational ACD is the same in men and women. There may be slight variations due to different types of working activities.

Influence of working activity

Most contact dermatitis patients who change their jobs do so for other reasons and not because of their dermatitis. On the contrary, many patients prefer to continue with their original working activity despite the onset of occupational dermatitis. In a follow-up study over 10-13 years, it was found that only 20% of workers with contact dermatitis had changed their job as a result of the disease. It has also been pointed out that in 11-28% of subjects, the dermatitis persists even after the end of the implicated working activity.

There are contrasting opinions on the influence of the working activity on prognosis, even if long-term evolution of the dermatitis seems better in subjects who change their jobs than in those who do not. In any case, there can be no doubt that prognosis is better in those who avoid exposure to the specific contactants that caused the dermatitis than in those who continue to be exposed to the allergens in question.

The jobs with the worst prognosis seem to be in the building and metalworking industries, followed by hairdressing, the food industry and, to a lesser extent, professional health care. However, it is also true that these activities involve “wet” conditions, and so it is quite possible that the allergy may be associated with contact irritation.

The prognosis of occupational contact dermatitis has not only a bearing on the percentage of healing, but also on the costs of working activities of the individual, as well as on the financial costs to be borne by the patient and the whole community. Since the 1990s, the quality of life has become an ever more important index in the evaluation of prognosis. It has been shown that 80% of patients with hand eczema complain of disturbances in their relational life due to the skin problem. In a list of 15 skin diseases generally considered as serious, professional contact dermatitis ranks seventh, pressure urticaria first and melanocytic nevus last. In a study involving 339 patients, those with professional ACD complained of greater interference of their disease with sleeping, social activities and home life than those suffering from non occupational contact dermatitis.

Some patients who changed their jobs reported a significant decline in their quality of life compared with those who continued with their chosen employment despite their allergic condition.

As to the economic burden of professional contact dermatitis, expenses include medical care, loss of working days and productivity, indemnities and job retraining. To these should be added economic costs of the effects on the quality of life. In terms of individual costs, it appears that an individual’s earning power is notably reduced. Estimates of the annual costs of occupational skin diseases are as high as US$222 million to 1 billion in the U.S., AUS$12 million in New South Wales, Australia, and DM 100,000-200,000 (figures for 1993) in Germany.

Influence of different allergens and site of the disease

The contact allergens causing the greatest persistence of the dermatitis, and hence the worst prognosis, are nickel in women (healing in 7-30% of cases) and chrome in men (healing in 10-72%). The prognosis for contact allergy to rubber additives seems to be slightly better (with a 50% rate of chronic disease), as also to epoxy resins, formaldehyde and its releasing agents.

The reason for the chronic nature of dermatitis resulting from these allergens very likely has to do with their ubiquity in the working and leisure environment. In fact, it is practically impossible to avoid contact with these substances in daily life.

Inevitably, the skin site with the worst prognosis is the hands. Various studies have reported a chronic rate of up to 90% of ACD of the hands, regardless of medical treatment and preventive norms. There are obvious reasons for this: the etiology of hand eczema includes exogenous and endogenous factors, namely, contemporary exposure to irritant and sensitising substances, together with individual variations in efficacy of the skin barrier.
Influence of atopy

According to some studies, a personal history of atopy, especially of the skin, seems to have a significant, negative effect on the prognosis of ACD. Conversely, other studies have not shown a significant difference in the prognosis of ACD in atopic versus non atopic workers, even in subjects suffering from allergy to chrome. Further epidemiological studies are needed to confirm or rule out the role of atopy in the chronic evolution of contact dermatitis.

Prognosis of contact allergy versus irritation

In general, there is stronger evidence for poor prognosis in subjects with irritant contact dermatitis (ICD) than with ACD, the estimated ratio of healing being approximately 2 to 3. Instead, some studies have reported a worse prognosis for ACD than ICD. To complete the picture, other studies have indicated no difference in prognosis between the two diseases. In our opinion, ICD has a worse prognosis than ACD. In fact, in the former the dermatitis is more likely to persist even after cessation of occupational contact with the irritant substances, owing to their ubiquity even in the non professional environment. Obviously, this applies to weaker irritants and not to strongly alkaline or acid substances for which more efficacious prevention can be undertaken.

Influence of patient instruction in preventive practices

Educating patients about how best to institute preventive practices in her/his life has a very important role in improving the prognosis of ACD. Various studies looking into this aspect have elicited extremely interesting data, showing that only 23% of patients still remember which allergens are responsible for their dermatitis at 2-3 years from patch testing. Only 55% keep preventive information leaflets and of these, 23% have difficulty in finding where they put them. In many cases the leaflets are not read carefully; this is particularly frequent in cases of polysensitisation and cross reactions (when the patient has to worry about several substances).

The same studies confirmed a notably improved prognosis in those patients who had accurate full knowledge of the disease and the allergens responsible, as compared with those who had difficulty in remembering the causal agent. As patients’ memory of the information imparted about their disease declines over time, it would be well to recall them for refresh sessions every 1-2 years.

Notwithstanding the undoubtedly positive trend of preventive measures on ACD prognosis, there is still some evidence in contrast. In 75% of subjects with nickel allergy, sensitisation persists despite careful avoidance of contact with the metal. Our personal data show that in 25.6% of cases with contact allergy to easily avoided substances (neomycin and other topical medications), patch tests are positive even after a number of years. These findings were confirmed in an interesting study that demonstrated that only 29% of patients sensitised to dinitrochlorobenzene or dibutyl esters of squaric acid (both used to treat alopecia areata) had lost their sensitisation when retested after 3-9 years. This occurred despite the fact that the patients were known never to have come in contact with the substances since the treatment of alopecia areata.

Conclusions

Unlike what occurs in some strains of mice, contact allergy in humans is thought to persist throughout life, or at any rate for many years. In the present work we have examined the most important epidemiological studies (albeit retrospective) on the progress of ACD in order to quantify the natural history of the disease. The present analysis shows that it is not yet possible to establish the duration of contact allergy and that its long-term prognosis in the general population remains unknown. In recent years the prognosis of ACD has improved remarkably: since the 1990s the proportion of negative results to previously positive patch tests has risen to mean values ranging from 18% to 40%. This means that in about 1/3 of cases there is clearance of the dermatitis, even if only after several years.

Various factors contribute to the chronic nature of ACD, above all the ubiquity of some allergens that are difficult for patients to avoid in daily life, as well as a lack of compliance with indicated prevention practices. Instead, the age of onset of the disease and the sex of the patient do not seem to affect prognosis; the tendency to a more chronic ACD of the hands in women is, in our view, only apparent, due to the frequent coexistence of contact irritation attributable to the wet
IS ALLERGIC CONTACT DERMATITIS A LIFELONG AFFLICTION IN MAN?  

BONAMONTE

Riassunto
La prognosi della dermatite allergica da contatto. Valutazione critica della letteratura

La prognosi della dermatite allergica da contatto (DAC) si riferisce al decorso nel tempo dell'affezione con e senza intervento medico. Essa comprende non solo la possibilità di guarigione, ma anche l'effetto sulla qualità della vita e della attività lavorativa, e così finanziari per il singolo individuo e l'intera comunità. La DAC è un'assicurazione a notoria natura cronico-recidivante, a tutt'oggi, tuttavia, la sua prognosi a lungo termine nella popolazione generale non è nota. Inoltre, non è definita se la DAC è una malattia esplosiva o una malattia cronica. Pertanto, la prognosi della DAC, pur essendo ancora oggi piuttosto povera, nel corso degli anni è migliorata, in particolare dopo gli anni '90, con tassi di guarigione che in alcuni studi arrivano al 70% e oltre (con valori medi del 18-40%). Il sesso e l'età influenzano la prognosi della DAC, ma non sembrano avere un effetto significativo sulla durata della malattia. La scomparsa di una siringa allergica da contatto può indicare un miglioramento della prognosi. In generale, la prognosi della DAC è peggiore rispetto a quella della dermatite acuta da contatto (ACD). Tuttavia, la prognosi della DAC è migliore rispetto a quella della dermatite cronica da contatto (ICD). In particolare, la prognosi della DAC è più povera, verosimilmente a causa delle difficoltà della prevenzione per la mancata conoscenza degli agenti in causa.


References
Atopy Patch Test with house dust mites and atopic dermatitis: an update

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It has been hypothesized that allergens usually responsible of atopic manifestations of respiratory type, which are the house dust mites (HDM), can act as triggers of the aggravation of the atopic dermatitis (AD) through the cutaneous direct contact. Many studies, carried out in the last 20 years using the patch test with HDM, suggest that the eczema can be elicited in the skin of a subgroup of patients with AD through an immunomediating mechanism. This patch test, that is also carried out with other airborne-allergens, has been called Atopy Patch Test (APT). In the present paper the main methodological problems of APT with HDM and the rates of positivity in the AD subjects, reported by the literature are examined. The evidences showing that an immunopathologic mechanism is involved in the outcome of APT are also reviewed. According to the available studies, the allergen, after the penetration in the skin, would stimulate a lymphocytic reaction via IgE-bearing Langerhans cells. In a premature phase the inflammatory infiltration is composed mostly by Th-2 lymphocytes, secreting IL-4 and IL-5. In a later phase a switch towards an infiltration composed mostly by producers of IFN-γ Th-1 lymphocytes has been observed. It has been proposed that APT can be used, in a subgroup of patients with AD, as a provocation test, analogous to bronchial or nasal provocation tests for asthma and rhinitis, and it has been supposed that the positivity of the test would have predictive significance for clinical worsening of AD after the allergen exposure. The papers supporting this hypothesis are reviewed. Finally, the problem of APT-positivities observed in some non-eczematous patients with respiratory or constitutional atopy and in some nonatopic subjects is considered and the possible explanations of this results are examined.

KEY WORDS: Atopic dermatitis - Atopy Patch Test - Dermatophagoides pteronyssinus - Dermatophagoides farinae - House dust mites.

The role of the house dust mites (Dermatophagoides pteronyssinus and Dermatophagoides farinae) in the physiopathology of the atopic dermatitis (AD) is still somewhat controversial, even if many clinical and experimental evidences give these organisms a central role as factors provoking the itch and worsening the clinical expression of the disease. The altered permeability of the atopic skin favours the contact sensitization of allergenic substances and atopic subjects are predisposed to this sensitization in the same way of the nonatopic ones. Therefore, it has been hypothesized that also allergens usually responsible of atopic manifestations of respiratory type, like the house dust mites, can act, with an immunomediating mechanism, as triggers of the aggravation of the eczema through the cutaneous direct contact. Many patients with AD have a
precocious IgE-mediated sensitization to the house dust mites, proved by elevated circulating specific IgE or by positive Skin Prick Tests (SPT). There are clinical evidences, moreover, that worsening of AD can be caused by the inhalation of the house dust mites. However, while the trigger action on the respiratory clinical manifestations in the subjects with AD and allergic rhinitis and in those with AD and bronchial asthma, induced by IgE-linked allergens, is universally recognized, the involvement of these allergens in the cutaneous manifestations of the patients with AD is still refused by many authors. They think, in fact, that the worsening or the arising of the symptoms can be caused by the irritant action of the dust on a highly sensitive skin, or by the direct inflammatory action of the mites through their proteolytic activity. Many studies, carried out in the last 20 years using the patch tests with house dust mites, suggest that the eczema can be elicited in the skin of a subgroup of patients with AD through an immunomedi­ated mechanism. This test, that is also carried out with other airborne-allergens, has been called Atopy Patch Test (APT).

**Atopy Patch Test. Methodology and standardization**

After the first study of Mitchell et al. in 1982, many reports in the literature have been performed using the APT. The rates of positivity in the subjects with AD varied, in the different studies, from 15% to 100%. This variability has been ascribed to different employed methods and to various degree of concentration and purification of the allergen. The test indeed has been carried out on scarified skin, after tape skin stripping and after sodium lauryl sulfate (SLS) application, in order to favor the penetration of the allergen, or on healthy skin. The allergen has been used at different concentrations, dosed in PNU or BU, solved in the solution employed for the SPT or vehicled in petrolatum. The main antigens of the *D. pteronyssinus* and of the *D. farinae* have been isolated from the stool and from the bodies of the mites (Der p1 and Der f1/ Der p 2 and Der f 2), but many studies have been performed using whole cultures of house dust mites and culture extracts, because of the high costs of purified allergens. Therefore, the proteic content of the extracts was not limited to allergenic proteins and sometimes the allergen concentration was not definite. Now trade extracts whose contents are titrated on the basis of the amount of Der p1 are available, and that make valid the dilution and reproducible the test results. Moreover, most of the more recent reports have been performed applying the patch test on the non pretreated healthy skin of the back, and this by now seems to be the technique with the higher specificity and reproducibility. The reading of APT is carried out usually after 48 and 72 h, employing the same criteria of patch tests used for the diagnosis of contact dermatitis. In this way the rates of positivity of APT range, in the different studies, between 20% and 80%. In Table I results of the main studies available in literature are reported, according to the different allergen extracts and methods used.

**Atopy Patch test and Skin Prick Test**

A high agreement between the APT-positivity and the positivity of the SPT for house dust mites or the presence of specific elevated serum IgE has been observed in many studies. Nevertheless it has been also found that a small percentage of APT-positive subjects had negative SPT for mites or low specific IgE. That leads to presuppose that, if an immunological mechanism is responsible of the positive results to the test, this can be not always closely correlated with the immunologic response of immediate type.

**Atopy Patch Test. Immunopathologic mechanism**

The immunological response that subtends to the positivity of APT has been explained by some studies carried out on the tested skin and on the serum of the patients. The allergen, after the penetration in the skin, would stimulate a lymphocytic reaction via the IgE-bearing Langerhans cells. They would then release chemotactic factors for eosinophils and basophils, that would migrate to the skin. The allergen, after the penetration in the skin, would stimulate a lymphocytic reaction via the IgE-bearing Langerhans cells. They would then release chemotactic factors for eosinophils and basophils, that would migrate to the skin. In a premature phase the inflammatory infiltration is composed mostly by Th-2 lymphocytes, secreting IL-4 and IL-5. In a later phase a switch towards an infiltration composed mostly by producers of IFN-γ Th-1 lymphocytes has been observed. This experimental model seems to be applicable also in the eczematous lesions of AD, in which lymphocyte infiltrates with analogous characteristics would be present respectively in the premature and in the chronic lesions, and it would clear also the role of the IgE and the antigen presenting cells in the pathogenesis of the disease. Langeveld-Wilschut et al. have, moreover, showed that a positive reaction to APT requires the presence of IgE+CD1a+ cells in the healthy skin, and Wistokat-Wulfing et al. have found as the APT-positivity is associated to the proliferation and activation of allergen-specific circulating T lymphocytes.
TABLE I.—Main reports on Atopy Patch Test (APT) with house dust mites: rate of positivity, allergenic extracts and employed methods.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Positivity</th>
<th>Allergenic extract and concentration</th>
<th>Vehicle</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark et al.</td>
<td>1989</td>
<td>37%</td>
<td>Extract for prick test w/v 1:20</td>
<td>Glycerine at 50%</td>
<td>Healthy skin; Tape stripping</td>
</tr>
<tr>
<td>Van Voorst Vader et al.</td>
<td>1991</td>
<td>29%</td>
<td>30-600-3 000-15 000 BU/mL; 100-2 000-10 000-50 000 AU/mL; 50 µg/mL P1/Ag</td>
<td>Saline solution</td>
<td>Healthy skin; Tape stripping</td>
</tr>
<tr>
<td>Seidenari et al.</td>
<td>1991</td>
<td>6.4-41.9%</td>
<td>Whole culture of Dp: 250 Dp/mg; Lyophilized extract of Dp: 1 000-10 000 PNU/g</td>
<td>Distilled water</td>
<td>Healthy skin; Tape stripping; DMSO; SLS; Slight abraded skin; Skin pretreated by prick test with commercial allergen</td>
</tr>
<tr>
<td>Imayama et al.</td>
<td>1992</td>
<td>39.2%</td>
<td>Extracted proteins by whole bodies and faeces of Dp: 0.8-0.08-0.008 mg/mL</td>
<td>Saline solution</td>
<td>Healthy skin; Tape stripping; DMSO; SLS; Slight abraded skin; Skin pretreated by prick test with commercial allergen</td>
</tr>
<tr>
<td>Seidenari et al.</td>
<td>1992</td>
<td>6-41%*</td>
<td>Whole culture of Dp: 250 Dp/mg; Alfa purified fractions of Dp: 1 000-2 000 AU/mL</td>
<td>Distilled water/glycerco-Cola solution</td>
<td>Healthy skin; Tape stripping; DMSO; SLS; Slight abraded skin; Skin pretreated by prick test with commercial allergen</td>
</tr>
<tr>
<td>Castelain et al.</td>
<td>1993</td>
<td>20.8%</td>
<td>Extracts of Dp: 100-400-1 600 AU/mL; 100-200-500 IR/g</td>
<td>White petrolatum/glycercol solution; Glycerine-saline solution/white petrolatum</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Vincenzi et al.</td>
<td>1993</td>
<td>36.3%-73%§</td>
<td>Whole bodies of Dp/Df at 20%</td>
<td>White petrolatum/petrolatum oil</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Gaddoni et al.</td>
<td>1994</td>
<td>47.8%</td>
<td>Whole bodies of Dp/Df at 20%</td>
<td>White petrolatum/petrolatum oil</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Langeveld-Wilschut et al.</td>
<td>1995</td>
<td>35.7-50.7%*</td>
<td>Dp: 100, 1 000, 10 000, 100 000 AU/mL</td>
<td>White petrolatum/petrolatum oil</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Darsow et al.</td>
<td>1995</td>
<td>47%</td>
<td>Lyophilized extract of Dp: 1 000-10 000 PNU/g</td>
<td>Lyophilized petrolatum</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Manzini et al.</td>
<td>1995</td>
<td>21.3-54.4%*</td>
<td>Alfa purified fractions of Dp: 40 000 AU/mL; Alfa purified fractions of Dp: 20 000-10 000 PNU/g</td>
<td>Buffered saline solution/glycercol 50%; Petrolatum/Petrolatum oil</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Cabon et al.</td>
<td>1996</td>
<td>26.8%</td>
<td>Dp: 200 IR; Dp: 200 IR</td>
<td>White petrolatum</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Ring et al.</td>
<td>1997</td>
<td>36.1%</td>
<td>Lyophilized extract of Dp: 1 000-10 000 PNU/g</td>
<td>Hydrogel; White petrolatum</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Holm et al.</td>
<td>1999</td>
<td>47%</td>
<td>Freeze-dried extract of Dp: 20 000-100 000 BU/mL</td>
<td>Phosphate-buffered saline solution; White petrolatum</td>
<td>Healthy skin; Tape stripping</td>
</tr>
<tr>
<td>Darsow et al.</td>
<td>1999</td>
<td>44%</td>
<td>Lyophilized extract of Dp: 3 000-5 000-7 000-10 000 PNU/g</td>
<td>Petrolatum/Petrolatum oil</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Varela et al.</td>
<td>1999</td>
<td>58.8%-35.3%</td>
<td>Mite extract-100 µL</td>
<td>Petrolatum</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Inzilov et al.</td>
<td>2000</td>
<td>58.8%</td>
<td>Whole purified bodies of Dp/Df at 20%</td>
<td>White petrolatum/petrolatum oil</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Janos et al.</td>
<td>2001</td>
<td>62.5-87.2%*</td>
<td>Whole bodies of Dp/Df at 20% diluted 0.1% and 1.25%</td>
<td>Petrolatum</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Seidenari et al.</td>
<td>2002</td>
<td>66.6%</td>
<td>Whole bodies of Dp/Df at 20%</td>
<td>Petrolatum</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Inzilov et al.</td>
<td>2003</td>
<td>47.7-66.8%</td>
<td>Whole purified bodies of Dp/Df at 20%</td>
<td>White petrolatum/petrolatum oil</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Bygum et al.</td>
<td>2003</td>
<td>37%</td>
<td>Dp: 2.5-10 mg/mL; Mite bodies of Df: 25 000 AU/mL</td>
<td>Aqueous solutions</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Seidenari et al.</td>
<td>2003</td>
<td>49%</td>
<td>Whole bodies of Dp/Df at 20% and 40% (Der P1: 300 µg/g)</td>
<td>Petrolatum/Petrolatum oil</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Inzilov et al.</td>
<td>2004</td>
<td>35.7-41.6%*</td>
<td>Whole purified bodies of Dp/Df at 20%</td>
<td>White petrolatum/petrolatum oil</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Inzilov et al.</td>
<td>2004</td>
<td>51.3%</td>
<td>Whole purified bodies of Dp/Df at 20%</td>
<td>White petrolatum/petrolatum oil</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Oldhoff et al.</td>
<td>2004</td>
<td>62.9-76.9%*</td>
<td>Whole purified bodies of Dp/Df at 20%</td>
<td>White petrolatum/petrolatum oil</td>
<td>Healthy skin</td>
</tr>
</tbody>
</table>

*) Different rates based on the different concentrations of allergens and on the different employed techniques; † Adults; § Children; #Dp; ^Df; † Extrinsic AD; ¶ Intrinsinc AD; Dp: Dermatophagoides pteronyssinus; Df: Dermatophagoides farinae; AU: Allergy Unit; AUR: Activity Unit by RAST; PNU: protein nitrogen unit; BU: biological unit; IR: index of reactivity.
All these data would confirm as the APT can be considered a specific test, whose positivity is determined from a delayed immunologic response, in which Langerhans cells with specific IgE fixed on their surface play a fundamental role. Probably Langerhans cells are not the only ones presenting the allergen to lymphocytes. In fact, it exists an observation according to the APT with house dust mite would be positive also in a rate of patients suffering from ‘intrinsic’ AD, namely the AD form in which total serum IgE are normal, specific SPT are negative and circulating specific IgE are low. Moreover, a recent study on the inflammatory infiltrate in the site of APT has shown a high epidermal migration and an activation of inflammatory dendritic epidermal cells (IDECs). IDECs are antigen presenting cells with FcεRI receptors on their surface which are observed with the Langerhans cells in the chronic phase of AD. The migration and activation of IDEC have been observed both in ‘extrinsic’ and ‘intrinsic’ AD. The aforesaid considerations suggest, therefore, that the presence of specific-IgE is not always a prerequisite for this type of immunologic reaction.

### Atopy Patch Test and skin irritation

As partly we have reported above, some criticism has been aroused to the specificity of APT and, consequently, to an immunologically mediated action of the house dust mites as worsening factor of AD. These perplexities are based on the proteolytic action of the mite, which would yield the inflammatory action with a direct mechanism, particularly when high concentrations of allergens are used. Deleuran et al., testing a group of subjects with house dust mites and trypsin and papain at the same time, observed a high number of false positive reactions, and concluded that there is a direct irritating action of the mite. Moreover, it is reported that house dust mites, through their proteolytic activity, can directly induce the release of proinflammatory cytokines from bronchial epithelium.

These remarks seem to be denied by the observations of Mascii et al., who showed that this direct action is not produced on the keratinocytes, and by the report of Bygum et al., in which no reaction to trypsin has been found in the APT-positive subjects.

Another criticism aroused to the specificity of APT is based on the irritability of atopic skin, which could easy cause false-positive responses. These doubts seem to be refused by some observations. For instance studies about the reproducibility of the test resulted satisfactory, showing values of statistic \( \kappa \) (Cohen coefficient) ranging from 0.60 to 1, in agreement with the variability of concordance obtained by patch tests used in contact dermatitis (Table II). Moreover, no difference has been found in cutaneous irritability, tested by SLS, between APT-positive and APT-negative AD patients.

### The Atopy Patch Test as a provocation test

Ring et al., assumed that APT can be used, in a subgroup of patients with AD, as a provocation test, similar to bronchial provocation test for asthma or nasal provocation test for rhinitis. According to these authors, the positivity of the test would have predictive significance for clinical worsening of AD after the allergen exposure. This hypothesis starts from some clinical observations. For instance the appearance of AD has been correlated with the exposure to high allergen concentrations of house dust mites in infancy. Some studies have described the improvement of AD after removal of environmental airborne-allergens, even if other studies have shown no regression of the total activity of the disease after the removal of domestic dust. The hypothesis that APT was a provocation test has in first time been confirmed from the observations of Darsow et al., who recorded a significant association between positive house dust mites-APT and an air-exposed clinical pattern of the eczema, in which lesions were mostly located on the exposed sites (face, hands, forearms). This remark has not been confirmed in the subsequent reports of the same authors, neither from reports published by other groups. Instead, according to other observations a positive correlation between clinical history of the patient and APT-positivity would exist, i.e. there is an association between the worsening of AD in APT-positive patients and their exposure to dust mites in houses. In this case some discordant observations exist as well: for instance, Gutgesell et al. have found in a group of patients an unexpected inverse correlation between the amount of the allergen in the dust of the mattresses and the reactivity to APT.

### Atopy Patch Test in the non-eczematous atopic patients and in nonatopic subjects: an open problem

Various reports have found an APT-positivity also in patients with respiratory or constitutional atopy.
in patients with AD. In one of the two reports the positive results with a significant lower rate and intensity than atopic patients without AD and the nonatopic ones showed defined the intensity of the response. In both reports the subjects, evaluating their positivity by a scoring, which patients with respiratory/constitutional atopy and in healthy used APT with house dust mites in patients with AD, in activity in these individuals is opened. Two recent studies confirmating a good reproducibility also of the grading of overlying in the 3 groups repeating the test some time after, percentages of positivity and the intensities of response were considered about the positive evidences of the specificity of the test, that was reproducible also in patients with respiratory atopy and in a small groups of healthy subjects rate ranging from 5% to 40%. On the basis of the aforesaid functional these cells and T-lymphocytes in the site of presenting cells could play a central role in these subjects as well. For this purpose, it would be interesting to study as well. For this purpose, it would be interesting to study as well. For this purpose, it would be interesting to study presenting cells could play a central role in these subjects as well. For this purpose, it would be interesting to study presenting cells could play a central role in these subjects as well. For this purpose, it would be interesting to study presenting cells could play a central role in these subjects as well. For this purpose, it would be interesting to study presenting cells could play a central role in these subjects as well. For this purpose, it would be interesting to study presenting cells could play a central role in these subjects as well. For this purpose, it would be interesting to study presenting cells could play a central role in these subjects as well. For this purpose, it would be interesting to study presenting cells could play a central role in these subjects as well. For this purpose, it would be interesting to study presenting cells could play a central role in these subjects as well. For this purpose, it would be interesting to study presenting cells could play a central role in these subjects as well. For this purpose, it would be interesting to study presenting cells could play a central role in these subjects as well. For this purpose, it would be interesting to study

**Table II.—Main reports on the reproducibility of the APT with house dust mites.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method</th>
<th>N. AD</th>
<th>Statistic test</th>
<th>N. NEAP</th>
<th>Statistic test</th>
<th>N. NA</th>
<th>Statistic test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langeveld-Wild-</td>
<td>1995</td>
<td>APT repeated in the same subjects after 6 months</td>
<td>5</td>
<td>Statistical Kappa (Cohen coefficient): 1</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>schut et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ingordo et al.</td>
<td>2000</td>
<td>APT repeated in the same subjects after a variable-period between 15 days and 18 months</td>
<td>17</td>
<td>Statistical Kappa (Cohen coefficient): 0.83</td>
<td>12</td>
<td>Statistical Kappa (Cohen coefficient): 0.65</td>
<td>11</td>
<td>Statistical Kappa (Cohen coefficient): 1</td>
</tr>
<tr>
<td>Seidenari et al.</td>
<td>2002</td>
<td>APT applied simultaneously on the right and the left sides of the back</td>
<td>30</td>
<td>Statistical Kappa (Cohen coefficient): 1</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Bygum et al.</td>
<td>2003</td>
<td>APT repeated after 6 weeks</td>
<td>23</td>
<td>RR: 0.69-0.81*</td>
<td>NT</td>
<td>25</td>
<td>RR: 0.65-0.96*</td>
<td></td>
</tr>
<tr>
<td>Ingordo et al.</td>
<td>2004</td>
<td>APT repeated in the same subjects after a variable-period between 3 months and 4 years</td>
<td>8</td>
<td>Statistical Kappa (Cohen coefficient): 0.60-0.71*</td>
<td>37</td>
<td>Statistical Kappa (Cohen coefficient): 0.75-0.77*</td>
<td>19</td>
<td>Statistical Kappa (Cohen coefficient): 0.85-0.73*</td>
</tr>
</tbody>
</table>

*) Different rates based on the different concentrations of allergens and on the different employed techniques; †Adults; § Children; #Dp; ^Df; † Extrinsic AD; ¶ Intrins

### Riassunto

Atopy Patch Test con acari della polvere domestica e dermatite atopica: stato dell’arte

Si è ipotizzato che allergeni normalmente responsabili di manifestazioni atopiche di tipo respiratorio, quali gli acari della polvere domestica (APD), possano agire, quali trigger dell’aggravamento della dermatite atopica (DA), attraverso il contatto diretto cutaneo. Numerosi studi, condotti nell’arco degli ultimi 20 anni utilizzando i patch tests con gli APD, suggeriscono che l’eczema possa essere elicitato sulla cute di un sottogruppo di pazienti con DA attraverso un meccanismo immuno-mediazione. Questo tipo di patch test, che viene effettuato anche con altri aeroallergeni, è stato chiamato Atopy Patch Test (APT). Nel presente articolo vengono esaminati i principali problemi metodologici dell’APT con APD e le percentuali di positività del test nei soggetti con DA testati, sulla base della letteratura. Vengono altresì riassunte le evidenze relative al coinvolgimento di un meccanismo immunopatologico nel la risposta positiva al test. Secondo gli studi disponibili, l’allergene, dopo essere penetrato nella cute, stimolerrebbe una reazione linfocitaria attraverso l’intervento di cellule di Langerhans che hanno le IgE fissate sulla loro superficie. In una fase precoce l’infiltrato infiammatorio è costituito prevalentemente da linfociti Th-2, produttori di IL-4 e IL-5. In una fase più tardiva si è osservato un viraggio verso un infiltrato costituito da linfociti prevalentemente Th-1, produttori di IFN-γ. È stato proposto che l’APT possa...
essere usato, in un sottogruppo di pazienti con DA, come un test di provocazione, analogamente a quanto avviene per il test di provocazione bronchiale nell’asma o il test di provocazione nasale nella riniti, ed è stato supposto che la positività del test abbia un significato predittivo per il peggioramento clinico della DA dopo esposizione all’allergene. Vengono riassunti gli articoli che confor- tano tale ipotesi. Infine viene considerato il problema delle pos- sistività all’APT occasionalmente rilevate in pazienti con atopia respiratoria o costituzionale e in soggetti non atopici, e vengono esa- minate le possibili spiegazioni di questi risultati.


References


INGORDO

INGORDO ATOPY PATCH WITH HOUSE DUST MITES AND ATOPIC DERMATITIS


Tinea faciei: a diagnostic challenge

M. R. ZAMPINO, F. OSTI, A. VIRGILI, M. CORAZZA

Tinea faciei is an unusual dermatophytosis which can mimic several facial dermatoses and thus lead to a delayed diagnosis and to an inadequate treatment. If topical steroids have been administered, this modifies the aspect of the dermatitis and induces a further delay in its recognition. We report 2 cases of tinea faciei; the first had an intriguing clinical aspect mimicking Demodex folliculitis, the other one had the clinical and histopathological aspect of chronic lupus erythematosus. The microscopic examination was decisive in both cases to make a correct diagnosis and treatment.

Key words: Dermatophytosis - Tinea faciei - Chronic lupus erythematosus - Demodex folliculitis.

Tinea faciei is an uncommon superficial dermatophytosis involving the facial glabrous skin. It has been reported worldwide, accounting for 3-4% of cases of tinea corporis.1 All age groups are involved, but two peaks have been observed: in children and in adults aged 20-40 years. Females are most frequently affected in adult age, while a prevalence for males has been observed in childhood.2 The etiological agents implicated in the pathogenesis of tinea faciei are usually Tricophyton rubrum, T. mentagrophytes and Microsporum canis.1-3 Tinea faciei may present atypical features, particularly in adulthood.2 Our case demonstrate the difficulty in recognising tinea faciei.

Clinical series

Case 1

A 29-year-old woman presented with a 4 months history of a slowly enlarging facial eruption. On clinical examination several erythematous papules, sometimes covered by scales, pustules or crusts, were symmetrically located on her cheek near the nasal vestibulum, around her lips and chin (Figure 1A). The patient complained of burning. She had previously applied a topical steroid cream for 2 months with a temporary improvement of the dermatitis. On stopping the treatment a worsening of the lesions occurred. She did not report any contact with pets or infected persons. Suspecting a Demodex folliculitis, the patient was sent for a microscopic search of the mites. Direct microscopic examination revealed a poor amount of fungal hyphal elements in the scale scraping. Despite the negativity of the cultural examination the diagnosis of tinea faciei was made on the basis of the clinical features and the microscopic survey. Treatment with oral itraconazole (200 mg daily) and topical econazole was started. Four weeks later, both the microscopic and cultural examinations were negative and clinical improvement was evident (Figure 1B).

Case 2

A 60-year-old man farmer, presented with a 1 month history of an erythematous and oedematous patch, moderately infiltrated, on the left cheekbone extending to the same cheek (Figure 2A). A clinical diagnosis of chronic lupus erythematosus

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Vol. 141 - N. 6
GIORNALE ITALIANO DI DERMATOLOGIA E VENEREOLOGIA
521
(CLE) was suspected and a skin biopsy for histopathological and immunohistochemical examination was obtained. The histopathology revealed epidermal parakeratosis, follicular keratosis, dermal elastosis and perivascular and perianexial lymphocytic infiltrate (Figure 2B). Direct immunofluorescence showed the presence of IgG, IgA, C3 at the dermal-epidermal junction. This finding suggested the diagnosis of CLE. Treatment with a topical steroid was started. Four weeks later, as there was no improvement of the lesion, a diagnosis of ringworm was suspected and a microscopic examination was made, revealing fungal hyphae; *Trichophyton mentagrophytes* was found on culture. Oral itraconazole (200 mg daily) was administered for 6 weeks until complete clinical recovery with negative microscopic and cultural examination.

**Discussion and conclusions**

*Tinea faciei* may frequently show atypical features, more often in adults. In a recent study on 84 patients with *tinea faciei*, was found a prevalence of 35.7% of atypical form caused by previous topical steroid treatments. The lack of scales and annular structures and the prevalence of papules, pustules and crusts may be deceiving and the clinical aspect may mimic other dermatoses. *Tinea faciei* may be asymptomatic or cause burning and/or itching; sunlight exposure sometimes exacerbates symptoms inducing the suspect of photosensitivity disorders. It has been estimated that *tinea faciei* is misdiagnosed in about 70% of the cases. Alteras *et al.*, in their analysis of 100 adult cases of *tinea faciei*, show that the most common misdiagnoses are discoid lupus erythematosus (52%), lymphocytic infiltration (15%), seborrheic dermatitis (11%), rosacea (8%), contact dermatitis (7%), polymorphous light eruption (3%), facial granuloma (3%). Clinical features may also mimic perioral dermatitis, psoriasis or *lichen ruber planus*.
In case 1, the clinical aspect suggested a diagnosis of *Demodex folliculitis*, however, during the microscopical search, a fungal infection was revealed. The negativity of cultural examination showed that this investigative tool is not an infallible method for diagnosis of *tinea faciei*. The histopathologic features of *tinea faciei* too, not only the clinical presentation, can be variable and aspecific. In case 2, in fact, the histological findings simulated discoid *lupus erythematosus*, like the case previously described by Meymandi *et al.* In our case, however, the diagnosis had been strongly sustained by the existence of direct immunofluorescence positivity together with the clinical and histological aspects. Alongside the possibility of histological errors, cases of coexistence of *tinea faciei* and discoid *lupus erythematosus* have also been described. The difficulty of a prompt recognition of the dermatophytic aetiology may lead to a delay in diagnosis varying from 1-6 months to several years. Misdiagnosis of *tinea faciei* frequently leads to inadequate therapy. In the Jorquera *et al.* series, 69.5% of the cases had previously been treated with topical steroids, causing the lost of typical morphologic features (*tinea incognito*) and recurrence or exacerbation of the fungal infections. Corticosteroids suppress the inflammatory reaction and symptoms; however, the impairment of the immune response may favour the persistence of the infection. Microscopic observation and cultural examination are usually performed to confirm a clinical suspect of *tinea faciei*. Nevertheless cultural negativity can occur in about 30% of cases, particularly in chronic infections. Sometimes even direct

Figure 2.—Case 2. (A) Erythematous and oedematous patch on the left cheekbone. (B) Histopathology: epidermal parakeratosis, follicular keratosis, perivascular and periadnexial lymphocytic infiltrate, evocative of discoid *lupus erythematosus*. Hematoxylin-eosin, x100.
microscopy investigation may be negative, probably because of the frequency of face washing. Deep scraping may be required to obtain a positive test, as fungal elements may be present chiefly within hair follicles.  

In conclusion, clinicians should be more strongly aware of the possibility that the atypical presentation of tinea faciei may lead to misdiagnosis and consequently avoid submitting the patient to unnecessary skin biopsies. Mycological investigation may be considered, therefore, an advisable step before proceeding to invasive measures; on the other hand, it should be remembered that negativity of microscopic or cultural examination may not exclude the diagnosis of tinea faciei.

Riassunto

Tinea faciei: una sfida diagnostica

La tinea faciei è una rara dermatofitosi che presenta caratteristiche cliniche simili a numerose altre dermatosi facciali, esponendo al rischio di diagnosi errate e di trattamenti impropri. Ulteriori difficoltà diagnostiche derivano dall’assenza di una apposizione flogistica, modificano l’aspetto clinico e istopatologico. Vengono descritti 2 casi di tinea faciei: nel primo l’aspetto clinico simula una follicolite da Demodex, nel secondo il reperto sia clinico sia istopatologico sono suggestivi di lupus eritematoso cronico. In entrambi i casi l’accertamento micologico è risultato decisivo per consentire il corretto inquadramento eziopatogenetico e il trattamento più adeguato.

PAROLE CHIAVE: Dermatofitosi - Tinea faciei - Lupus eritematoso cronico - Follicolite - Demodex.

References

Coeliac disease associated with scleroderma
A study of two cases

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Coeliac disease is characterised by gluten intolerance which determines malabsorption, owing to atrophy of the villi of the small intestine. It is caused by the inappropriate activation of certain immune responses, the mechanism of which is still unclear. It has an estimated prevalence in western countries of between 0.3% and 0.5%. Numerous autoimmune-based disorders, such as connective tissue disease, thyroiditis and a number of dermatoses may be associated with coeliac disease. The authors report the cases of a 21-year-old woman and a 12-year-old girl affected by scleroderma and celiac disease. The peculiarity of the cases is the rarity of the association; moreover, it is interesting to reflect on the clinical and immunopathogenetic links between scleroderma and celiac disease. Our own experience and reports in the literature show that the prevalence of autoimmune disorders in celiac disease is related to the patient's age at diagnosis. The relationship has been explained by the duration of exposure to gluten. In celiac disease local immune reaction, besides causing injury to the intestinal mucosa, also increases intestinal permeability, thus promoting the development of new autoimmune reactions. Based on this evidence, it can be hypothesised that the introduction of a gluten-free diet and the subsequent recovery of the integrity of the intestinal mucosa may slow down the evolution of scleroderma.

KEY WORDS: Coeliac disease - Scleroderma - Skin.

Clinical series

Case 1.—C.I., 21, female, followed for about 10 years at our operative unit, and a 12-year-old girl who recently came to us, are reported. Both were suffering from scleroderma and coeliac disease, an association that has only rarely been reported in the literature.3-7

The cases of a 21-year-old woman, followed for about 10 years at our operative unit, and a 12-year-old girl who recently came to us, are reported. Both were suffering from scleroderma and coeliac disease, an association that has only rarely been reported in the literature.3-7

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er refused intestinal biopsy) and a gluten-free diet was recommended. After following the gluten-free diet for about 3 years with evidence of good weight increase, the girl’s mother put her on a free diet. Raynaud’s phenomenon began at the age of 7 and at 9 small telangiectatic patches appeared, first on her face and then on her upper extremities and trunk. At the age of 12, sclerotic plaques appeared on her legs (Figure 1). The girl was referred to our division where she underwent cutaneous biopsy which confirmed the clinical diagnosis of scleroderma, and periungual capillaroscopy; measurement of autoantibodies showed positivity of the antinuclear antibodies (ANA) with a nucleolar pattern (titre 1:160) and Ab anti-histone positivity. In addition, a duodenal biopsy showed villus atrophy and crypt hyperplasia, and measurement of antiendomysial antibodies (EMA) with weakly positive outcome and antigliadin antibodies (AGA) with negative outcome. The patient was once again subjected to a strict gluten-free diet and she was advised to undertake a cycle of therapy with nifedipine for Raynaud’s phenomenon. From that moment on the skin lesions stopped advancing and Raynaud’s phenomenon was no longer seen. In 1997 at the age of 14, however, manometry evidenced initial oesophageal involvement. This was treated with H2 receptor antagonists and subsequently with proton pump inhibitors. At the time of writing, the patient has periodic clinical, haematocclinical and instrumental follow-ups which thus far have shown no signs of further worsening in the scleroderma.

Case 2.—I. P., 12, female, recently referred to us. At the age of 9, she was admitted to a pediatric hospital for poor weight growth. During her hospitalization she was diagnosed with coeliac disease by measuring AGAs, EMAs and antitransglutaminase antibodies (TG) (all were positive) and intestinal biopsy. The patient was put on a gluten-free diet. About 1 year after starting the diet, a sclerotic looking, long, hyperchromic plaque appeared at the abdomen at the site of a cigarette burn; over the next few months a similar lesion appeared in the left lumbar region. The plaques then extended progressively over the skin, reaching maximum dimensions of 10 cm. The child has recently been examined at our division. She presented 2 extensive, long, sclerotic, smooth surfaced hyperchromic plaques, one (Figure 2) extending from the epigastric region to left side (max diameters: 10×6 cm) and one (Figure 3) in the left lumbar region (maximum diameters: 8×4 cm), and other patches of smaller dimensions on the trunk about 1 cm in diameter. The child underwent skin biopsy with the following result: “the mor-
phological picture shows an epidermis within normal limits. The superficial derma appears slightly homogenized, the reticular shows a thickening of the collagen bands with initial extension to the hypodermal septa, with relative rise of the eccrine adnexa. The histochemical stain for elastic fibres showed thick fibres with parallel rearrangement at the epidermis. Irrelevant inflammatory quota: Routine haematological examinations proved to be within normal limits and the following autoantibodies were also measured: ANA weakly positive (titre 1:80), anti-centromere and anti-Scl 70 antibodies negative. The instrumental investigations carried out (spirometry, chest X-ray, EGDS, capillaroscopy) have thus far excluded any systemic involvement on the part of the scleroderma. In consideration of the tendency of skin signs to extend, therapy was undertaken with low dose methotrexate (10-15 mg/m²/week s.c.), a drug that is effective in controlling skin involvement, associated with the topical application of 0.03% tacrolimus ointment (1 application twice a day for 3 weeks then once a day).

**Discussion and conclusions**

Various auto-antibodies may be evidenced in the serum of coeliac subjects, even in the absence of clinical evidence of the corresspective diseases, just as AGA can be observed, even in the absence of symptoms and signs of gluten intolerance, in subjects with autoimmune diseases such as systemic lupus erythematosus, scleroderma, rheumatoid arthritis. This observation is probably related to an anomalous response to proteins in food. However, real associations between coeliac disease and many other autoimmune diseases have been reported. The prevalence of autoimmune diseases in coeliac subjects increases in relation to the age of the patient at the time of diagnosis. The literature contains few cases of association between gluten enteropathy and scleroderma. The first report goes back to 1986, the year in which Zammitt-Maempel et al. reported the case of a 63-year-old man suffering from coeliac disease associated with sclerodactyly, without any other clinical or serological features of scleroderma. In 1993 Sheehan and Stanton-King described the case of a young woman suffering from numerous autoimmune-based pathologies (coeliac disease, systemic sclerosis, rheumatoid arthritis, idiopathic thrombocytopenic purpura, pernicious anaemia, Hashimoto’s thyroiditis, exocrine pancreatic insufficiency), stressing the clinical and immunogenetic correlations between these various diseases. In 1995 Marguerie et al. reported 2 cases of patients suffering from scleroderma and coeliac disease. Recently in 2004, Gomez-Puerta et al. reported a personal series comprising 6 patients suffering from this association; the patients were prevalently female (4 of 6 cases), 5 of the 6 cases presented the localized form of scleroderma; in one case, the enteropathy had been diagnosed late at the age of 49.

Apart from the rare reports of similar cases of scleroderma-coeliac disease association in the literature, the cases described by us appear interesting because of what they say as regards possible clinical and pathogenetic correlations between the two diseases. It can in fact be hypothesized that in the coeliac patient, the intestinal immune reaction typical of the condition provokes an increase in local permeability with the possible entry of various antigens into the submucosa, which could in its turn favor the development of new autoimmune reactivity. Studies of this nature would seem to point to a connection between the increased permeability and the associated autoimmune pathologies, evidencing that the prevalence of autoimmune diseases in coeliac sufferers varies with the age of the patient at the moment of diagnosis and therefore of the gluten exposure time. This fact is confirmed by our clinical experience (Table I). In the case of the first patient diagnosed with suspected coeliac disease at the age of about 1 year, the gluten-free diet had been followed for 3 years and then interrupted until the age of 12, whereas in the case of the second patient, the diet had been initiated only at the age of 9, when coeliac disease was diagnosed.
The recovery of the integrity of the intestinal mucosae in coeliac patients suffering from connectivitis, probably permits a slow down in the evolution of this latter pathology, as the case of the young woman followed for about 10 years at our operative unit demonstrates.

Parole chiave: Celiacia - Sclerodermia - Cute.

References
Confluent and reticulated papillomatosis (Gougerot - Carteaud): report of a case successfully treated with tazarotene

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Confluent and reticulated papillomatosis of Gougerot and Carteaud is an uncommon dermatosis, which is most frequent after the puberal age. It occurs sporadically, although familial cases have been reported. It is characterized by flat, verrucous papules, that mainly appear on the neck and on the trunk. They have a tendency to coalesce, forming plaques, with a reticulated pattern, peripherally. The eruption is chronic with exacerbations and remissions. A keratinocyte differentiation and maturation alteration is the most probable aetiology. Endocrine disorders, genetic factors, photosensitivity and abnormal tissue reaction to fungi have also been suggested as causative agents. Ultraviolet light exposure and avitaminosis have been reported as triggering factors. Many therapies have been suggested: antibiotics, retinoids, calcipotriol, antifungals, but also vitamin A, urea, salicylic acid and sodium thiosulfate. We describe the case of an 11-year-old child with asymptomatic, well-demarcated, grey-brownish papules and plaques on the neck and on the trunk in a typical confluent and reticulated pattern. The child was otherwise in good health. She was treated with 0.05% tazarotene gel, twice daily and within 2 months the lesions had completely regressed. Therefore, we believe that, in the confined form, treatment with local retinoids may be an effective, safe alternative to systemic retinoid therapy.

KEY WORDS: Papillomatosis, Papillomatosis, reticulated - Keratinization - Tazarotene - Therapy.

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ulating cell differentiation, like topical and systemic retinoids, besides calcipotriol.7

We describe a case of confluent and reticulated papillomatosis of Gougerot and Carteaud, successfully treated with tazarotene. As far as we know, this drug has been used only one time in the therapy of confluent and reticulated papillomatosis.5

Case report

An 11-year-old Caucasian female was referred to us by her parents in September 2005. About 2 years before, a hyperpigmented, roundish, well-demarcated, small, scaling patch had appeared in the nuchal region. Subsequently, it had enlarged in size until it increased the whole nuchal region. One year before, hyperpigmented, roundish patches with a diameter ranging from 0.5 to 1.5 cm appeared on the neck, axillae and trunk (Figure 1). A diagnosis of acanthosis nigricans had been made; no endocrinological alteration had been found. At first observation, the patient was in good health, as by routine laboratory investigations.

The histological examination confirmed the clinical diagnosis of confluent and reticulated papillomatosis and showed, in the epidermis, verrucous hyperplasia, hyperkeratosis and basal hyperpigmentation. In the dermis, there was a perivascular lymphomononuclear infiltrate (Figure 2).

The patient was treated with 0.05% tazarotene gel, twice daily. Complete recovery was obtained after 2 months of therapy (Figure 3).

Discussion and conclusions

Confluent and reticulated papillomatosis of Gougerot and Carteaud is an uncommon dermatosis who-
se pathogenesis isn’t known at all. Different aetio-pathogenetic hypotheses led to different therapeutic approaches with various successes.

Topical and systemic retinoids and calcipotriol regulate cell differentiation and inhibit keratinocyte proliferation. Antifungals have a direct action against *Pityrosporum orbiculare* or other fungi, whose presence has been demonstrated in some lesions. It is common experience that most patients are prescribed topical or oral antifungals, because of a possible diagnosis of pityriasis versicolor, even if not confirmed by any laboratory exam.

Antibiotics, in particular tetracycline (minocycline), are used for their anti-inflammatory and immunosuppressive actions. In addition, they are able to inhibit the growth of bacteria like *Staphylococcus*. This micro-organism has been sometimes isolated from the skin lesions; its ability to produce toxins, leading to keratinization abnormalities, has been demonstrated.

Vitamin A, sodium thiosulfate, thyroid extracts and ultraviolet (UV) phototherapy have also been used.

Our patient’s response to tazarotene therapy, that had been proposed by Boyman et al. seems to confirm the hypothesis that confluent and reticulated papillomatosis is a keratinocyte hyperproliferative disorder, due to an abnormal cell differentiation. We don’t believe that confluent and reticulated papillomatosis is caused by fungi because of: 1) the inconstant isolation of different fungi from the lesions; 2) the occasional positive response to antifungal drugs.

The efficacy of systemic retinoids is confirmed by different studies; it was preferred to use a topical retinoid (tazarotene) rather than systemic therapy, in order to avoid the well known, possible side-effects of systemic retinoids.

**Riassunto**

Papillomatosi confluente e reticolata (Gougerot - Carteaud): caso clinico trattato con tazarotene

La papillomatosi confluente e reticolata di Gougerot e Carteaud è una rara dermatopatia, più frequente dopo l’eta puberale. Sono segnalati generalmente casi sporadici, sebbene siano stati descritti casi familiari. È caratterizzata da papule appena rilevate, verrucose che si localizzano generalmente al collo e al tronco. Esse tendono a confluirne formando placche, assumendo un aspetto reticolato perifericamente. L’eruzione è cronica, con esacerbazioni e remissioni.

La più probabile ipotesi eziologica è un’alterazione del processo di differenziazione e maturazione dei cheratinociti. Sono stati considerati tra gli agenti causali anche disordini endocrinologici, fattori genetici, fotosensibilità e un’anomala reazione tessutale a miceti. Sono stati considerati come fattori scatenanti l’esposizione alla luce ultravioletta e avitaminoosi.

Sono stati proposti vari approcci terapeutici: antibiotici, retinoidi, calcipotriolo e antimitocicici, ma anche vitamina A, urea, acido salicilico e tiosolfato di sodio.

In questo lavoro viene descritto il caso di una paziente pediatrica di 11 anni con papule e placche asintomatiche, ben delimitate, di colore grigio-brunastro localizzate al collo e al tronco, con tipico aspetto confluen e reticolato. La paziente era per il resto in buona salute. È stata trattata con tazarotene gel 0,05%, due volte al giorno. Dopo 2
mesi di trattamento, il quadro clinico era completamente regredito.

Gli Autori ritengono che, nelle forme delimitate, il trattamento con retinoidi locali possa essere una valida alternativa alla terapia con retinoidi sistemici.

**Parole chiave:** Papillomatosi - Papillomatosi, reticolata - Cheratinizzazione - Tazarotene - Terapia.

**References**

Xanthoma disseminatum (XD) is a rare benign form of non-Langherhans cell histiocytosis and represents a variant of normolipemic mucocutaneous xanthomatosis of unknown etiology. It is mainly reported in young to middle-aged men with a male/female ratio of approximately 2:1 and is characterized by widespread papular eruptions with preference for main body flexure and, in about 40% of cases, for mucous membranes of the mouth and the upper airways. Diabetes insipidus, attributed to xanthomatoid cells infiltration of the hypothalamic-pituitary region, develops in about 40-50% of the patients and can represent the first symptom of disease. The coexistence of anterior pituitary deficiencies with XD in adults has been described only in other 2 cases. We present a patient in whom diabetes insipidus and multiple hypopituitarism preceded the appearance of the hypothalamic infiltration as well as of the brown to red-yellowish papulonodular lesions. Histological, immunohistochemical and ultrastructural features led to the diagnosis of XD.

Key words: Xanthoma disseminatum - Non-Langherhans cell histiocytosis - Diabetes insipidus - Hypopituitarism - Hypothalamic infiltration.

Xanthoma disseminatum (XD), described for the first time as a distinct entity by Montgomery and Osterberg in 1938, is a rare benign form of non-Langherhans cell histiocytosis (NLCH) and represents a variant of normolipemic mucocutaneous xanthomatosis of unknown etiology. Caputo et al. evaluating 7 cases, proposed 3 clinical variants of XD on the basis of their evolution and prognosis: 1) a self-healing form, with a spontaneous resolution of the disease even after several years; 2) a persistent form characterized by the persistence of the mucocutaneous lesions that can cause disfiguration or severe functional complications; 3) a progressive form characterized by organ involvement as central nervous system.

Case report

In February 1997, a 26-year-old man, affected by diabetes insipidus and treated with desmopressin for 3 years, referred to the Endocrine Unit of our University Hospital. Endocrine investigation confirmed central diabetes insipidus and showed also hypogonadotropic hypogonadism, based on the decrease of serum follicle-stimulating hormone (FSH: 0.3 U/L, normal values 0.7-11.1), luteinizing hor-
mone (LH: 0.59 U/L, normal values 0.8-7.6), free testosterone (FT: 1.1 pg/mL, normal values 5.6-27) and total testosterone (TT: 0.3 ng/mL, normal values 1.8-7.7) levels, while other endocrine functions were normal. On the basis of these evidences, desmopressin treatment was continued and testosterone enantate substitution was started. Magnetic resonance imaging (MRI) of the head, performed by using a 1.5 Tesla unit (Philips Gyroscan S) with sagittal and coronal thin sections (3 mm) T1 weighted spin echo images, did not demonstrate abnormalities of the hypothalamic-pituitary region. One year later, endocrine function was reinvestigated. Diabetes insipidus and hypogonadism were still evident, but also serum growth hormone (GH: 0.1 ng/mL, normal values 0.2-2) and insulin-like growth factor I (IGF-1: 84 ng/mL, normal values 91-355) levels were decreased and the stimulation test with Pyridostigmine (PD, 120 mg per os) + growth hormone-releasing hormone (GHRH, 1 µg/kg, i.v.) did not increased serum GH appropriately (peak: 3.6 ng/mL, n.v. >16.5). Imaging of sellar region was still negative. Two years later, however, a new MRI of the head showed an isointense space-occupying lesion of the hypothalamus (10×12 mm in diameter), at the level of the tuber cinereum and the infundibulum, with a moderate and homogeneous enhancement after i.v. injection of gadolinium DTPA. Histological examination of the mass was proposed, but the patient, informed about the risk of a surgical approach, denied the authorization at the biopsy of the lesion. However, MRIs, repeated every 6 months, did not show changes in the size of the lesion and the follow-up was continued without evidences of new endocrine dysfunctions.

In May 2003, the patient noticed the onset of multiple and symmetrical yellow papular skin eruptions on the upper and lower limbs, which progressively extended to the trunk and the abdominal region, without mucous membranes involvement. Physical examination revealed cutaneous lesions involving abdomen, trunk, upper and lower limbs, more profuse at large flexures (Figure 1). They were roundish, had an elastic consistency and a diameter ranging from 3 to 7 mm.

Figure 1.—Red-yellowish nodules localized on the upper limb.

Figure 2.—Histopathological examination reveals foamy histiocytes, diffusely proliferated in the whole dermis and mixed with rare lymphocytes and polymorphonuclear leukocytes (H&E, original magnification ×25).

Their hue was variable from brown to yellow-red. The scalp, periorbital regions, palms, genitalia and oral mucosa were spared. Familiarity for lipid abnormalities or xanthomatosis was not reported.

Skin biopsy was performed for histological, immunohistochemical and ultrastructural examinations. The histological examination showed a dermal nodule composed mainly of foamy histiocytes, diffusely proliferated in the whole dermis and mixed with rare lymphocytes and polymorphonuclear leukocytes. Rare Touton and foreign body giant cells were present. The overlying epidermis was normal (Figure 2). By immunohistochemical studies, it was found the presence of a monocyte-macrophage infiltrate expressing the following immunophenotype: CD1a (OKT6) negative and S-100 protein negative.
with a MRI-documented lesion near the pituitary stalk, and somatotropic function in a 53-year-old patient (non-Langerhans cell histiocytosixanomatosis) associated with hypogonadotropic hypogonadism and multiple hypopituitarism (hypogonadotropic hypogonadism and GH deficiency).

Discussion and conclusions

The XD is mainly reported in young to middle-aged men with a male/female ratio of approximately 2:1 and is characterized by the presence of widespread papular eruptions with preference for the main body flexure and, in about 40% of cases, for the mucous membranes of the mouth and the upper airways. Although rarely, it is possible the involvement of other organs, including bone, liver, conjunctiva and cornea with respiratory complications due to the obstruction of the airways up to death for respiratory problems or secondary infections. Sporadic and unrelated associations of XD with systemic diseases, as multiple myeloma, Waldenström’s macroglobulinaemia and monoclonal gammopathy, or with endocrine diseases, as hypo- and hyperthyroidism, were also reported.

Diabetes insipidus, due to the infiltration by xanthomatoid cells of the hypothalamic-pituitary region, occurs in about 40-50% of the patients and can represent the first symptom of the disease. Also, in our patient diabetes insipidus preceded both the MRI evidence of hypothalamic infiltration and the appearance of the skin lesions by many years. Diabetes insipidus, together with growth hormone deficiency (GHD), is the main endocrine manifestation reported in patients with histiocytosis, while hyperprolactinemia (due to loss of the inhibitory dopaminergic tone), hypogonadotropic hypogonadism or panhypopituitarism are diagnosed more rarely.

To our knowledge, the coexistence of XD with hypopituitarism in adults was described only in 2 cases. Puig et al. reported that, in 1 of 4 patients with a thickened pituitary stalk, skin eruptions appeared 4 years after the beginning of diabetes insipidus, and Mahnel et al. showed impairment of gonadotropic and somatotropic function in a 53-year-old patient with a MRI-documented lesion near the pituitary stalk, histologically classified as nonspecific granulomatous disease by stereotactic biopsy. Also in our case MRI showed a hypothalamic hyperintense mass, but we did not perform a histological evaluation of the lesion.

In our patient, the disseminated papular skin eruptions, with histological and immunohistochemical features of XD, appeared 9 years after the beginning of diabetes insipidus, 6 years after the diagnosis of hypogonadotropic hypogonadism, 5 years after the evidence of GH deficiency and 3 years after the appearance of a hypothalamic mass at MRI, proving that also this rare NLCH is slow-growing and can be occult for years.

In conclusion, histiocytosis is frequently associated with diabetes insipidus but not with multiple endocrine deficiencies in adults. To our knowledge, this is the third reported case in whom XD is associated with multiple hypothalamic-pituitary dysfunction and with a MRI-proven hypothalamic infiltrative lesion.

Riassunto

Xantomatosi disseminata con infiltrazione ipotalamo-ipoisofisiaria e ipopituitarismo parziale

Nell’ambito delle istiocitosi non langerhansiane, lo xantomatosi disseminato è una xantomatosi mucocutanea normoipermética a eziologia sconosciuta. Patologia piuttosto rara, prevalentemente osservata in soggetti giovani o di età media, di sesso maschile (M/F = 2:1), è caratterizzata dalla comparsa a carattere eruttivo di elementi papulo-nodulari, di colorito variabile dal rosso al bruno camoscio, a elettiva localizzazione alle sedi flessorie, dove tendono a confluire in placche; è relativamente frequente (40% dei casi) il coinvolgimento delle mucose, in particolare cavo orale e alte vie respiratorie.

Nel 40-50% dei casi il quadro cutaneo è associato a diabete insipido, dovuto a infiltrazione xantomatosa della regione ipotalamo-ipofisiaria, e tale evenienza può rappresentare il sintomo di esordio della sindrome.

Gli Autori descrivono un caso di xantomatosi disseminata, confermata dalle indagini istologiche, immunostochimiche e ultrastrutturali, osservata in un giovane seguito da circa un decennio in ambiente endocrinologico per il progressivo subentrare di diabete insipido, ipogonadismo ipopituitarismo, deficit di ormone somatotropo e al quale era stata diagnosticata mediante IRI la presenza di massa ipotalamica.

L’associazione di questa rara sindrome, oltre che con diabetes insipido, con plurimo coinvolgimento delle funzioni ipotalamo-ipofisarie è evenienza eccezionale e questo caso rappresenta ad oggi il terzo descritto in letteratura.

References


Multiple basal cell carcinomas after X-ray epilation for *Tinea capitis*  
A case report

M. CACCIALANZA, R. PICCINNO, L. BRAMBILLA, R. GIANOTTI, S. PERCIVALLE, S. MARCA

It is reported the case of a female patient, who underwent epilation with ionizing radiations for *tinea capitis* when she was 6 years old. After 52 years it was observed the progressive onset of 10 flat and pigmented lesions on the scalp, diagnosed as pigmented basal cell carcinomas by means of histopathological investigation. Since traumatic or local irritative factors were lacking and since the role of sunlight exposure was seemingly secondary, the clinical case is reliably explained as expression of the late oncogenic action of ionizing radiations.

**Key words:** Radiation induced neoplasms - Skin neoplasms - Basal cell carcinoma - *Tinea capitis*.

Since their discovery up to the 60ies, ionizing radiations have been largely employed in medicine, also in the treatment of non-neoplastic diseases. An example is represented by the epilation action of X-rays applied to the treatment of *tinea capitis*, in times preceding the coming of modern antifungal agents. Year after year the oncogenic role of ionizing radiations has become evident and made clear, especially as far as regards the stochastic damage induced by radiotherapy.2 6

**Case report**

A woman aged 68 presented to our observation. She had undergone roentgen-epilation for *tinea capitis* when she was 6 years old, with technical modalities that obviously she was not able to describe. Over 10 years the patient has noticed the progressive onset of flat, pigmented, asymptomatic and oval shaped lesions, with a diameter ranging from 1 to 4 cm with finely scaling surface and slightly elevated borders on healthy skin, on the whole scalp. At the time of our observation such lesions were present in number of 10 (Figure 1). Besides, the patient reported she had observed a diffuse thinning of the hair (seemingly androgenetic alopecia) in the last 15 years. Family history was negative for neoplasms and in the personal history the only relevant element was the presence of diabetes type II. The patient reported she had observed a diffuse thinning of the hair (seemingly androgenetic alopecia) in the last 15 years. Family history was negative for neoplasms and in the personal history the only relevant element was the presence of diabetes type II. The patient reported she had avoided photoexposure of the scalp. Besides, no injuries or irritative factors to the scalp were reminded by her. One of the lesions of the scalp was biopsied with histopathological assessment (Figure 2), with diagnosis of pigmented basal cell carcinoma (BCC).

**Discussion and conclusions**

In the literature one can find many reports demonstrating the higher incidence of carcinoma of the scalp
(mainly BCC) in patients irradiated for tinea capitis, respect to control groups.1, 7 According to Ron et al., in particular, such risk is four-fold greater in 10 834 patients respect to the control group, while in 98% of cases the histotype is that of a BCC.

Moreover, some isolated cases of patients with BCCs of the scalp have been described, that can be attributed undoubtedly to a previous roentgen-epilation for scalp ringworm.9, 10 The interval between the irradiation and the onset of BCC in the case here described is of 52 years, and it is in the mean of the cases reported in the literature, ranging from 4 to 60 years.9, 10

It is nearly impossible to determine the total doses of ionizing radiations administered to the scalp of our patient, so as it is in most similar cases appeared in the literature. Nevertheless we could hypothesize that, since it might be probable that the patient underwent a roentgen-epilation with the method of Kienboeck and Adamson (or of 5 fields with X-ray beams partially crossing on skin surface),11 the total dose should range between 3 and 3.6 Gy for field of irradiation. However, we could not exclude that it was administered a greater dose, of about 7.5 Gy, as reported by some authors.12 Such doses are not negligible and it is to consider that sometimes previous irradiation techniques employed not filtered radiations, that were, therefore, more injuring for the skin. Finally the hypothetic role of ultraviolet radiation played on the induction of BCC on the scalp of our patient is to be discussed. Even considering the poor filtering action carried out by the sparse hair (in the last 15 years), we think we can argue that sunlight exposure have had a secondary role, as a concomitant cause, respect to the more important risk factor represented by the previous radiotherapy.

In conclusion, on the basis of all the data registered, we think we could suitably evaluate the BCC of the scalp of our patient as radiation induced.

The patient should be followed with particular attention in the future, not only as far as regards the choice of the best treatment of her BCC, but also to monitor the possible onset of other radiation induced cutaneous and/or extracutaneous neoplastic lesions.13

Riassunto

Carcinomi a cellule basali multipli dopo roentgen-epilazione per tinea capitis: descrizione di un caso

Viene riportato il caso di una paziente sottoposta, all’età di 6 anni, ad epilazione con radiazioni ionizzanti per tinea capitis. Dopo 52 anni si è avuta al cuoio capelluto la progressiva comparsa di 10 lesioni piane, pigmentarie, istopatologicamente confermate come carcinomi pigmentati a cellule basali. In assenza di traumi e di altri fattori irritativi locali ed essendo verosimilmente di secondaria importanza il ruolo della luce solare, il caso viene con attendibilità interpretato come espressione dell’azione oncogenetica a distanza delle radiazioni ionizzanti.

Parole chiave: Radiazioni - Neoplasie, radioindotte - Neoplasie cutanee - Carcinoma a cellule basali - Tinea capitis.

References

We present the case of a male patient aged 68, Italian, suffering from lepromatous leprosy, a form of leprosy brought on by a deficiency in the individual’s cell-mediated immunity. The man, who had lived in Venezuela for about 20 years, presented a widespread eruption of erythematous plaques that were not associated with any other symptoms. A biopsy of the lesions revealed the presence of a granulomatous infiltrate in the dermis, containing foamy macrophages and some lymphocytes. Ziehl-Neelsen staining revealed the presence of acid-alcohol fast bacilli in the cytoplasm of the macrophages. A search for microbacteria in the nasal mucosa using Ziehl-Neelsen staining gave a positive result, confirming the presence of acid-alcohol fast bacilli. The nasal cartilage also proved to be perforated. As a result, on the basis of the clinical, histopathological and bacteriological data, lepromatous leprosy was diagnosed. The patient was sent to a centre specialised in treating Hansen’s disease to start specific chemotherapy. Leprosy can appear in a variety of manifestations, which may go unrecognised, so it is important to perform a differentiated diagnosis with other skin diseases, particularly in countries where the disease is not endemic. This diagnosis must, therefore, be borne in mind in the presence of skin lesions and/or heat and pain anaesthesia. The case described offers the opportunity to underlinethe need to gather a detailed medical history regarding any time spent in endemic areas in the last 10-15 years, in the event of a suspected case. We also illustrate new theories regarding cell-mediated immunological mechanisms involved in the infection that affect the clinical and histopathological polymorphism of Hansen’s disease.

**KEY WORDS:** Hansen’s disease - Lepromatous leprosy - Skin.

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**LEPROMATOUS LEPROSY**

A case report

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Leprosy or Hansen’s disease is a systematic chronic infection caused by the acid-alcohol fast bacillus *Mycobacterium leprae*, which primarily affects the peripheral nervous system and the skin, and more rarely the other organs and systems.1, 2 In 1962, Ridley and Jopling proposed a 5-form classification of the disease on the basis of clinical, immunological and histopathological criteria, which is still valid.3 This classification considers two immunologically stable poles: the tuberculoid form, with a good cell-mediated immune response, a low bacterial load and a limited number of lesions, and the lepromatous variety, with an inadequate immune response, and the consequent multiplication of the bacillus and its diffusion throughout the organism, with multiple, disseminated lesions. Three variants are normally recognised between the two poles: lepromatous borderline, central borderline and tuberculoid borderline. In addition to the full-blown forms, there is also an initial form of
leprosy, known as indeterminate leprosy, in which the immune status is not yet defined.4

The incubation period of Hansen’s disease varies greatly: 3-5 years in hyperergic forms and 10-20 years in anergic forms.4

The disease is endemic in many tropical and subtropical countries of central and southern Africa, central and South America and Southeast Asia. In Italy, up until the 1970s, cases of leprosy were mainly indigenous; since then the trend has changed and today, with the exception of sporadic indigenous breeding grounds, leprosy is a disease imported by Italians who have lived in areas where it is endemic, and among immigrants from these same areas. In indigenous cases, the borderline lepromatous and lepromatous forms are most common, whereas among imported cases, the number of borderline tuberculoid patients far exceeds the others, and there are few cases of tuberculoid leprosy.4,5

Lepromatous leprosy is distinguished by a large number of highly contagious skin lesions. They break down into a polar form, in which cell-mediated immunity is completely absent, and a subpolar form. The polar form starts with widespread infiltration, affecting the face (facies leonine) and extremities in particular. The subpolar form presents papules, nodules and places with ill-defined borders and a smooth surface, both bilateral and symmetrical. In the initial stage, neither lepromatous form presents sensory loss.4

In the polar form, there is a skin infiltrate made up almost entirely of foamy macrophages that protect the papillary dermis; microbacteria are numerous. In the subpolar form the dermis is invaded by a granulomatous infiltrate made up of macrophages, with a limited number of lymphocytes and plasma cells separated from the dermis by an intact subpapillary area. Numerous mycobacteria are present.4

We present the case of a male patient aged 68, Italian, suffering from lepromatous leprosy.

**Case report**

A male patient aged 68, of Italian nationality, born and resident in Camerota, in the province of Salerno, came to our attention because of a skin condition that had emerged about 5 months earlier. The patient said that he had lived in Venezuela for about 20 years and that he had returned to Italy 7 years earlier.

A dermatological examination revealed the presence, all over his skin and particularly on the front of his chest and the
lumbar regions, of large areas of erythema, lightly infiltrated (Figures 1, 2). The rash on his extremities and on the backs of his hands was covered with light scaling, whitish in colour, while those on his trunk had a smooth surface and were rounded, the size of a coin, forming patches of erythema with polycyclic borders. On his sides, the patches of rash were finger-shaped. This rash, which showed little tendency to regress, was not associated with any other symptoms.

The patient’s medical history revealed a sclerotic-hypertensive heart condition that was being treated with ACE-inhibitors. Routine blood tests showed an increase in the inflammatory indices, particularly CRP and ESR, and the presence of a peak in the gamma zone on the electrophoretic protein scale; beta2microglobulin was 7.38 mg/L (v.n. 1.16-2.52). The markers for hepatitis B and C were negative. 

The chest X-ray was within the norm, while a scan of the upper abdomen showed a slightly enlarged spleen. A biopsy of the lesions revealed that the thickness of the epidermis was normal, with a granulomatous infiltrate of cells with a clear cytoplasm and oval nucleus (CD 1-, CDE 68 +, CD 45 +, S100 -), foamy in appearance, referable to macrophages, mixed with lymphocytes both T (CD3+) and B (CD20+) and mastocytes (CD117+). Ziehl-Neelsen screening revealed the presence of acid-alcohol fast bacilli. An ENT examination revealed that the nasal cartilage was perforated. A search for mycobacteria in the nasal mucosa using Ziehl-Neelsen screening gave a positive result, confirming the presence of acid-alcohol fast bacilli. An ENT examination revealed that the nasal cartilage was perforated. As a result, on the basis of the clinical, histopathological and bacteriological data, led to a diagnosis of subpolar lepromatous leprosy; a form seen exceptionally in imported cases, in which paucibacillary forms are evident, primarily borderline tuberculoid and more infrequently tuberculoid leprosy.

The changes in the epidemiology of Hansen’s disease, which may not be limited to sporadic indigenous breeding grounds, but may be imported into any part of the country, make it necessary to gather a detailed medical history regarding any time spent by patients in endemic areas in the last 10-15 years. Our patient was born and lived in Camerota, in the province of Salerno, an area where no indigenous breeding grounds are reported, but he had lived in Venezuela for about 20 years.

A biopsy of the lesions revealed that the thickness of the epidermis was normal, with a granulomatous infiltrate of cells with a clear cytoplasm and oval nucleus (CD 1-, CDE 68 +, CD 45 +, S100 -), foamy in appearance, referable to macrophages, mixed with lymphocytes both T (CD3+) and B (CD20+) and mastocytes (CD117+). Ziehl-Neelsen screening revealed the presence of acid-alcohol fast bacilli. An ENT examination revealed that the nasal cartilage was perforated. A search for mycobacteria in the nasal mucosa using Ziehl-Neelsen screening gave a positive result, confirming the presence of acid-alcohol fast bacilli. As a result, on the basis of the clinical, histopathological and bacteriological data, lepromatous leprosy was diagnosed. The patient was sent to a centre specialising in treating Hansen’s disease to start specific chemotherapy treatment.

Discussion and conclusions

Due to the increase in immigration from countries where it is endemic, a diagnosis of Hansen’s disease must be borne in mind in the case of skin lesions and/or heat and pain anaesthesia. The symptoms and signs of the infection may go unrecognised since leprosy can appear in a variety of manifestations, which mean that it is important to perform differential diagnosis with numerous other skin-diseases, particularly in countries where the disease is not endemic, partly due to the lack of familiarity with the disease of Italian doctors. Even in the case of our patient, the skin disease was initially and mistakenly diagnosed as parapsoriasis or skin lymphoma. Subsequently, the clinical (the large number, symmetry, bilaterality, and “dry leaf” colour of the lesions), histological (granulomatous infiltrates containing macrophages with a foamy appearance, the presence of numerous bacilli), and bacteriological data, led to a diagnosis of subpolar lepromatous leprosy; a form seen exceptionally in imported cases, in which paucibacillary forms are evident, primarily borderline tuberculoid and more infrequently tuberculoid leprosy.

The changes in the epidemiology of Hansen’s disease, which may not be limited to sporadic indigenous breeding grounds, but may be imported into any part of the country, make it necessary to gather a detailed medical history regarding any time spent by patients in endemic areas in the last 10-15 years. Our patient was born and lived in Camerota, in the province of Salerno, an area where no indigenous breeding grounds are reported, but he had lived in Venezuela for about 20 years.

The case was also an opportunity to examine the pathogenetic mechanisms of the disease. In leprosy, the distribution and number of lesions depends on the effectiveness of the individual’s cell-mediated immune response to the micro-organism. In the tuberculoid form, the macrophage engulfed the mycobacterium and presents its antigens to the T lymphocytes, which in turn produce lymphokines. These activate and inhibit the migration of the macrophages. As a result, the inflammation is circumscribed and most of the bacilli are destroyed. In lepromatous leprosy, on the other hand, there is a strictly selective deficiency in the cell-mediated immune response to M. leprae. After having engulfed the bacillus, the macrophages are not activated and, therefore, do not cause them to be destroyed. What is more, because their migration is not inhibited, the macrophages disseminate the bacterium in the organism. The cell-mediated immune deficiency highlights the humoral immune response by producing antibodies, some specific, others aspecific or self-directed. In these conditions, the release of antigens that takes place when a specific treatment is started, may cause vasculitis due to immunocomplexes. Recent studies are shedding light on the mechanisms behind these immunological phenomena, which would appear to involve numerous cytokines. The two polar forms, in particular, seem to be linked to the involvement of different subsets of T lymphocytes: in the tuberculoid form, Th1 lymphocytes seem to be involved, producing interleukin-2 (IL-2) and interferon-gamma (IFN-γ) and an efficient immune response; in lepromatous leprosy, the lymphocytes intervene, with a deficiency of IL-2 and IFN-γ, and anergy. Interleukin-12 (IL-12) also seems to play an essen-
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vano delle lesioni evidenzia la presenza di un infiltrato granu-
o, che è costituito da macrofagi schiumosi e
2. Sasaki S, Takeshita F, Okuda K, Ishii N. Mycobacterium leprae and
3. Ridley DS, Jopling WH. A classification of leprosy for research pur-
4. Nunzi E, Fiallo P, Labrada J, Veraldi S, Caputo C, editors. Dermato-
tion of interleukin-10 and interleukin-12 in mononuclear cells from leprosy patients with a Toll-like receptor 2 mutation. Immunology 2004;112:674-80.
12. Fafutis-Morris M, Guillen-Vargas CM, Navarro-Fierro S, Morales-Ortiz R, Armendariz-Borunda J. Serum IL-1ra is elevated in leproma-
Dear Editor,

We describe a case of a solitary giant keratoacanthoma (KA) of the skin and the vermillion border of the upper lip of a female patient for the peculiarity of its location.1 A 48 year-old woman was referred to the State Hospital for Skin and Venereal Diseases of Thessaloniki, Greece, with a 3.2 cm lesion on the vermillion border and the upper lip. A crateriform nodule with a depressed central core (Figure 1) appeared at the site of minimal trauma over a 6-week period.2 Histological examination confirmed the clinical diagnosis of KA, with no suspicion of malignancy.3 Due to the large size, the critical position, the benign nature and the strong possibility of spontaneous regression of the lesion, surgical excision was not attempted.4 The patient was treated with oral isotretinoin 0.5 mg/kg daily for a 3 months period.5 Two months after presentation, the tumor was still increasing in size (5.1 cm). Four months after presentation, the tumor started to regress (Figure 2) and 3 months after cessation of treatment it was completely resolved. The entire process lasted 6 months in total and left a cosmetically acceptable scar (Figure 3).

References


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Figure 1.—Lesion on the skin and the vermillion border of the upper lip.

Figure 2.—Initiation of regression of the tumor.

Figure 3.—Final clinical outcome.
Widespread tinea incognito in immunodepressed subject

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Dear Editor,

Trichophyton mentagrophytes (TM) is both a zoophile and an anthropophile species and is the etiological agent for many forms of tinea transmitted by both animal-human and human-human direct contact.

We report here a case of widespread tinea incognito by TM in a patient affected by iatrogenic Cushing’s syndrome.

A 46-year-old male was referred to our observation for the appearance 2 years before of erythematous lesions which were finely scaling and slightly itchy. They were widespread over trunk, abdomen, upper and lower limbs and face (Figure 1). Numerous follicular pustules were also present on the last-mentioned site (Figure 2). The nails on hands and feet were all dystrophic with hyperkeratosis of the nail-bed and onycholysis. Skin lesions had been treated with topical steroids, associated with calcipotriol and reliever creams but without effect. The patient, who was a worker in the zootechnical field, referred that he had been using intramuscular betamethasone in large quantities for about 3 years to relieve intense articular pain caused by arthritis. At general examination, the patient presented facies lunaris, striae distensae, muscular hypotrophy and centripetal obesity. He complained of profound astenia and marked weight loss. In addition, blood pressure values were high (AP 210/110).

KOH mycological test on skin and nail material showed numerous septate hyphae. The sample was sown onto Sabouraud dextrose agar augmented by chloramphenicol and then incubated at 37°C. After 8 days, flat creamy-white pulvulvent colonies appeared. Colony verso was brown in colour. Lactophenol blue colouring revealed macroconidia and a limited number of microconidia. Macroconidia were club-like with multisepitate, fine, smooth elements inserted into the hypha by means of narrow attachments. Microconidia were inglobate and arranged lengthwise along branched conidiophores in the characteristic bunch-like formation arranged in a cross-wise fashion with rare spiroid elements. These characteristics lead to the diagnosis of tinea incognita by TM in a patient affected by iatrogenic Cushing’s syndrome. Terbinafine was prescribed at 250 mg per day for 12 weeks. This produced total remission in skin and nail symptoms and negativity of laboratory findings. The patient also received cortone acetate at increasing lower dosage until complete suspension. The patient’s wife, who was a housewife, presented a typical large round erythmato-desquamatative patch of slow radial development, with clear scaling edges on the collar-bone area. Culture-tests revealed the presence of TM. Terbinafine at 250 mg per day for 15 days was prescribed as therapy and the clinical picture resolved. Tinea incognita is a mycotic variant which modifies clinically with the use of steroids, either systemic or topical, prescribed for pre-existing pathologies or erroneously prescribed for the treatment of the mycosis itself. The lesions have an irregular morphology, they are nonpolycyclic and appear as livid, erythematous, slightly scaling and with well-defined edges. In long-term lesions multiple follicular papules, pustules and small nodules may appear, in particular on the face. Host resistance is of fundamental influence on the clinical course of the lesions. Even though dermatophytes proliferate at corneal level and do not invade other cutaneous layers, they activate the immune system. Fungal antigen inoculation under test conditions, in particular of tricophytine and membrane glycoprotein, gives a type I acute reaction and a type IV delayed reaction. In vivo, the mycete stimulates a specific T-mediated immune response in addition to humoral reactions.

Figure 1.—Diffuse erythematodesquamative lesions on the upper limb.

Figure 2.—Follicular pustules on the face.
immunity. During Cushing’s, these systems crucial to host defence are deactivated, especially in the T-mediated component.4 Furthermore, steroids play a physiological role in the metabolism that favours the growth of many pathogenic fungi.5 Our case of tinea incognita is of peculiar interest due to the widespread nature of the dermatosis; so widespread, indeed, that most of the skin surface was involved. The literature refers no other cases of tinea incognita by TM during iatrogenic Cushing’s, although there have been many reports on atypical mycotic infections in the course of Cushing’s disease. According to the literature, treatment of choice in immunosuppressed subjects follows the standard protocols for tinea in general, although longer periods than would otherwise be applied are recommended to avoid relapses.

References

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More light on cyclosporin treatment: a case of Pyoderma gangrenosum

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Dear Editor,

Pyoderma gangrenosum is a pathology characterised by progressive cutaneous necrosis of unknown origins, with the rare possibility of self-healing, the onset of which can be characterised by pustulous, bullous or ulcerous lesions. It mainly appears in adults of both sexes, it can be associat-ed with systemic pathologies such as monoclonal gam-mopathy, myeloproliferative syndromes, arthritis, chronic inflammatory diseases of the intestine.

Often the case history is associated with a prior trauma, particularly to the lower limbs, the pain is variable, sometimes it is intense and often it is accompanied by fever, malaise and arthralgia. The diagnosis is essentially clinical, the histological aspect is often aspecific. Where the presence of systemic pathologies normally associated with Pyoderma gangrenosum is excluded, the treatment that is generally more effective consists of systemic therapy with the combined use of cortisone and cyclosporin.1-4 Other forms of treatment used with variable results are sulfones, cofazimine, minocycline, tetracyclines, vancomycin, mezlocillin, azathioprine, methotrexate, chlorambucil, cyclophosphamide, thalidomide and methylprednisolone. Local topical treatment had little effectiveness.

This case deals with a 60-year old patient who had lost of substance over an irregularly shaped area measuring 7 cm × 6 cm in diameter on the right leg (Figure 1). The lesion had edges that were slightly raised, undermined and yellowish-grey in colour. The base had purulent tracts and granulation tissue of a bright red colour. The perilesional skin was bright red in colour. Onset of an erythematous nodular element surmounted by pustulous vesicles had been reported about 20 days beforehand, which had then evolved in a loss of substance with pain and stinging. The general conditions of the patient were good.

The blood tests showed an alteration in the VES, PCR, TAS, iron, ferritin, transferrin and direct bilirubin values that then normalised; the tumoral markers were within the norm. Lymphocyte phenotypisation had highlighted a modest depression of clone B immunopoietic with the absence of pathological clones; the cutaneous swab performed on the ulcer had already highlighted the presence of proteus mirabilis. The gastroenterologic examination, chest X-ray and ecography of the abdomen did not reveal any significant pathological picture. The histological outcome of the cutaneous biopsy showed: “skin with subepidermal cut containing red blood cells, granulation tissue in the derma beneath, granulomatous phlogosis formed by foreign body giant cells in the hypoderma at the adipose tissue sects”. On the basis of the clinical
manifestations, the evolution thereof, the aspecific histological alterations. *Pyoderma gangrenosum* was diagnosed. Therefore, treatment was started with 325 mg/day of cyclosporin combined with methylprednisolone fl i.m. at a dose of 30 mg/day to be scaled down gradually. Treatment with cyclosporin was continued with a considerable improvement in the clinical and symptomatological picture that the ulcerative lesion closed over a span of 2 months. The steroid dosage was gradually reduced until being completely suspended after about 15 days from closure of the lesion.

A month and a half after starting the cyclosporin treatment, gingival hyperplasia appeared in the oral cavity of the patient; during the same period there were numerous papillomatous vascular neoformations on the surface of the repaired tissue of the ulcer (Figure 2). A biopsy sample was taken by shaving one of the papillomatous neoformations on the right leg; the histological results showed: "macroscopically it was a pedunculate flesh-colored tumor with a major axis of 0.6 cm; histopathologic examination showed a mantle of moderately reactive epidermis (hypergranulosis with hyperkeratosis) covering a protuberant delicate fibrovascular core with dilated thin-walled vessels and diffuse chronic inflammatory cell infiltrate". At 6 months from beginning the treatment with cyclosporin, gradual reduction and subsequent suspension of the dose, both the gingival hyperplasia and the papillomatous manifestation at the site of the ulcer scar on the right leg (Figure 3). There is no existing lesion scar on the right leg (Figure 3). There is no existing

- **References**

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Use of a modified Rieger’s nasal flap in ten patients

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Dear Editor,

The Rieger’s flap is a classical method used for repairing nasal tip defects of approximately 2 cm in diameter. It is achieved by moving skin from both the nasal tip and middle area of the eyebrows; it was initially devised in the 20ies by Gillies, and diffused by Rieger in the 60ies. This flap is described as a rotation flap with a vascular base localised on the side of the nose, associated with an important back cut in the central area of the glabella and a wide submining to guarantee a good vascular supply.

The flap was modified by Marchac through the removal of the excess skin on the lateral side of the defect, in order to prevent dog-ears and improving the movement of the flap on a more limited ipsilateral peduncle, fed by the vessels of the medial side.

Rigg also describes a variation to Rieger’s flap which made it possible to use a smaller amount of dorsal and glabellar skin, with a back cut limited to the eyebrow area.

In 1995, Green and Angelats proposed a further variation of the Rieger’s flap, which is moved on an ipsilateral peduncle, without back cut in the glabella and the need to remove thick skin from the forehead and transfer it, with antiaesthetic results, to the periorcular area.

According to these authors, the incision is made starting from the nasal tip defect, along the lateral nasal groove reaching the middle at the top and is completed with a horizontal back cut near the nasal sella. In this way it is possible to move almost the entire skin of the nose and avoid incisions in the eyebrow area.

We used an our own variation of Rieger’s flap to correct sizeable nasal tip defects in 10 patients, whose average age was over 70, 8 patients were male and 2 female.

In 9 cases the defect was caused by the radical removal of a basal cell carcinoma, and in 1 case a squamous cell carcinoma.

All our patients were treated under local anaesthetic using diluted lidocain, added to adrenaline and tamponed with bicarbonate; we used a 4.0 and 5.0 reabsorbable suture mate-

Figure 1.—The defect on the tip of the nose and project of the flap.

Figure 2.—The stitched flap in its final position.
rial (green Safil) and 5.0 nonreabsorbable monofilament material (Surgipro).

In all the patients the nasal tip defect was rounded in shape, with a diameter either equal to or slightly greater than 2 cm.

We designed the flap by drawing a semicircle with a wide radius. Said semicircle began from the side of the surgical gap, and moved upwards to encircle the side of the nose, reaching the medial commissure of the eyelids. It was then completed by a small Burrow’s triangle, the tip of which was turned towards the commissure of the eyelids. This Burrow’s triangle would be removed (Figure 1).

After having administered the local anaesthetic, we incised following the written lines and we had made a wide submining of the skin at the nose, which reached the root of the nose. A careful haemostasis with a diathermocoagulator was carried out.

The flap was positioned, and its length compensated with the Burrow’s triangle at the medial commissure of the eyelids, the pointed tip of the flap adapted to the round shaped defect and secured with two stitches (Figure 2).

At this stage, we removed the excess fold of skin which rises near the nasal side opposite the flap rotation. This was done trying to leave the scar in correspondence of the upper edge of the nasal ala (Figure 3).

The aesthetic result was very good in all 10 patients, only in 2 cases did we observe very small areas of necrosis at the top of the flap which were removed with topical medication without jeopardising the final result. Both cases were elderly male smokers who had neither cut down nor stopped smoking, not even immediately after the surgery.

After the operation, we noticed the appearance of considerable hematomas in almost all our patients, located at the periorcular tissue, which regressed spontaneously with a short space of time.

Our variation of the Rieger’s flap makes execution simpler and achieves good aesthetic results; the scars are placed on natural folds and away from the centre of the face; the skin employed is matching that which has been removed and the vascular base of the flap is increased.

References

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Benign symmetric lipomatosis: report of two cases

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Dear Editor,

The benign symmetric lipomatosis (BSL) is a rare disease characterized by symmetric and disproportionate accumulation of normal subcutaneous fatty tissue on neck, upper back, shoulder girdle, and proximal part of the extremities.1

BSL is closely associated with alcoholism, detected in 60-90% of patient, hepatopathy, impaired glucose tolerance, or even overt diabetes mellitus, hypertension, hyperlipidemia, hyperuricemia and malignant disease, particularly squamous cell carcinomas of the upper airways.2, 3

The pathogenesis of BSL is still unknown, but it has been suggested that it may represent a specific primary disease of the adipose tissue, with a defect of the catecholamine-stimulated lipolysis.4
We report the case of two women affected by BSL, without the classic associated diseases.

A 70-year-old female, A. D. P., affected by mycosis fungoides and in photochemotherapy came to our attention for the presence of an enlarged subcutaneous tissue, especially localized in her upper arms (Figure 1), neck and thighs, progressively enlarging during the latest months. She presented a pseudo-athletic appearance of the upper part of the body, caused by marked symmetric and disproportionate fat deposits, that contrasted with the normal appearance of the lower half of the body, especially with forearms and shanks. At the physical examination the subcutaneous adipose tissue deposits seemed to be continuous on palpation, with a clear demarcation with the surrounding tissue and presenting a venous congestion of the skin.

The patient had no history of alcohol consumption in the past.

The laboratory investigation excluded hepatopathy, impaired glucose tolerance or diabetes mellitus, hyperlipidemia, hyperuricemia and endocrinological syndromes. Neoplastic markers and the instrumental investigation did not reveal any malignant tumor at that moment. A diagnosis of BSL has been made.

R. G., a 53-year-old woman, noted in the last 6 years a progressive swelling of the subcutaneous fatty tissue involving the upper arms (Figure 2A) and the neck. Laboratory and instrumental examinations revealed normal or negative results, especially no hepatopathy or diabetes mellitus were found. The patient had no history of alcohol abuse. The adipose masses led to serious functional deficits that prevented the woman to develop common daily activity. In order to improve the mobility and the functioning of her arms, she underwent surgical lipectomy with liposuction of adipose tissue in the upper part of arms (Figure 2B). A diagnosis of BSL has been made.

In conclusion, BSL is a relatively common disease in Europe, but it is uncommon in American and English literature. The condition mainly affects middle aged men, with a sex ratio of 15:1 to 30:1. It is characterized by diffuse hyperproliferation of normal subcutaneous tissue indistinguishable from solitary lipomas.

The development of BSL shows a high correlation with alcoholism and it is often associated with metabolic disorder such as hyperuricemia, liver disease, neurologic abnormalities and diabetes. In literature, BLS has been even associated to malignant tumors, such as lung carcinoma, Kaposi’s sarcoma, carcinoma of the tongue, and urothelial carcinoma.

Our patients had no history of alcohol abuse; they had no diabetes or others metabolic alterations and no solid tumors. One of our patients was affected by mycosis fungoides, a T cell cutaneous lymphoma, but we have no sufficient data to explain the correlation between the two diseases, never described in literature before.

Due to the limited etiological insights, the therapeutical approach is often unsatisfying. Surgical treatment seems to be the best therapeutic option, but it is attempted only in patients with functional impairment due to large masses of fatty tissue, or with the compression of important structures such as trachea, larynx, mediastinal organs, or for psychological reasons. The second patient was treated with surgical lipectomy with liposuction of adipose tissue in the upper part of arms because of the limitation of daily activity and no clinical recurrences have been observed until now.

References


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Agminate lichen follicularis with cysts and comedones or retroauricular follicular lichen planus tumidus?

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Dear Editor,

Retroauricular follicular lichen planus tumidus (RFLT) with cysts and comedones usually presents tumid, violaceous plaques with scattered milia and comedone-like lesions. Histological picture is that of lichen planus (LP) pilaris with follicles and cysts surrounded by a lichenoid infiltrate.

When tumid features lack, the disease is best termed agminate lichen follicularis with cysts and comedones.

A 54-year-old woman, without any relevant previous diseases, presented with a 2-year history of asymptomatic grouped milium-like whitish papules and comedone-like lesions in left retroauricular fold (Figure 1). The skin between the lesions was normal. She denied taking any drug or contact with topical agents applied to the postauricular areas.

The histologic picture was characterized by cystic dilatation of the infundibular portion of the hair follicles with an associated dense lichenoid infiltrate of lymphocytes. Some histiocytes were present as well as a few plasma cells and sporadic eosinophils (Figure 2).

The infundibular epithelium was thinned and showed occasional collection of CD1a + Langerhan’s cell (pseudo-Pautrier abscesses) (Figure 3). The cysts contained laminated keratinous material. The interfollicular epidermis and the deeper portions of the follicles appeared uninvolved.

Belaich et al. first named lichen plan folliculaire tumidus retro-auriculaire a monolateral form of LP characterized by retroauricular reddish or violaceous plaques with milia and comedone-like lesions.

In other reports the lesions were bilateral. Other involved sites were the neck, cheeks, ears, scalp, fronto-temporal region and trunk. The affected patients may display typical LP lesions on mucous membranes and in other sites. Generally itching is not an important symptom.

In the differential diagnosis we have to include discoid lupus erythematosus, nodular elastosis with cysts and comedones, follicular mucinosis and milia en plaque (MP). In our case the first disease may ruled out by clinical and histopathological feature; the second involves the sun-exposed areas and shows histological evidence of elastosis; the absence of mucin in hair follicles consents to exclude follicular mucinosis. Tsoitis et al. described an exceptional case of retroauricular sebocystomatosis: it seems unique in the literature. Rarely paraffin products in shaving soaps, inadequately rinsed, may cause the development of retention cysts and comedones.

MP and RFLT have a similar picture. MP is characterized by multiple milia-like lesions in the retroauricular area; histologically there is no lichenoid tissue reaction but keratin-filled epidermoid cysts surrounded by mild mononuclear infiltrate.

Figure 1.—The patient showed asymptomatic grouped milium-like whitish papules and comedone-like lesions in left retroauricular fold.

Figure 2.—A, B) Some histiocytes were present as well as a few plasma cells and sporadic eosinophils.

Figure 3.—The infundibular epithelium was thinned and showed occasional collection of CD1a + Langerhan’s cell.
The formation of milia is a described phenomenon during the course of RFLT, while the association of milia with other types of LP has been described in few cases, even if degeneration of the basal layer is typical of the disease. According to Lucke et al., milia could be a transient feature of the healing phase of LP. Our case seems to confirm this observation.

Because in our patient tumid features lack, we think that this case is best termed, like that described by Rongioletti et al., agminate lichen follicularis with cysts and comedones.

References


Drug-induced bullous pemphigoid: a case report

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G Ital Dermatol Venereol 2006;141:553-4

Dear Editor,

The literature contains cases of pemphigoid induced or exacerbated by diverse exogenous factors including numerous drug therapies. The pathogenetic link between the appearance of various bullous skin disease and the taking of the drug is hypothesized initially on clinical observation and case-history with clinical resolution of lesions on suspension of the drug in question. In some cases, in vitro tests, such as the inhibition of macrophage migration, may be of help in the identification of the drug in question. Recent cases have been reported of calcium antagonist-induced pemphigus and pemphigoid.

Our case is a 73-year-old patient under nifedipine therapy for hypertension who came to our attention due to the appearance, 10 months prior to our first observation, of firm domed bullous lesions, aphlegmasic, 2-3 cm in diameter, slightly itchy, and containing clear serum (Figure 1). The lesions were sun-exposed and located on the back, chest, and proximal parts of the arms. The pathologic examination of the lesion showed a dermoeipidermic bullous detachment (Figure 3).

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lesions appeared in groups of 4-6 at a time, at approximately 15-day intervals, and were mostly localized on the back, although some elements also appeared on the upper limbs. The lesions persisted for about 2 weeks before spontaneously clearing leaving hyperpigmented subatrophic scarring (Figure 2).

Histological examination performed on the edge of a lesion showed dermo-epidermic bullous detachment with perivascular lymphocytic and eosinophilic infiltrate (Figure 3).

Direct immunofluorescence assay revealed an IgG and C3 linear deposit at dermo-epidermic junction (Figure 4).

Testing on separated skin after 1 molar NaCl incubation showed detachment at lamina lucida level with linear IgG and C3 deposits on the roof. Indirect immunofluorescence findings proved negative. We can not perform IIF on separated skin and IB or ELISA on the patient’s serum. The patient informed us that the first lesions had appeared with the initiation of nifedipine therapy.

The antihypertension therapy was duly modified and in about 4 weeks after nifedipine suspension the patient noticed a progressive reduction in the number of bullous manifestations until complete resolution was achieved. Follow-up after about 8 months confirmed the absence of new manifestations and the continued presence of hyperpigmented subatrophic scarring.

Pemphigoid may be induced by many drugs including furosemide, penicillamine, penicillin and its derivatives, ACE-inhibitors, nalixidic acid, ibuprofen, phenacetine, psofurosemide, penicillamine, penicillin and its derivatives, various types (phototoxic reaction, polymorphous erythema major, Steven Johnson’s syndrome, pemphigus and pemphigoid). In vitro studies have revealed diverse forms of cellular detachment induced by the drug, among which a so-called pemphigoid-like mechanism with acantholysis, and a pemphigoid-like with dermo-epidermic split mechanism. As regards the pathogenesis of pemphigoid-like dermo-epidermal detachment, various hypotheses have been put forward. It has been suggested that the drug links to the lamina lucida so inducing autoantibody production and consequent detachment and also that the drug induces the formation of new epitopes that stimulate autoimmune response. In addition, in vitro studies have shown the appearance of bullous reactions only in certain skin samples subjected to nifedipine challenge leading to a further hypothesis that there may be an individual genetically-determined susceptibility to the drug as has already been observed in certain autoimmune diseases.

Indeed, previous studies have shown specific histocompatibility antigens (HLA) linked to the onset of drug-induced autoimmune diseases. Large numbers of patients undergo calcium antagonist treatment. In view of the scarcity of reports as to calcium antagonist-induced bullous diseases we would suggest there could be an underestimation of iatrogenic cases.

Our case was characterized by an onset in bullous lesions contemporaneous to nifedipine therapy initiation, and their persistence for the entire duration of this therapy.

The lesions, which were of note both for their localization and their clinical evolution, resolved spontaneously at suspension of the drug.

On the basis of case-history, clinical response to drug suspension, histological and immunofluorescence findings, the diagnosis of nifedipine-induced iatrogenic bullous pemphigoid was made. Differential diagnosis was in relation to acquired bullous epidermolysis and Provost’s scarring pemphigoid. The first was excluded on observation of deposits at lamina lucida level.

The second, although showing similar clinical, histological and immunofluorescence findings, was excluded because our case did not have the characteristic evident fibrosis and neoangiogenesis present in scarring. In addition, Provost’s has a chronic course and does not resolve on suspension of pre-existing therapies.

References


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**Tacrolimus ointment in the treatment of atopic hand eczema**

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Dear Editor,

Atopic hand eczema (AHE) is a form of atopic dermatitis, it is a chronic relapsing skin disorder that presents with erythema, edema, itching and fissures, located to fingers and dorsum of hands. It is most frequently treated with topical steroids and emollients.1 Tacrolimus ointment (Protopic®, Fujisawa, Japan) is a new immunomodulator, which has been found to be effective and safe in the treatment of atopic dermatitis.2-4 This pilot study was initiated to evaluate the efficacy of Protopic® 0.1% ointment in the treatment of AHE.

This study was an open-label noncomparative study using Protopic® 0.1% ointment in patients with AHE. A total of 10 patients, 7 women and 3 men aged 22-48 years, were enrolled into the study. Duration of the skin disease ranged from 10 months to 5 years. Inclusion criteria included patients with hand eczema, known history of atopic dermatitis, hay fever or asthma. Other possible causes for hand eczema like contact dermatitis or psoriasis were ruled-out. Patients had to stop topical application of steroids and systemic use of antihistamines 4 weeks before entering the study. After the first screening patients applied Protopic® 0.1% ointment twice daily for 4 weeks. Evaluation was made before treatment after 4 weeks of treatment and after a follow-up period of 4 weeks. During the follow-up treatment patients used emollients. Assessment of treatment efficacy was established at each visit based on these parameters: itch (and/or burning sensation), dryness, erythema, lichenification, itching, erosions and fissures, using a score of 0-3 (0=none, 1=mild, 2=moderate, 3=severe) for each of the signs and symptoms. The global investigator score was based on the assessment of the total score. We determinate severity index of the disease by using the total score. Patient with total score of 4-6 mild disease, 7-11 moderate, and more then 12 severe. The score of 0-3 determinate marked or complete improvement.

Of 10 patients who entered the study 4 patients had marked or complete improvement at the end of treatment, in 4 cases partial improvement was found, while in one patient treatment failed. One patient left the study due to side effects. During the follow-up period most of the patients did not experience significant relapse. Patients noted that itching and burning sensation were the first symptom to resolve during the first days of treatment. The investigator global score before, after the treatment and at the end of the follow-up is seen in Table I. One patient left the study because of local side effects. He complained of severe irritation caused by application of Protopic® ointment.

The incidence of AHE in patients with atopic background suffers greatly in published reports and range from 22-49%. It is well known that patients suffered from atopic dermatitis during childhood, if still affected as adults, frequently, have their eczema localized to hands.1 Although it is quite common it is less recognized among dermatologists. AHE may involve the dorsal or the palmar parts of the hands. The most common type of AHE involves the dorsal aspects of the hands and is characterized by dryness, mild erythema, lichenification, itching, erosions and fissures. Nummular lesions present another type of dorsal AHE. Two forms of palmar AHE are also known; the vesicular type, which characterized by vesicular eruption of the palms—pompholyx form, and the dry lichenified form.1 Protopic® ointment is known to be both effective and safe in the treatment of atopic dermatitis in children and adults.2-4 Yet, as far as we know, there is no specific study in which tacrolimus ointment was used in the treatment of AHE. In other forms of hand eczema tacrolimus ointment was found to be effective; Schnopp et al.5 compared the efficacy of tacrolimus 0.1% and mometasone furoate 0.1% ointments in patients with chronic palmar dyshidrotic eczema and found similar results.

The results of our study suggest that tacrolimus could be an alternative effective treatment to topical steroids in the treatment AHE.

**Table I.—Severity index.**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Before treatment</th>
<th>After 4-weeks of treatment</th>
<th>After 4-weeks of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mild</td>
<td>0</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Complete clearance</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

N= number of patients. One patient left the study due to side effects.

**References**


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Rosacea-like tinea incognito

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Dear Editor,

The term Tinea incognito describes a fungal infection whose clinical morphology has been modified by the application of topical steroids. Diagnosis may be very difficult and depends on the site of infection and steroid-therapy duration. It is often a misdiagnosed clinical entity which mimick different cutaneous disorders like rosacea, lupus erythematosus, contact dermatitis, seborrhoeic dermatitis, psoriasis and eczema.1, 2 In some cases, steroid administration may induce the formation of red papules or purulent folliculitis indicating follicular penetration by fungi (Majocchi’s granuloma).

We present a case where rosacea-like tinea incognito was diagnosed for the presence of a onychomycosis of the fingernails.

A 83-year-old Italian man came to our department in April 2005 because of a pruriginous face dermatitis of 6 months duration unsuccessfully treated with topical steroids. The patient reported that topical steroids had offered some relief at the beginning, but the symptoms had relapsed quickly after the cessation of treatment.

The clinical examination revealed numerous red and itching papules located on the forehead, cheeks and chin causing aesthetic concern (Figure 1). An initial diagnosis of suspected steroid-induced rosacea was made.

The patient was continuously scratching his face with thickened yellowish fingernails. We decided to undress him completely. Physical examination revealed slight erythema on the neck with a sharp reddish edematous border at the base of the neck. Large intensely erythematous scaly patches with ill-defined polycyclic borders were present on the perianal area, buttocks and thighs. The toenails were normal.

Direct microscopic examinations of scales from the face and buttocks and the fingers revealed branching fungal hyphae. Fungal cultures on Sabouraud dextrose agar incubated, at 35°C, for 4 weeks, yielded *Trychophyton rubrum*.

The patient was treated with oral terbinafine 250 mg daily and topical amorolfine nail lacquer weekly. Cutaneous signs cleared after 5 weeks of treatment, which was continued for 2 months. Complete resolution of the nail symptoms was obtained at the sixth month follow-up visit.

In our patient subjective symptoms only appeared when *T. rubrum* invaded the face, producing itching. From then on, repeated use of topical steroids had gradually altered the clinical features and promoted the spreading of the dermatophytes to other cutaneous sites.

It was difficult to identify the first cutaneous site of infection since the patient did not recollect where the disease started, but it was possibly the groins. Fingernails may have been invaded successively due to the repetitive scratching. The general examination of the patient allowed us to observe the large intensely erythematous scaly patches with ill-defined polycyclic borders, which were localized on the perianal area, buttocks and thighs.

Our case shows an example of *tinea incognito* mimicking *rosacea*: this pathology should be included in the differential diagnosis of inflammatory dermatoses erroneously treated with corticosteroids.

Figure 1.—Red papular lesions of the face mimicking a rosacea.
Cutaneous metastases from undiagnosed lung carcinoma

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Dear Editor,

A 84-year-old woman presented two pinkish-violet coloured nodular lesions with a diameter of approximately 3 cm and symmetrically located on the superior abdominal quadrants (Figure 1). These lesions had a hard wooden consistency, were barely movable on the tissue underneath and painful to light palpation.

The patient, affected by type II diabetes mellitus, chronic ischemic cardiopathy and renal lithiasis, reported a mild fever, asthenia and lack of appetite accompanied by weight loss. Haematocrit assessment revealed an increased erythrocyte sedimentation rate and normochromic-normocytic anaemia, elevated levels of CEA and CA 19.9.

Histology of lesional skin demonstrated a desmoplastic pattern. Numerous dipped spindle-shaped cells in a connective stroma with thickened collagen fibres and wide vascular gaps were present. In deep derma some spots of neoplastic cells with wide nucleus were generally grouped in neoplastic thrombi inside vessels (Figure 2). The immunohistochemical study using wide range monoclonal antibodies reacting to a cytokeratins pool (5, 6, 8, 17 and 19) of low- and medium-molecular weight (40-58 kDa) (Monoclonal Mouse Anti-Human Cytokeratin, MNF116 Clone, Dako, Milan) and vimentin (Vimentin, V9 Clone, Dako, Milan) showed that the deep neoplastic cells were positive for cytokeratins and negative for vimentin. The latter reacted with the spindle-shaped cells.

These findings supported the clinical diagnosis of cutaneous metastases (CM) of poorly differentiated carcinoma.

Chest X-ray showed a roundish opacity with irregular contours in the lower lobe of the left lung, which indicated the presence of a pulmonary neoplasm. The patient, however, refused to carry out the assessments in order to characterize and stage the lung carcinoma. She died approximately 3 months after our observation.

CM from visceral carcinoma, derived from a contiguous primary tumor or from vascular or lymphatic embolization, are a relatively uncommon clinical event in fact in several cases.
retrospective studies frequencies for CM range between 0.7% and 10.4%, generally after an average period of 30 months from the primary diagnosis of visceral tumor. Moreover, CM may be the presenting sign of an underlying malignancy and it is also possible that the site of primary neoplasm remains unknown. CM typically present as multiple firm papules or nodules, single or multiple lesions, are generally not inflamed, are skin-colored to slight erythematous in appearance, and are sometimes ulcerated. Additional clinical presentations are rare and include inflammatory “carcinoma erysipeloides” and cicatricial or sclerodermoid CM; rarely, CM may present as bullous lesions, sometimes in a zosteriform pattern, and scarring alopecia. Regardless of their clinical appearance, CM tend to grow rapidly and do not recover spontaneously. Cutaneous involvement is faster when the kidney, lung, thyroid and ovary are the primary tumor sites. The most frequent location in the trunk (40%), followed by the head and neck (28%) and limbs (18%); in a minority of cases (14%) more sites are involved. For carcinomas of the abdomen and pelvis, local metastases can occur in pre-existing surgical scars; intra-abdominal carcinomas can metastasize to the skin of the umbilicus: this is called Sister Mary Joseph’s nodule and it is not unusual for gastric and pancreatic carcinomas. On the basis of some observations there could be a correlation between the site of the primary visceral neoplasm and skin metastases: for example renal carcinomas most often metastasize to the scalp. The described case is unusual in that CM in primary lung cancer rarely occurs in comparison with other organ involvement, especially in women; the lung is the sixth organ in women associated with CM. The most frequent CM histopathological pattern is adenocarcinomatous. In our patient, instead, the histologic features were predominated by a desmoplastic response: dermis is replaced by fibrovascular proliferation that resembles a hypertrophic scar, with malignant cells containing wide hyperchromatic nuclei. Our discordant immunohistochemical findings (deep dermal neoplastic cell stained positive for cytokeratins, desmoplastic scar-like tissue stained positive for vimentin) raise some questions about the role of the desmoplastic response in the realization of the CM. Such a response could be a secondary stromal reaction or an independent aspect of metastatic spread, characterized by a second spindle-shaped cellular cytotype vimentin-positive, which has likely lost antigenic specificity for cytokeratins.

References


Contact dermatitis induced by temporary henna tattoo

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Dear Editor,

Henna is the Arabic name used for a plant, Lawsonia inermis, cultivated in North Africa, India and Sri Lanka. Leaves are dried, powdered and mixed with water and oil, to obtain a dark red paste used as a hair dye or applied to the skin for decorative temporary tattoos. Various natural, e.g. lemon juice, eucalyptus oil, instant coffee powder and vinegar, as well as chemical, e.g. paraphenylenediamine (PPD) and N-isopropyl-N-phenyl-4-phenilenediamine, substances are added to enhance the darkness, to shorten the time of application of the paste on the skin and to prolong the duration of the tattoos. Unlike henna and other natural

Figure 1.—Allergic contact dermatitis (ACD) following application of temporary henna tattoo on the right forearm.
substances, chemical substances are well known and strong sensitizers and, therefore, in parallel to the growing diffusion of temporary tattoos, the incidence of allergic contact dermatitis (ACD) is raised and their clinical presentation may be particularly severe.

We describe a 18-year-old Caucasian male who underwent a temporary tattoo on the right forearm in Egypt. After approximately 3 weeks, he developed erythema, swelling and vesicles, accompanied by itching, strictly localized to the area of the tattoo (Figure 1). After ten 10 days of treatment with desoxymethasone 0.25% cream twice a day and oral loratadine 10 mg once a day, the acute inflammatory reaction disappeared leaving a hypertrophic scar. He denied previous skin lesions that could raise the suspicion of an ACD. Patch testing was performed with the SIDAPA series integrated by the following substances: propolis, ethylenediamine dihydrochloride, mercapto mix, clioquinol, quaternium, imidazolidinyl urea, mercury ammonium chloride, sesquiterpene lactone, disperse red, disperse orange, disperse black, toluuidesulfonamide-formaldehyde resin (F.I.R.M.A., Florence, Italy). Patch testing showed a strong (3+) reaction to PPD; 2+ reactions to N-isopropyl-N-phenil-4-phenilenediamine, disperse yellow and disperse red and weak (1+) positivity to disperse blue, propolis and thiuram mix (Figure 2). Patch testing with "pure" natural henna powder (Biokyma, Arezzo, Italy) in petrolatum as well as 10% and 20% aqueous solutions gave negative findings. Photopatch testing (Hermal Kurt-Herrmann, Hamburg, Germany) was negative.

The present patient had an ACD to a temporary tattoo. The inflammatory reaction was so strong to induce the development of a persistent hypertrophic scar. The prolonged interval (3 weeks) between the application of the tattoo and the onset of the dermatitis suggests that sensitisation was induced, and not only elicited, by the tattoo.

A multisensitization to chemicals that are usually added to the tattooing paste was assessed by patch-testing. We found positivities to PPD, N-isopropyl-N-phenil-4-phenilenediamine, thiuram mix, disperse yellow, disperse orange, disperse blue and disperse red that are well known sensitizer contained in tattooing products. In addition, we have assessed a sensitisation to propolis. The simultaneous, multiple and strong sensitization may be related to high allergenic potential, high concentration, and prolonged skin contact of these chemicals as well as the use of vehicles, e.g. oils and solvents, that may enhance the presentation of chemicals into the skin.

In contrast henna seems to have a weak sensitising activity and although it is widely used worldwide, cases of ACD to henna are quite rare. Unfortunately, the list of substances contained in tattooing mixture is not usually reported in detail, the product itself is not accessible to clients because in the hands of the tattooer, and this is often convinced to make a tattoo with pure henna. It is, therefore, obvious that only the use of temporary paint-on tattoos with certified pure henna should be recommended and, otherwise, it should be discouraged particularly in countries without specific health regulations and controls.

References


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