Paraneoplastic pemphigus

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Introduction and AIMS

Short Definition in Layman Terms

Paraneoplastic pemphigus (PNP) is an autoimmune disease, with severe blistering of the lips and oral mucosa, and occurs in the presence of an underlying neoplasm.

Learning Objectives

After reading this chapter you will:

1. Be able to recognize the spectrum of clinical manifestations of paraneoplastic pemphigus.
2. Know which neoplasms are most often associated with paraneoplastic pemphigus.
3. Know the tools and pitfalls in the diagnostic approach of paraneoplastic pemphigus.

Case Study: Part 1

A 69-year old female with painful erosions and hemorrhagic crusts covering her lips and buccal mucosa was seen at the emergency department. Erythematous macules and erosions were seen on her trunk and extremities. In addition, bullae were present on palms and soles. The patient mentioned having lost 10 kg in the last 6 months.

Didactical Questions

The manifestations of paraneoplastic pemphigus may be clinically indistinguishable from those of other blistering diseases.

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How can we differentiate between paraneoplastic pemphigus and other clinically similar diseases? And why is this differentiation important?

Facts and Figures

Definitions and Classification

PNP is characterized by a painful oral stomatitis, a variety of skin manifestations, and a complex autoimmune response. It occurs in the presence of an underlying neoplasm, of which it may be the first sign in 10–30% of cases. PNP is sometimes be referred to as paraneoplastic autoimmune multiorgan syndrome (PAMS), because next to the mucous membranes and the skin, other organs such as the lungs may be affected, and because the histological hallmark for pemphigus, i.e. intraepidermal acantholysis, is not always present in PNP [1, 2].

The clinical hallmark of PNP is a painful stomatitis

Epidemiology

Up to-date around 500 PNP cases have been described worldwide, since 1990. It comprises 3–5% of all pemphigus cases. The underlying neoplasm is most often lymphoproliferative in nature, such as non-Hodgkins lymphoma, thymomas and leukemia. Sarcomas and other solid malignancies may also be found. In addition benign lymphoproliferative diseases may be underlying, such as Castlemans disease, which is most prevalent in young-adults and children with PNP [1–3].

The underlying neoplasm in PNP is most often lymphoproliferative in nature

Pathogenesis

The autoantibody response in PNP is directed against multiple antigens found in skin and mucosa, including the proteins of the plakin family (such as envoplakin, periplakin, desmoplakin and BP230), the protease inhibitor alpha-2-macroglobulin-like 1 protein (A2ML1) and the desmosomal cadherins desmoglein 3 and less often desmoglein 1. These antigens are involved in cell-cell or cell-matrix adhesion. The source of these autoantibodies and their exact role in the pathogenesis of PNP is not yet fully understood. Neoplastic cells may produce these autoantibodies themselves, or may stimulate B-cells to do so. The autoantibodies are thought to induce blisters of mucosa and skin, via acantholysis or other means. Cellular auto-immunity also plays a role in PNP. The variety of clinical manifestations of PNP is attributed to the balance between the cellular and humoral response. A cellular autoimmune reaction produces more lichenoid clinical features, whereas the humoral autoimmune reaction leads to more pemphigus and pemphigoid-like clinical manifestations [3, 4].

The balance between the humoral and cellular autoimmune response determines the type of cutaneous manifestations in PNP

Diagnosis Paths

History and Physical Examination

PNP usually affects adults, with an average age of onset being 60 years. Rarely children may also be affected.

The most characteristic clinical feature of PNP, is a painful severe oral stomatitis, with hemorrhagic crusts and erosions of the intra-oral mucosa, extending to include the vermilion border of the lips. Conjunctival and genital mucosa may also be involved. Cutaneous manifestations range from flaccid to tense blisters as seen in pemphigus vulgaris and bullous pemphigoid, painful erythema and skin detachment as seen in toxic

epidermal necrolysis, targetoid lesions as seen in erythema multiforme, and lichenoid papules and plaques as seen in lichen planus, or the variable manifestations of graft versus host disease, but may also be absent in a subset of patients. The distribution typically involves the face, trunk and extremities, but may also include palms and soles, which distinguishes it from the classical pemphigus variants. A subset of patients, ranging from 8 to 93%, may develop shortness of breath or even respiratory failure, due to bronchiolitis obliterans [5, 6]. Not frequently, also other auto-immune disease can develop, as myasthenia gravis, glomerulosclerosis or paraneoplastic neurological syndrome [2].

A subset of PNP patients develop bronchiolitis obliterans

Diagnostics

Diagnosis of PNP is based on three main features (Table 10.1). The demonstration of envoplakin and periplakin antibodies is most sensitive and specific. Immunoblotting, immunoprecipitation, and indirect immunofluorescence on rat bladder urothelium (Fig. 10.1) are suitable tools to detect these antibodies [7]. Direct immunofluorescence of patient skin may also be used but is not very sensitive and specific for PNP (Fig. 10.2).

The diagnosis of PNP is confirmed by the demonstration of envoplakin and periplakin, and/or A2ML1 antibodies in patient serum

In a small subset of PNP patients, often with lichenoid skin lesions, no circulating antibodies are detected, probably because the cellular autoimmune response, and not the humoral, dominates in these patients with 'lichenoid PNP'.

Histological features of PNP vary, including intra-epidermal acantholysis, subepidermal blistering, interface dermatitis and keratinocyte apoptosis and necrosis. Therefore histology alone is not sufficient to confirm the diagnosis of PNP [1, 4].

Table 10.1 Diagnostic criteria for paraneoplastic pemphigus [3]

#	Criterium
1	Presence of severe stomatitis (cheilitis)
2	Histology of acantholysis and/or interface dermatitis
3	Presence of an underlying neoplasm
4	The demonstration of envoplakin and periplakin and/or A2ML1 antibodies in the serum of patients

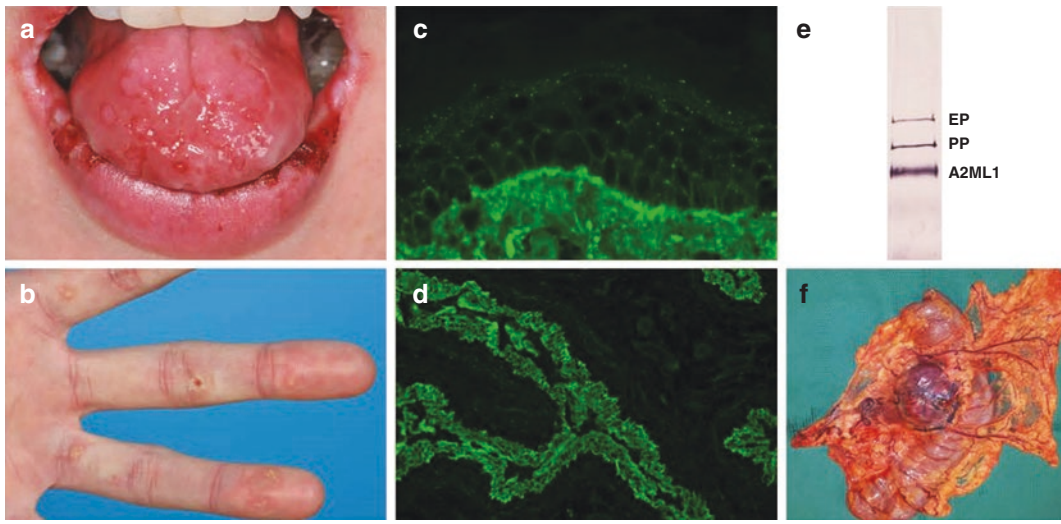

Fig. 10.1 Paraneoplastic pemphigus (**a**) hemorrhagic cheilitis and stomatitis (**b**) punctate keratoses on the palms (**c**) immunodepositions both, on the epithelial cell surface and along the basement membrane zone (**d**) serum immunoassay positivity on rat bladder (**e**) autoantibodies to envoplakin (EP), periplakin (PP) and alpha-2-macroglobulin-like 1 (A2ML1) (**f**) intra-abdominal tumor: follicular dendritic cell sarcoma.

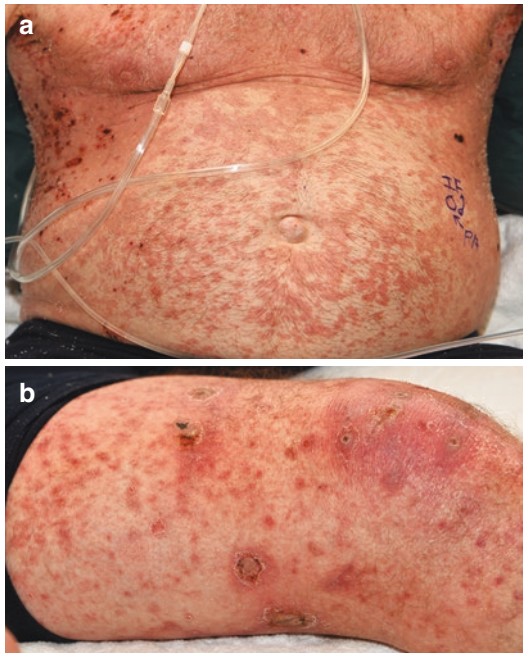

Fig. 10.2 Paraneoplastic pemphigus in a male with lichenoid phenotype showing (**a**) macular erythema with fine scales on the trunk and erosions in the flanks. (**b**) On the upper leg lichenoid plaques are discernable

A small subset of PNP patients are seronegative

Case study: Part 2
Drug history was negative, ruling out toxic epidermal necrolysis. Serology showed negative immunoblot results, but a positive IgG staining of the rat bladder urothelium by indirect immunofluorescence. The diagnosis PNP was made. Further imaging studies revealed multiple abdominal masses, which were cytologically diagnosed as non Hogdkin lymphoma.

Treatment and Prognosis

Despite aggressive treatment, mortality rates are high, with a 5-year survival rate of 38% [3] Rituximab and traditional immunosuppressiva as corticosteroids, cyclosporine, cyclophosphamide, azathioprine and mycophenolate mofetil are used [3]. More recently, several cases are published over PNP treatedwith ibrutinib, a Bruton's kinase inhibitor, alemtuzumab an anti-CD52 monoclonal antibody and tocilizumab, an anti-IL-6 monoclonal antibody with various outcomes [3].

Noteworthy, in addition to the medical treatment, the underlying neoplasm must be treated. The presence of bronchiolitis obliterans or toxic epidermal necrolysis-like clinics seems to be independent negative prognostic factors for death in PNP [3] Deaths occur mainly due to infections and progression of the underlying malignancy [6]. Patients with Castleman disease seem to have a better prognosis for survive.

Case Study: Part 3
The patient was started on R-CHOP chemotherapy (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisolone), but after 1 week developed a *S. aureus* sepsis and respiratory failure. Three weeks later, she died of multi-organ failure.

Review Questions

1. PNP patients are characterized clinically by:
   (a) A severe stomatitis.
   (b) The combination of flaccid and tense blisters.
   (c) lichenoid plaques.
2. Which of the following results confirm the diagnosis PNP?
   (a) Cell surface staining of serum IgG in monkey esophagus mucosa.
   (b) A dual ECS and BMZ IgG deposition pattern in patient skin.
   (c) Serum IgG binding to rat bladder urothelium.
   (d) Positive anti-desmoglein 3 IgG serum antibodies by ELISA.
   (e) Serum IgG binding to the roof of salt-split skin.
3. Theoretically, which subset of PNP patients is more likely to have negative serology?
   (a) Patients with flaccid intraepidermal blisters.

(b) Patients with tense, subepidermal blisters.
(c) Patients with lichenoid plaques, showing interface dermatitis in histology.

4. Which autoantibodies are most sensitive and specific for PNP?
   (a) envoplakin and periplakin antibodies .
   (b) BP230 antibodies.
   (c) desmoglein 3 antibodies.
   (d) A2ML1 antibodies.

Answers

1. a
2. c
3. c
4. a

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