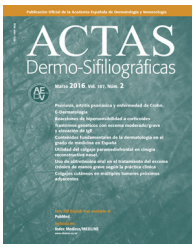
Actas Dermosifiliogr. 2017;108(10):902–910

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org



REVIEW

Paraneoplastic Pemphigus. A Life-Threatening Autoimmune Blistering Disease

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Received 26 November 2016; accepted 18 April 2017

KEYWORDS
Paraneoplastic pemphigus;
Rituximab;
Antibody production;
Lymphoproliferative origin;
Prognosis;
Pemphigus

Abstract Paraneoplastic pemphigus (PNP), a subset of pemphigus, is a unique autoimmune blistering condition that can affect multiple organs other than the skin. It is a life-threatening disease associated with an underlying malignancy, most commonly of lymphoproliferative origin. The clinical picture may resemble pemphigus, pemphigoid, erythema multiforme, graft-versus-host disease, or lichen planus. The earliest and most consistent finding is a painful, severe, chronic and often recalcitrant stomatitis. Treatment of PNP is difficult. Immunosuppressive agents are required to decrease blistering, and treating the underlying tumor may control autoantibody production. In this review, we included essential diagnostic aspects of PNP and the most useful treatment options in the dermatologist practice.

PALABRAS CLAVE
Pénfigo paraneoplásico;
Rituximab;
Producción de anticuerpos;
Origen linfoproliferativo;
Pronóstico;
Pénfigo

Pénfigo paraneoplásico. Una enfermedad ampollosa autoinmune grave

Resumen El pénfigo paraneoplásico (PNP), una variedad de pénfigo, es una enfermedad ampollosa autoinmune que puede afectar a múltiples órganos distintos de la piel. Es una enfermedad grave asociada con una malignidad subyacente, comúnmente de origen linfoproliferativo. Las lesiones clínicas pueden parecerse al pénfigo, penfigoide, eritema multiforme, enfermedad de injerto contra huésped o liquen plano. El hallazgo más temprano y más consistente es una estomatitis dolorosa, grave, crónica y, a menudo, recalcitrante. El tratamiento del PNP es difícil. Se requieren agentes inmunosupresores para disminuir la formación de ampollas y el tratamiento del tumor subyacente puede controlar la producción de autoanticuerpos. En esta revisión se incluyeron los aspectos diagnósticos más esenciales del PNP y las opciones de tratamiento más útiles en la práctica dermatológica.

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1578-2190

Introduction

In 1990, Anhalt et al.[1] reported a new clinical entity named as ''Paraneoplastic pemphigus'', fulfilling five diagnostic criteria. Subsequently, their findings were confirmed by several studies.[2–9] Nguyen et al.[10] described PNP as a heterogeneous autoimmune syndrome that affects several internal organs, and that its pathophysiology is not limited to antibodies targeting adhesion molecules like other subtypes of pemphigus. In 2001, they proposed the term ''Paraneoplastic autoimmune multi-organ syndrome'' instead of PNP. This is because the autoantibodies in the disease bind to the kidney, smooth and striated muscle, as well as the epithelium of the small intestine, colon and thyroid.[3] The term more widely used in most reports and reviews, including the present paper, is PNP. About the position of PNP among skin disorders, some studies[11–13] propose to include it as a type of pemphigus with an associated tumor, whereas others[14–16] describe it as an independent autoimmune disorder; moreover, PNP does not fully meet Curth's criteria for cutaneous paraneoplastic syndrome (Table 1).

Paraneoplastic pemphigus is closely related to benign or malignant tumors. The most often reported malignancies are lymphomatoid and hematologic (B-cell lymphoma, chronic lymphocytic leukemia, Castleman's disease, Waldenstrom's macroglobulinemia, and thymoma, with or without myasthenia gravis). Interactions between the immune system and concomitant neoplasm seem to be key pathogenic steps with autoantibodies directed against both desmosomal and hemidesmosomal antigens. In PNP, most patients develop autoantibodies against periplakins and envoplakins.

In 1990, Anhalt et al.[1] first described five cases of patients with a rare form of atypical pemphigus that were all associated with lymphoproliferative diseases. PNP mostly affects adults between 45 and 70 years old, but it may also be found in younger patients, in whom Castleman's disease is more commonly seen. There is no known correlation between incidence of the disease and specific gender, race, or geographical distribution.[3]

Based on its very unique clinical pictures, as well as its histologic and immunologic features, and most of all its elevated mortality (90% if untreated), diagnosis should be stated promptly.[3,17–20] Prognosis depends on the nature of the associated tumor. Some patients experience rapid improvement after excision of a benign tumor, such as PNP associated to Castleman's disease. However, malignant tumors are often accompanied not only by higher mortality from the associated malignancy but also because the PNP can be severe and often recalcitrant.

Table 1 Curth's criteria for the diagnosis of cutaneous paraneoplastic syndrome.

Criteria
Both conditions began simultaneously (neoplasia and paraneoplasia).
Development of a parallel course (treatment of the neoplasia results in regression of the skin lesion; recurrence of the neoplasia implies recurrence of the skin lesion).
The skin lesion is not associated with a genetic syndrome.
There is a specific type of neoplasia that occurs with paraneoplasia.
The dermatosis is rare in the general population.
There is a high frequency of association between both conditions.

PNP: paraneoplastic pemphigus.

Epidemiology

The exact incidence of PNP is unknown but it is less common than pemphigus vulgaris or pemphigus foliaceus. There appears to be no age preference.[4] Although PNP presents most often in older patients aged between 45 and 70 years, it also occurs in younger patients. The disease has been reported in patients ranging from 7 to 83 years-old.[5] Ogawa et al.[21] studied 496 patients with malignancy and recorded 25 cases of pemphigus (5%), an elevated number when compared with controls. There was a positive correlation with advancing age. The mean age of pemphigus patients with malignancy was 64.7 years.[21] It appears to be no gender predilection.[2,22]

The associated malignant or benign neoplasm may be occult or already diagnosed at the point of PNP presentation. PNP may also develop after the tumor has been treated.[6,7] The most commonly associated tumors are hematological, accounting for nearly 84% of all cases, these include non-Hodgkin's lymphoma (38.6%), chronic lymphocytic leukemia (18.4%), Castleman's disease (18.4%), thymoma (5.5%), Waldenström macroglobulinemia (1.2%), Hodgkin's lymphoma (0.6%) and monoclonal gammopathy (0.6%).[4] Non-hematological neoplasms include carcinomas (8.6%), sarcomas (6.2%)[23] and melanoma (0.6%).[4]

In children and adolescents, PNP is most commonly associated with Castleman's disease[8] and PNP is often the presenting sign of Castleman's disease.[9] This tumor is rare in the general population but is the third most common neoplasm associated with PNP.[24]

Etiopathogenesis

PNP is an autoimmune disorder launched by an underlying neoplasm (Fig. 1). Etiopathogenesis of PNP is not fully described.[4] Skin lesions are thought to be originated by an antibody-mediated autoimmune response to tumor antigens that cross-react with epithelial antigens. Tumor autoantibodies produce and release cytokines (such as interleukin-6) that enhance B-cells differentiation[5] and foster to develop the humoral response.

PNP is often a clinical marker of benign and malignant neoplasms, most commonly malignancies of the lymphatic system.[6] Ohzono et al.[7] described the associated tumors in 104 PNP cases. Their clinical and histopathological findings were similar to those in previous reports.[3,4,6]

Some patients have tumors that are difficult to diagnose, such as follicular dendritic cell sarcomas located in the retroperitoneal space.[8] Studies of patients with non-Hodgkin lymphoma revealed that most severe lesions during the PNP occur 2–3 years after diagnosis of lymphoma.[6] Castleman's disease, also known as giant lymph node hyperplasia, occurs most commonly in children.