Abstract

**Background** Neoplasia-induced lichen planus is described as a cell-mediated reaction to unknown epithelial antigens. Paraneoplastic pemphigus (PNP), characterized by the presence of a specific array of autoantibodies, probably represents a different form of presentation of the same autoimmune syndrome where the mucocutaneous expression depends on the dominant pathologic mechanism.

**Methods** The authors report a case of PNP with predominant lichen planus-like lesions and review the relevant literature. We observed a 74-year-old female with vesico-bullous, erosive, target-shaped and flat papular lichenoid lesions on the lower legs, palms and soles, evolving for 3 weeks. Histopathology revealed a lichenoid dermatitis. Direct immunofluorescence showed C3 deposition around keratinocytes and epidermal IgG intranuclear deposition. Indirect immunofluorescence revealed circulating IgG with intercellular staining on rat bladder substrate. Immunoblotting demonstrated bands of 130, 190, 210 and 250 kDa antigens. A pararenal B cell lymphoma was found.

**Results** Oral corticotherapy with 40 mg prednisolone daily was initiated with a good cutaneous response. Four months later, cyclophosphamide (50 mg/day) was introduced because of a discrete enlargement of the pararenal mass. The patient died on the seventh month of follow up as a result of respiratory insufficiency.

**Conclusion** PNP has different forms of presentation and the lack of a consensus about diagnostic criteria may contribute to underdiagnosed cases. Advances on the knowledge of the sensitivity and specificity of diagnostic criteria have allowed a better accuracy of diagnosis.

Introduction

Paraneoplastic pemphigus (PNP) is an autoimmune bullous disease with mucocutaneous involvement, individualized in 1990 by Anhalt et al.1

Before this nosological individualization, several cases were reported in the literature as unusual pemphigus vulgaris, unusual erythema multiforme or as unusual paraneoplastic bullous diseases.2,3 Since the first description, different forms of presentation of PNP have been recognized and advances on the sensitivity and specificity of the diagnostic criteria originally proposed have been made.

We report a case of PNP with predominant lichen planus-like lesions and review the relevant literature.

Case Report

We observed a 74-year-old White woman with mucocutaneous lesions evolving for a period of 3 weeks. She presented with painful, erythemato-papular, vesico-bullous, erosive and target-shaped lesions on the lower legs (Fig. 1), palms, soles and abdomen along with flat-topped violaceous lichenoid papules in the same distribution. Erosive and lichenoid lesions of oral mucosa, lips and eyelids were also present. Lichenoid lesions predominated and were found isolated, or overlapping the other ones. She had mild conjunctivitis, no genital involvement, and the physical examination was otherwise normal. Her medical history was noncontributory. The clinical impression was of lichen planus pemphigoid.

Histopathology of lichenoid and target lesions revealed an interface cell-rich dermatitis, accompanied by dermal–epidermal hydropic changes (Fig. 2). No acantholysis was found. Direct immunofluorescence (DIF) on perilesional skin displayed colloid body deposition at the Dermoepidermal junction (DEJ) and papillary dermis with IgG and C3, C3 focal deposition in vessel walls of papillary dermis and around basal keratinocytes, and focal epidermal IgG intranuclear deposition. Indirect immunofluorescence (IIF) identified circulating IgG with cell surface staining present to a titer of 1 : 10 on monkey
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Figure 1 Vesicles, erosions and target-shaped lesions on the lower leg. Some flat topped violaceous lichenoid papules are also observed.

Figure 2 Histopathology in target lesion revealed an interface cell-rich dermatitis without acantholysis, accompanied by dermal–epidermal hydropic changes (stain type – Hematoxylin and eosin; original magnification ×100).

Figure 3 Indirect immunofluorescence on rat bladder showing intercellular staining with IgG (stain type – Fluorescein; original magnification ×400).

Figure 4 Immunoprecipitation preparation demonstrating the characteristic pattern of PNP.

esophagus and rat bladder (Fig. 3) along with nuclear epithelial staining with IgG on normal skin and monkey esophagus. The patient’s sera immunoprecipitated an antigenic complex composed of several proteins – 130 kDa, 190 kDa, 210 kDa and 250 kDa – that, respectively, correspond to desmoglein 3, periplakin, envoplakin and desmoplakin I (Fig. 4). All these findings were consistent with paraneoplastic pemphigus.

Lane 1. Patient Sera
Lane 2. Normal
A left pararenal mass of 6.5 × 4 cm was identified on CT scan. Pathological examination of the mass revealed a low-grade B cell lymphoma which was bcl2 positive, CD20 and CD10 negative. The relevant abnormal laboratory findings included a positive serum Antinuclear Antibodies (ANA) with homogeneous pattern and an IgM lambda monoclonal gammapathy. Oral corticotherapy with 40 mg prednisolone daily was initiated along with topical application of betamethasone. The lymphoma, at this time, was maintained on surveillance and no specific treatment was initiated.

Almost complete clearing of lesions was observed by the third month and tapering of prednisolone was therefore undertaken. This did not modify the dermatological picture. By the fourth month of follow up, warfarin (5 mg/day) and cyclophosphamide (50 mg/day) were initiated, respectively, as a result of a leg deep vein thrombosis and a discrete enlargement of the pararenal mass. Sparse lichenoid lesions were the only cutaneous manifestation.

Two months later she was hospitalized in another institution because of dyspnea and fatigue, dying from respiratory failure after a few weeks. The arterial blood gas analysis and chest radiography were inconsistent with the severity of the dyspnea. The probable cause for this fatal pulmonary complication was the development of obliterative bronchiolitis, as reported in other similar cases. Unfortunately a biopsy for the diagnosis of obliterative bronchiolitis was not undertaken.

Discussion

The mucocutaneous lesions of PNP have several clinical presentations. Patients can present a pruritic skin eruption that is bullous pemphigoid-like, with vesicles, bullae, erosions and crusting, but can also have erythematous papules with central vesiculation resembling erythema multiforme. The trunk, proximal extremities, head and neck are the most commonly affected regions, although in our patient they predominated on the lower legs. Nikolsky sign can occasionally be elicited. PNP spectrum also includes, a lichen planus pemphigoid-like eruption that can precede or follow the symptoms of the neoplasm. Blister and lichenoid lesions on the palms and soles are frequently seen, helping to differentiate it from pemphigus vulgaris. An intractable stomatitis, similar to that of sole are frequently seen, helping to differentiate it from pemphigus vulgaris. An intractable stomatitis, similar to that of pemphigus foliaceous, with staining of the epidermal cell surface and/or basement membrane zone.

In one third of cases, the neoplasm is found after the development of mucocutaneous disease. On histological examination, suprabasilar acantholysis, dermoeidermal cleavage, keratinocyte necrosis, epidermal necrosis, interface changes with dense lichenoid infiltrate in the papillary dermis and eosinophilic spongiosis, can be found.

Direct immunofluorescence (DIF) on perilesional skin should reveal IgG and/or C3 cell surface deposition, like in pemphigus vulgaris, sometimes with sparse focal deposition. Granular-linear deposits of C3 at the basement membrane zone may also be seen. The possibility of false-negative results demands, if necessary, repeated exams.

The IIF pattern is identical to that of pemphigus vulgaris and pemphigus foliaceous, with staining of the epidermal cell surface and/or basement membrane zone. Rat bladder is the preferred substrate, because of its richness in desmosomes, having a sensitivity of 86% and a specificity of 98% in the screening of PNP. These antibodies can bind other substrates with lower sensitivity and specificity. This may explain why the PNP spectrum goes beyond the mucocutaneous manifestations and includes antibody deposition on different organs namely respiratory epithelium, colon epithelium, intercalated disks of myocardium, skeletal muscle and thyroid epithelium.

Because of its specificity, IIF on rat bladder can be used instead of immunoprecipitation studies.

PNP sera can recognize one or more of several proteins (Table 1). It is probable that desmoglein 3, because of its transmembrane location, will be the target antigen in PNP, initiating the acantholytic process. Antibodies to desmoglein 3 have been proven to be pathogenic and it has been recently demonstrated that they can be detected by ELISA in 100% of the patients. This first attack would expose additional
Table 1 PNP autoantigens

<table>
<thead>
<tr>
<th>Autoantigen</th>
<th>kDa</th>
</tr>
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<tbody>
<tr>
<td>Desmoplakin I</td>
<td>250</td>
</tr>
<tr>
<td>Desmoplakin II</td>
<td>215</td>
</tr>
<tr>
<td>Bullous pemphigoid antigen I (BPAG I)</td>
<td>230</td>
</tr>
<tr>
<td>Enoplakin</td>
<td>210</td>
</tr>
<tr>
<td>Periplakin</td>
<td>190</td>
</tr>
<tr>
<td>Desmoglein 1</td>
<td>165</td>
</tr>
<tr>
<td>Desmoglein 3</td>
<td>130</td>
</tr>
<tr>
<td>Undetermined trans-membranous antigen</td>
<td>170</td>
</tr>
</tbody>
</table>

Table 2 Anhalt et al. criteria

**Clinical**
- Painful mucosal ulcerations and blisters and a polymorphous skin eruption, with papular lesions progressing to blisters and erosive lesions on the trunk, extremities, palms and soles, in the context of occult neoplasm.

**Histologic findings**
- Vacuolar interface change, keratinocytes necrosis and intra-epidermal acantholysis.

**DIF**
- Deposition of IgG and C3 in the intercellular spaces, and granular-linear complement deposition along the epidermal basement membrane zone.

**IIF**
- Serum antibodies that bind not only to cell surfaces of skin and mucosa in a pattern typical of pemphigus vulgaris, but also to simple, columnar, and transitional epithelia.

**Immunoprecipitation**
- Serum antibodies that recognize epidermal antigens of 250, 230, 210, 190 kDa.

Table 3 Camisa and Helm criteria

**Major criteria**
- Polymorphous mucocutaneous eruption
- Concurrent internal neoplasia
- Characteristic serum immunoprecipitation findings

**Minor criteria**
- Positive cytoplasmatic staining of rat bladder by IIF
- Intercellular and basement membrane zone immunoreactants on direct immunofluorescence of perilesional tissue
- Acantholysis in biopsy specimen from at least one anatomic site of involvement

Table 4 Joly et al. criteria

**High specificity and sensitivity**
1. Association with lymphoproliferative disorders
2. IIF positive on rat bladder
3. Immunoblotting detection of antibodies against envoplakin and periplakin

**Low sensitivity and high specificity**
1. Polymorphous eruption
2. Histology
3. DIF
4. Immunoblotting detection of antibodies against desmoplakins and BPAGI

Of the several etiopathogenic mechanisms proposed, the most consensual include:
1. The tumor induces a cell-mediated lichenoid interface dermatitis that will uncover previously hidden antigens.17
2. An immune response against the tumor cross-reacting with normal epithelial proteins (antigenic mimicry).17
3. Dysregulation of cytokine production by tumor cells, with secretion of massive amounts of IL6.1,14,17

All or some of these mechanisms can be present in a single patient, influencing the clinical, histological and immunological features.

Lichen planus is a mucocutaneous disease that can have several triggers, including neoplasms. The few well-characterized cases of LP in patients with malignancy are related to lichen planus pemphigoides.19

The lichen planus pemphigoides-like variant of PNP is characterized by tense blisters on previous lichenoid lesions or normal skin; lichenoid dermatitis on histological examination and eventual linear IgG and/or C3 deposition at the dermoepidermal junction on DIF.4 It lacks the circulating autoantibodies against 200 and 180 kDa epidermal antigens of LP pemphigoides13 and has the specific array of autoantibodies of PNP. However, in some patients with neoplasia and lichenoid dermatitis, auto-antibodies never occur. These cases have been designated neoplasia-induced lichen planus.19

We think that all these different forms of presentation are part of an auto-immune reaction mainly humoral in PNP and mainly cellular in neoplasia induced lichen planus, and
evidence suggests that there are similar triggers. Why the different inaugural characteristics, sometimes with the same underlying neoplasm, is still obscure. It is also difficult to explain why in some patients, the clinical, histological and immunological features change over time with the appearance of acantholysis and autoantibodies, while in others this never happens. The term PNP should therefore be applied to patients that in spite of lichenoid lesions have the specific autoantibodies.

The progression of PNP associated with malignant neoplasms is poor with a rapidly fatal outcome in a few months. Camisa et al. report a case of prolonged survival suggesting a subgroup with a more favorable outcome. It seems that with indolent B-cell lymphomas, the paraneoplastic reaction could offer some protection against the progression of the disease. It should be kept in mind that disease progression doesn’t parallel that of the neoplasm, as observed in our patient.

These neoplasms have been associated with other paraneoplastic syndromes, and some suggest the name “paraneoplastic autoimmune multiorgan syndrome” PAMS. A particularity of our clinical report was the absence of aggressive involvement of the oral mucosa. The patient also showed good response to oral corticotherapy, with a prolonged remission. The deep vein thrombosis was, in our opinion, another paraneoplastic manifestation and the presence of antinuclear antibodies an evidence of a patent dysimmunoreactivity.

PNP manifested has lichenoid eruptions is more common then previously accepted and the potential role of cell-mediated immunity at the DEJ as a participant in the pathogenesis of PNP can’t be underestimated.

References


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