

The Uncertain Status of Cutaneous Pseudolymphoma

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Abstract. Cutaneous pseudolymphomas (CPLs) include a wide range of clinicopathological presentations sharing in common the presence of clinical and histopathological features mimicking those of primary cutaneous lymphomas. Although immunophenotypical studies and molecular analysis of clonality have been shown to be reliable tools, providing significant help in the differential diagnosis between primary cutaneous lymphoid malignancy and pseudolymphoma involving the skin, the identification of an etiological agent and prolonged follow-up remain the key steps to ascertain the benign, reactive nature of a skin lymphocytic infiltrate.

Key words: pseudolymphoma, acquired immunodeficiency syndrome.

EL ESTADO INCIERTO DEL PSEUDOLINFOMA CUTÁNEO

Resumen. Los pseudolinfomas cutáneos incluyen una amplia gama de presentaciones clínico-histológicas que tienen en común la presencia de características clínicas e histológicas que remedan a las de los linfomas cutáneos primarios.

Aunque los estudios inmunofenotípicos y el análisis molecular de clonalidad han demostrado ser técnicas fiables, que facilitan de forma significativa el diagnóstico diferencial entre neoplasia linfoide cutánea primaria y pseudolinfoma, la clave para identificar la naturaleza benigna y reactiva de un infiltrado linfocítico cutáneo estriba en la identificación de un agente causal y un periodo de seguimiento prolongado.

Palabras clave: pseudolinfoma, síndrome de inmunodeficiencia adquirida.

Pseudolymphomas have been described as cellular infiltrates predominantly including T and/or B-lymphocytes, although the presence of non lymphoid cells such as polymorphonuclear leukocytes and eosinophils has been recognized for long as one of the hallmarks of reactional infiltrates¹. Besides the skin, this heterogenous entity has been reported in several organs including the lungs, digestive tract, eye, spleen and lymph nodes as a non exhaustive list. Although it has been proposed that any infiltrate mimicking lymphoma at the clinical or histopathological level might be considered as pseudolymphoma (PL), most recent attempts converged to a common frame of infiltrates sharing clinical and histopathological features of lymphoid malignancies.

Clinical Presentation and Histopathological Features: A Basis for an Accurate Classification of Cutaneous Pseudolymphomas

Attempts to discriminate between pseudolymphoma and true lymphoid malignancy based on clinical features led to the identification of a set of criteria including the lesion type and location, and the size as the major ones. Thus, skin areas more exposed to exogenous stimuli including insect and arthropods bites, e.g. cephalic area, the upper parts of limbs, have been logically associated with reactive infiltrates. On the other hand, the presence of nodules and large sized or ulcerated lesions, are classically considered as suggestive of malignant skin lymphoid infiltrate. However, none of these criteria can be considered as robust as, for instance, severe erythroderma with enlarged lymph nodes has been reported in human immunodeficiency virus (HIV)-related CD8⁺ cutaneous T cell pseudolymphoma, and superficial ulceration may be observed in insect bite cutaneous reactions^{2,3}.

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Histopathological studies led to the definition of different patterns based on the architecture of the infiltrate, e.g. band-like versus nodular, and the presence and the intensity of cytonuclear abnormalities are still considered as one of the key criteriae in the differential diagnosis. However, the attempts to raise a reproducible, automatized technique allowing a discriminating measure of these abnormalities failed to design a reliable tool to be used in routine practice^{4,5}. According to this statement, the “golden eye” of the pathology expert, and the confrontation with clinical and follow-up features, provide major contribution in the differential diagnosis between cutaneous lymphoma and CPL.

Immunophenotypical Features: Still Helpful After All These Years

Immunohistochemical studies of skin infiltrates did benefit from the design of monoclonal antibodies allowing to assess the expression of antigens at the membrane and/or intracellular level. Indeed, the use of monoclonal antibodies reacting against T- and B-cell antigens led to a subclassification of predominantly T-cell, predominantly B-cell, and mixed infiltrates^{1,4-6}. This subclassification has then been correlated, when possible, in an etiological context. However, etiological investigations fail to identify a causal factor in a significant proportion of non malignant cutaneous infiltrates, and it is probably worth considering the denomination of “cutaneous infiltrates of undetermined significance” rather than “idiopathic cutaneous pseudolymphoma”, as the long term potential of malignant course is still unknown in these cases, due to the lack of large-sized prospective cohorts. However, aberrant phenotypes defined mostly by the lack of expression of antigens commonly shared by most mature T lymphocytes, such as CD2, CD3 and CD5, have been shown to correlate with T lymphoid malignancies. On the other hand, the expression of proliferation antigens, such as Ki-67, has been shown to contribute to discriminate between malignant and reactive, predominantly B-cell infiltrates, since a strong expression of this proliferative marker is more frequently observed in the latter, while its expression is lower or lacking in most cases of primary cutaneous follicle-centre cell lymphoma⁶. Again, none of these features should be considered as decisive *per se*, and only its confrontation in an etiological and clinical context, in addition to histological and molecular features, and follow-up, may allow to firmly establish the nature of a persistent skin infiltrate.

Molecular Methods: New Tools, New Questions

The recent advances in molecular genetics led the design of molecular techniques allowing the detection of mono-

clonal cellular subsets with a low threshold. The clonality status of skin infiltrates is now currently assessed using polymerase chain reaction (PCR)-based amplifications of TCRg V(D)J junctions, and of immunoglobulin heavy chain locus (IgH) VJ rearrangements, in samples which nature remains ambiguous after clinicopathological confrontation.

However, a large set of data indicate that the presence of a dominant clonal population within a polyclonal infiltrate is not synonymous of malignancy, and that predominant T-cell and B-cell clones may be detected in benign infiltrates, without evidence of malignant transformation during follow-up^{7,8}. However, it is worth to notice that most clonal populations observed in reactive infiltrates are usually not massively predominant when using semi-quantitative PCR-based analysis. From a practical point of view, the presence of a persistent, massively predominant lymphocytic clonal subset raises the suspicion of lymphoma, but only the confrontation with clinicopathological investigations may help to accurately solve these difficult cases.

On the other hand, the biology of B- and T-cells may explain why molecular analysis of clonality may fail to detect a dominant clone, mostly in follicle centre cell lymphoma. In the latter case, the V_H-J_H rearrangement at the DNA level is associated with somatic hypermutations, some of which may hamper the hybridization of oligonucleotides to their template⁶. Again, confrontation with conventional histopathological and immunohistochemical features and the use of appropriate oligonucleotides may help to solve these problems. Another major caveat in the interpretation of PCR-based clonality studies is the pseudoclonal pattern which may be observed in lesions with mild infiltrate⁹. This might lead to misinterpretation, and emphasizes the need for a confrontation of clonality investigations with results of histopathological and immunophenotypical studies.

Finally, new molecular markers have been investigated to address more accurately the discrimination between pseudolymphoma and lymphoma. These attempts led to the identification of several candidates in the setting of cutaneous T-cell infiltrates. Likewise, expression of the T isoform of the plastin family (T-plastin) has been identified as associated with Sézary syndrome, a leukaemic aggressive form of cutaneous T-cell lymphoma, while its expression is missing or very faint in peripheral blood lymphocytes from patients with benign conditions¹⁰. Unfortunately, T-plastin is expressed in many cellular types other than hematopoietic cells including skin fibroblasts, making this marker uneasy to use to assess the nature of skin lesions. Recently, studies reported that a polymorphic variant of the killer-inhibitory receptors (KIRs) family, called KIR3DL2, is specifically expressed by malignant T-cells in a majority of mycosis fungoides (MF) skin lesions¹¹. Although PCR-based detection of KIR3DL2 transcripts has

been proposed as a promising tool for the differential diagnosis between cutaneous T-cell lymphoma (CTCL) and benign chronic dermatoses, extensive prospective studies are required in order to accurately evaluate its diagnostic impact in routine practice.

Identification of a Causal Factor: A Key Step in the Diagnosis of Cutaneous Pseudolymphoma

Establishing the diagnosis of pseudolymphoma still relies in the identification of an etiological factor with strong evidence. The etiological classification of pseudolymphoma has been of great help, with well defined entities showing clinical, histopathological, immunophenotypical and evolutionary characteristics^{1,12}. The main etiological entities of cutaneous PLs are listed in table 1.

Drug-induced pseudolymphomas have been reported as predominantly T-cell or B-cell pseudolymphomas, even though the incidence of the former appears to be much higher. The clinical presentation of drug-induced T-cell PL may be subdivided as localized, MF-like form, while a diffuse subtype possibly resulting in erythroderma has also been described. Anticonvulsant drugs or benzodiazepines have been causally involved in both subtypes, while antibiotics such as penicillin and trimethoprim-sulfamethoxazole have been causally involved in the latter¹³.

PLs related to ultraviolet (UV) radiation exposure may mimic primary CTCL, mostly in cases of severe chronic actinic dermatitis¹⁴. Although the potential of this latter entity has been raised, it is more likely that these cases overlap with true CTCL worsening following UV-exposure¹⁵. UV-induced PLs usually show a predominant CD8+ T cell phenotype, although mixed CD4+/CD8+ phenotypes are not exceptional.

Cutaneous pseudolymphomas related to infectious agents have been reported following bacterial, parasitic or viral infections. A prototypic example of bacterial agent is PL induced by *Borrelia* infection, as one of the manifestations of the secondary phase of infection. The topography of lesions, often localized on the cephalic area including the ear lobes and upper part of limbs, and anamnesis searching for a history of tick bite and/or general symptoms, help to raise the suspicion which may be confirmed by specific serological detection. The borrelial lymphocytoma is a predominantly B-cell PL characterized by the presence of prominent germinal center formation, with T cells at the periphery¹⁶. Retrospective detection of *Borrelia burgdorferi* DNA in primary cutaneous B-cell lymphomas raised the hypothesis that *Borrelia*-related cutaneous PLs may evolve towards cutaneous lymphoma, although this is likely to be a very rare event in the natural history of infection, mostly in treated patients.

Table 1. Etiological classification of cutaneous pseudolymphomas

<i>Predominant T cell CPL</i>
Drug induced
Localized (nodular histological pattern, mostly CD4+)
Diffuse (bandlike histological pattern, peripheral blood eosinophilia may be observed)
UV-induced: chronic actinic dermatitis (bandlike pattern, predominantly CD8 or mixed CD4/CD8)
HIV-related (bandlike pattern, CD8+)
Insect bite reactions
Idiopathic T-cell CPL (nodular or bandlike, CD4+)
<i>Predominant B-cell CPL</i>
<i>Borrelia</i> -related cutaneous lymphoid hyperplasia (CLH)
Varicella-zoster virus-related CPL
Vaccination-induced CLH
CLH secondary to tattoo
CPL secondary to insect bites
Drug-induced (rare)
Idiopathic B-cell CPL

CPL: cutaneous pseudolymphomas.

In the field of CPL secondary to infectious agents, recent reports pointed out the causal role of human immunodeficiency virus (HIV) replicative infection as an etiological factor in a syndrome mimicking MF or Sézary syndrome^{3,17,18}. The CD8+ cytotoxic T lymphocyte (CTL) predominant phenotype, the polyclonal pattern and, most of all, the consistent remission of skin symptoms following efficient highly active antiretroviral therapy support the dysimmune, non malignant nature of this severe syndrome which may also present with nodal and spleen involvement^{19,20}. This hypothesis has been reinforced by evidence that skin-infiltrating CTLs specifically recognize HIV-derived antigens. Since this syndrome is mostly observed in patients showing a low absolute CD4 peripheral blood count, it is tempting to speculate that a defect of immunoregulatory function and, especially, a defect of regulatory T-cells (Tregs), accounts at least partly for this dysregulated T-cell response²⁰.

Another recently recognized entity is CPL related to vaccination, which may lead to cutaneous lymphoid hyperplasia, mostly described with vaccines including aluminum hydroxide as an adjuvant^{21,22}. Notably but not exclusively reported following anti-hepatitis B virus vaccination, this type of PL may be associated with reactive locoregional lymph nodes, and sometimes with fatigue. The detection of adju-

vant inclusions in macrophages localisation by using specific staining, and cautious anamnestic investigation are of great help to identify this etiology²¹. Using vaccinations lacking aluminum hydroxide is recommended in these patients, who often require surgical excision or intralesional corticosteroids to induce sustained remission.

Idiopathic Cutaneous Pseudolymphoma: An Entity of Uncertain Significance

Finally, there is a significant proportion of skin infiltrates of ambiguous nature after confrontation of clinicopathological and molecular features, and for which etiological investigations fail to identify a causal factor. These cases raise the relevance of pseudolymphoma denomination, since the main issue remains the evolutive potential towards cutaneous B- or T-cell lymphoma. To avoid any ambiguity, we and other authors propose to rebaptise these skin infiltrates as cutaneous lymphocytic infiltrates of undetermined significance, referring to the denomination of monoclonal gammopathies. Such classification would take into account the uncertain nature of these entities on the long term, and would stress more the need for clinicians to settle a long-term follow-up of these patients, as well as long-term prospective studies on a large number of cases. So far, published studies of B- or T- predominant idiopathic CPLs led to reassuring conclusions but, again, these series cannot be considered as definitive due to their limited size and/or follow-up duration^{23,24}.

Conclusion: Integrating Modern Biology and Clinicopathological Features

A key lesson from these last years is that excessive expectations that one single tool would provide the definitive diagnostic answer in the management of cutaneous lymphocytic infiltrates led to big deception. The current realistic view is that these modern techniques, reflecting the major advances in the knowledge of lymphocyte cell subsets, provided new tools but also required new standard evaluation in well-defined entities. The accurate integration of these results in the setting of clinicopathological confrontation has already provided major help in the diagnosis of difficult-to-classify cases. Long-term follow-up studies are now warranted to address the malignant potential of cutaneous lymphocytic infiltrates of undetermined significance.

Conflict of interest

Dr. Bachelez declares that his consulting activities for Abbot, Centocor, Schering Plough, Wyeth are his main conflicts of interest.

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