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CASE REPORT

Paraneoplastic Pemphigus or Paraneoplastic Autoimmune Multiorgan Syndrome. Report of 2 Cases in Children and a Review of the Literature

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Abstract

Paraneoplastic pemphigus is an autoimmune blistering disease associated with an occult or previously diagnosed tumor. Its clinical, histological, and immunological features have been clearly defined. It is characterized by the presence of polymorphic skin lesions and by erosions of the oral and genital mucosae that are refractory to conventional treatments. The histology can be variable and includes acantholysis or lichenoid dermatitis. Circulating autoantibodies are a constant feature and confirm the diagnosis. We describe 2 girls with paraneoplastic pemphigus associated with Hodgkin lymphoma in one and Castleman disease in the other. Both children had oral and genital lesions that did not respond to conventional treatments. Biopsy revealed acantholysis in one and a lichenoid reaction in the other, and immunoassays confirmed the diagnosis. Chemotherapeutic treatment of the underlying disease was performed in both cases, together with high-dose corticosteroids for the skin and mucosal lesions. Both patients died due to respiratory failure. We suggest that paraneoplastic pemphigus, although rare in childhood and adolescence, should be included in the differential diagnosis of periorificial erosive dermatitis; this may assist in the detection of an occult neoplasm. © 2010 Elsevier España, S.L. and AEDV. All rights reserved.

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PALABRAS CLAVE

Pénfigo paraneoplásico;
Enfermedad
de Castleman;
Linfoma de Hodgkin;
Bronquiolitis
obliterante;
Edad infantil

Pénfigo paraneoplásico/síndrome multiorgánico autoinmune paraneoplásico. Presentación de dos casos en la edad infantil. Revisión de la literatura

Resumen

El pénfigo paraneoplásico es una enfermedad ampollosa autoinmune asociada a una neoplasia oculta o previamente diagnosticada, con manifestaciones clínicas, histológicas e inmunológicas bien definidas. Se caracteriza por erosiones de la mucosa orogenital refractarias a los tratamientos convencionales y la presencia de lesiones cutáneas polimorfas. La histología puede ser variada, con presencia de acantólisis o dermatitis liquenoide. La presencia de anticuerpos circulantes es un hallazgo constante que confirma el diagnóstico. Presentamos dos niñas con pénfigo paraneoplásico asociado a linfoma de Hodgkin y enfermedad de Castleman respectivamente. Presentaban compromiso orogenital refractario a tratamientos convencionales. En la histopatología se observó acantólisis y reacción liquenoide respectivamente. Los estudios inmunológicos confirmaron el diagnóstico. Ambas realizaron tratamiento quimioterápico para su enfermedad de base conjuntamente con altas dosis de corticosteroides para sus lesiones cutáneo-mucosas falleciendo por fallo respiratorio. Es de nuestro interés destacar que si bien es infrecuente la presencia de pénfigo paraneoplásico en la edad infantil y en la adolescencia, debe ser tenido en cuenta entre los diagnósticos diferenciales de las dermatosis erosivas periorificiales facilitando, de esta manera, el hallazgo de una neoplasia oculta.

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Introduction

Paraneoplastic pemphigus is an autoimmune bullous disease associated with an underlying tumor. It is characterized by painful erosions of the mucosae and polymorphic skin lesions. Histopathology is variable, and includes signs of acantholysis and interface dermatitis. The presence of autoantibodies against plakins is a constant finding that confirms diagnosis. Lung involvement is one of the main causes of death. Paraneoplastic pemphigus is very rare in childhood and the most commonly associated tumor in these patients is Castleman disease.

We describe 2 patients, one with Hodgkin lymphoma and one with Castleman disease, who presented a disorder of the skin and mucosae that was refractory to different treatments and in whom the clinical and immunopathology findings indicated a diagnosis of paraneoplastic pemphigus.

Case Description: Patient 1

The patient, a 10-year-old girl with no personal or family history of interest, presented with erosions and blisters of the oral, anal, and genital mucosae that had developed 45 days prior to consultation. The patient's general condition was poor, with asthenia and weight loss, and she was unable to eat. Physical examination revealed erosions covered by hemorrhagic crusts and a yellowish secretion in the mouth and on the lips and there was cheilitis of both lips (Figure 1). In the genital area, there was intense edema of the clitoris and labia majora and minora associated with large erosions and anal fissures. During her admission, the patient developed acute chest pain and hematemesis.

A number of additional tests were performed.

- 1) Histopathology of the cheek mucosa that revealed an eroded lesion with almost total loss of the epidermis, suprabasal acantholytic fissures, separation of keratinocytes due to acantholysis, and a dense, predominantly mononuclear inflammatory infiltrate in the dermis (Figure 2A). Direct immunofluorescence showed immunoglobulin (Ig) G deposits (+/++++) surrounding keratinocytes in small foci throughout the epidermis.
- 2) Indirect immunofluorescence with monkey esophagus and rat bladder. This revealed that the circulating antibodies were directed against the intercellular substance and the epithelial basement membrane in both tissues (Figure 3).



Figure 1 Case 1. Erosive cheilitis with serohemorrhagic scabs. Tongue with erosions covered by whitish membranes.

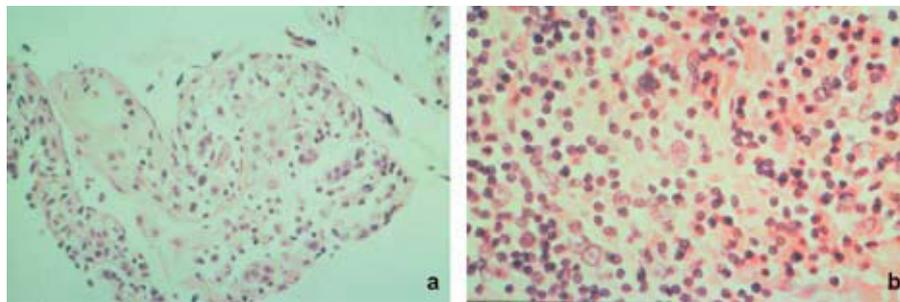


Figure 2 Case 1. a, Biopsy of the lip: Suprabasal acantholytic fissures and detachment of keratinocytes due to acantholysis. Mononuclear cell inflammatory infiltrate in the dermis. Hematoxylin-eosin, original magnification $\times 20$. b, Mixed cellularity Hodgkin lymphoma with areas of sclerosis. Hematoxylin-eosin, original magnification $\times 20$.

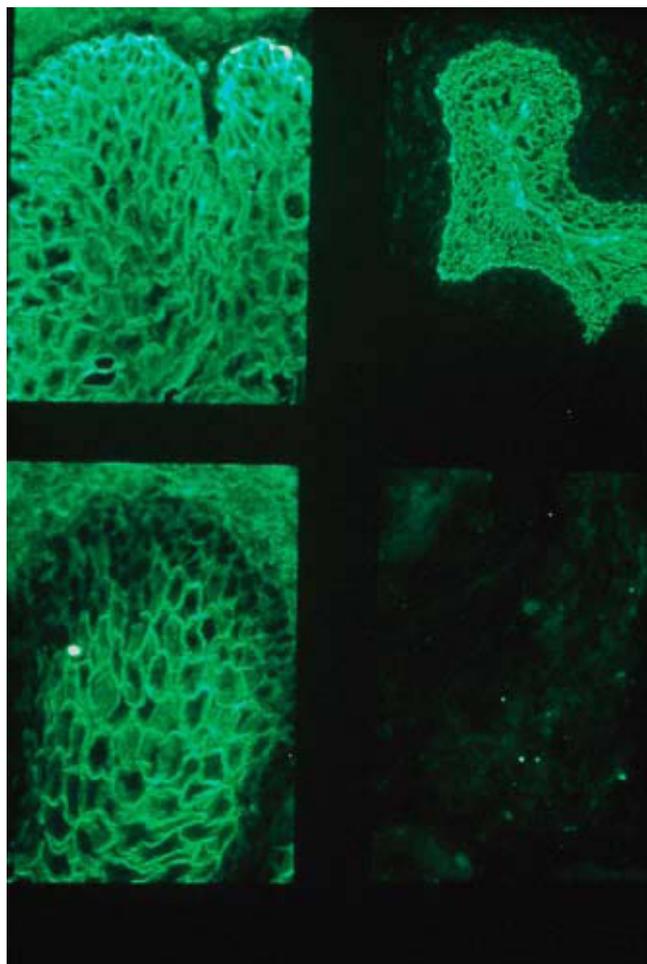


Figure 3 Case 1. Indirect immunofluorescence. Circulating immunoglobulin G directed against the intercellular substance and epithelial basement membrane of monkey esophagus and rat bladder (left) in comparison with the control, pemphigus vulgaris, in which the circulating immunoglobulin G only bound to monkey esophagus epithelium (right).

3) Immunoprecipitation, which was positive for desmoplakin I (250 kd), bullous pemphigoid antigen (230 kd), desmoplakin II and envoplakin (210 kd), periplakin (190 kd), and an unidentified 170-kd antigen.

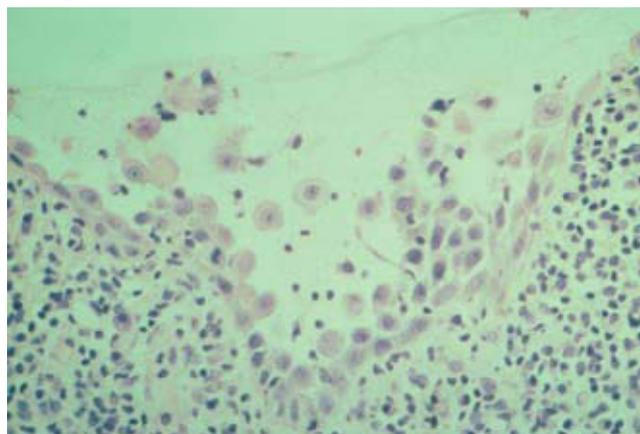


Figure 4 Case 1. Biopsy of esophagus: Acantholysis of the basal cells with signs of necrosis and spongiosis. Hematoxylin-eosin, original magnification $\times 20$.

- 4) Computed tomography of the thorax, revealing a solid mass measuring $7 \times 7 \times 9$ cm containing regularly shaped hypodense areas and microcalcifications. The mass was located in the anterior mediastinum to the left of the midline; the injection of contrast produced partial enhancement of the hypodense areas, compatible with necrosis.
- 5) Histopathology of the mediastinal tumor, which revealed a lesion with a diffuse proliferation of mature lymphocytes separated by variable amounts of collagen and associated with large cells with voluminous hyperchromatic nuclei, some of which were lobulated and contained prominent nucleoli, interspersed within the lymphoid population. Immunostaining showed the small lymphocytes to be positive for CD20, CD3, and PAN-T, and the atypical cells were positive for fascin. Stains for cytokeratins, epithelial membrane antigen (EMA), CD34, CD15, and CD30 were negative. The findings were compatible with mixed-cellularity Hodgkin lymphoma with areas of sclerosis (Figure 2B).
- 6) Esophagoscopy. Ulcers were present from the oropharynx to the distal third of the esophagus. Histopathology of these lesions showed acantholysis in the basal layer with signs of necrosis (Figure 4).

A diagnosis of paraneoplastic pemphigus associated with stage IIB (1 symptom) Hodgkin lymphoma was confirmed on the basis of clinical characteristics, additional tests, and pathology findings.

The patient underwent treatment with 2 pulses of methylprednisolone, 30 mg/kg/d, and 2 cycles of chemotherapy for the lymphoma, with a 1-month interval. The first cycle was performed with bleomycin, 15 mg/m², and doxorubicin, 37.5 mg/m², and the second with vinblastine, 9 mg/m², dacarbazine, 560 mg/m², bleomycin, 15 mg/m², and doxorubicin, 37.5 mg/m². The tumor disappeared and the lesions of the skin and mucosae improved slightly after the second cycle of chemotherapy. During therapy, the patient developed acute respiratory failure that required mechanical ventilatory assistance. However, there was a progressive deterioration and she died 7 months after onset of disease.

Case Description: Patient 2

The patient was a 12-year-old girl with no personal or family history of interest. Over the previous 5 months she



Figure 5 Case 2. Severe stomatitis: erosions covered in whitish membranes and hemorrhagic crusts.

had developed painful erosions and ulcers in the oral cavity (mucosa of the tongue and cheeks), on the lips (Figure 5), and on the genital and anal mucosae. The lesions had not responded to the treatments prescribed. She subsequently developed difficulty eating, weight loss, and general malaise. Three months later, a hard, painless tumor with a diameter of 9 cm was detected in the lateral region of the neck. The following month, she developed painful erosions with fissures and bloody crusts on the palms and soles, associated with paronychia and onychodystrophy (Figure 6). A number of additional tests were performed:

- 1) Nuclear resonance magnetic imaging [MRI] of the neck, which revealed a lymph-node mass of 8×5.3 cm in diameter located in the left lateral cervical chain, displacing adjacent structures.
- 2) Computed tomography of the thorax, demonstrating a nodular image with central cavitation in the apical segment of the right lower lobe.
- 3) Histopathology of a biopsy of the palm, which indicated orthokeratotic hyperkeratosis, acanthosis with lengthening of the interpapillary pegs, dyskeratotic keratinocytes, spongiosis, and vacuolization of basal keratinocytes with occasional apoptotic bodies. In the dermis there was a band-like lymphoplasmacytic inflammatory infiltrate in contact with the basal layer that obscured the dermal-epidermal junction, compatible with a lichenoid reaction (Figure 7A). Direct immunofluorescence was negative.
- 4) Histology of the lip and cheek mucosa, revealing an eroded epithelium and an underlying stroma with a marked, predominantly mononuclear inflammatory infiltrate with occasional multinucleated giant cells. The diagnosis given by the pathologist was of signs of chronic inflammation with changes suggestive of pemphigus.
- 5) Histopathology of the tumor. This revealed a lymph node parenchyma with preserved architecture, follicles with prominent reactive germinal centers, abundant histiocytes in the sinuses and interfollicular zone, and widespread, thin fibrous septa. The findings were compatible with lymph node hyperplasia due to hyaline-vascular Castleman disease (Figure 7B).



Figure 6 Case 2. a, Erosions and fissures on the palms. b, Periungual inflammation with onychodystrophy.

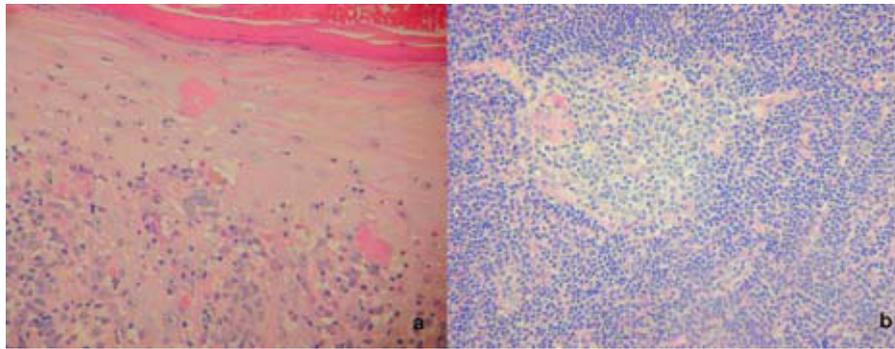


Figure 7 Case 2. a, Lichenoid reaction. Dyskeratotic keratinocytes, spongiosis, and vacuolization of basal keratinocytes. Band-like lymphoplasmacytic inflammatory infiltrate. Hematoxylin-eosin, original magnification $\times 20$. b, Hyaline-vascular Castleman disease. Follicles with prominent reactive germinal centers and abundant histiocytes. Hematoxylin-eosin, original magnification $\times 20$.

6) Indirect immunofluorescence, which detected antibodies to cement substance in monkey esophagus (positive +++/++++), though the result was negative with rat bladder.

The patient underwent 3 cycles of treatment with oral methylprednisone, 60 mg/m², combined with rituximab, 375 mg/m², cyclophosphamide, 750 mg/m², vincristine, 1.4 mg/m², and doxorubicin, 37.5 mg/m², with 21-day intervals between the cycles. Three weeks after beginning treatment, the skin lesions showed improvement but there was no change in the tumor. She developed respiratory difficulty 2 months after commencing treatment. Computed tomography of the thorax revealed widespread areas of hypoperfusion in a mosaic pattern with a ground-glass appearance in both lungs, multiple areas of peripheral consolidation, and mild peribronchovascular interstitial thickening. Spirometry showed severe obstructive changes (forced expiratory volume in the first second, 21%). The findings were compatible with bronchiolitis obliterans. The patient died 2 months later.

Discussion

Paraneoplastic pemphigus, first described by Anhalt et al in 1990, is an autoimmune bullous disease that presents in the context of an occult or previously diagnosed tumor.¹⁻¹⁰ In 2001, Nguyen et al¹² proposed the term paraneoplastic autoimmune multiorgan syndrome because of multiple organ and skin involvement and because the pathogenesis of the disease is not limited to the presence of antibodies against the known antigen complex. This syndrome is most frequently associated with myeloproliferative diseases and hematologic neoplasms such as non-Hodgkin lymphoma, chronic lymphocytic leukemia, Castleman disease, thymomas, Waldenström macroglobulinemia, monoclonal gammopathy, and Hodgkin lymphoma.¹⁻¹⁰ The most commonly associated tumor in children and adolescents is Castleman disease.^{1-3,6} In adults, however, non-Hodgkin lymphoma and chronic lymphocytic leukemia are more frequent.^{1,2} We believe that the difference in the frequency of the different tumors associated with paraneoplastic pemphigus in adults and children could be due to the different

rates of presentation of these tumors, regardless of their association with paraneoplastic pemphigus. Similar to the findings reported in the literature, the paraneoplastic pemphigus was associated with Castleman disease in one of our patients, and with Hodgkin lymphoma in the other. The latter association is very rare and has been described in only 0.6% of cases.²

Neoplastic pemphigus presents mainly in individuals aged between 45 and 70 years, although the age range varies between 7 and 83 years.^{2-4,8,9}

The pathophysiological mechanisms that produce the lesions of the skin and mucosae in paraneoplastic pemphigus are not fully understood. Both cellular and humoral immunity are implicated. Four hypotheses have been proposed:^{1,3,4,8,10-15}

- 1) Tumors express epithelial proteins that cross-react with the patient's epithelial proteins. An immune response to the tumor would therefore also affect the epithelia, producing the skin and mucosal lesions. Zhang et al¹¹ showed that various epitopes present in the plakins of epithelia were detected in Castleman disease and thymomas.
- 2) Dysregulation of the immune system caused by the tumor, as in the case of thymomas, leads to the production of a pemphigus-like autoantibody against components of desmosomes and hemidesmosomes. Increased levels of interleukin (IL) 6 have also been demonstrated, due to secretion by tumor cells. This has been observed in non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Castleman disease. This situation favors B-cell differentiation and immunoglobulin production. High levels of IL-6 are related to certain autoimmune diseases such as myasthenia gravis and the autoimmune cytopenias. When the tumors involved are excised, the symptoms of the autoimmune disease disappear, indicating that changes in the immune system play an important role.
- 3) The role of cellular immunity in the pathophysiology of this disease. Nguyen et al¹² demonstrated the presence of cytotoxic T lymphocytes, macrophages, and natural killer cells in the tissues affected by paraneoplastic pemphigus. Natural killer cells and macrophages have

been shown to induce a nonantigen-specific cytotoxic response in tumor cells, while cytotoxic T lymphocytes recognize molecules of the major histocompatibility complex with fragments of antigenic peptides expressed on the cell surface of tumor cells. This association of humoral and cytotoxic responses is also observed in autoimmune diseases.¹⁴

In a patient with paraneoplastic autoimmune multiorgan syndrome, Reich et al demonstrated the selective accumulation of CD8 lymphocytes in the epidermis together with increased production of interferon- α and tumor necrosis factor- α and significant expression of the HLA-DR antigen in leukocytes. Apoptosis is the key mechanism involved in the keratinocyte death.¹⁴ In a case series, Cummins et al¹⁵ reported 4 patients with a lichenoid variant of paraneoplastic pemphigus in which no autoantibodies were observed, concluding that cellular immunity rather than autoantibodies played a dominant or exclusive role in the pathophysiology of some cases of paraneoplastic pemphigus.

4) The theory of epitope spreading. This phenomenon is defined as the mechanism by which an autoimmune disease can cause tissue damage in such a way that certain previously occult epitopes are exposed and subsequently generate an autoimmune response. This mechanism could be involved in cases where paraneoplastic pemphigus initially presents as a lichenoid reaction.^{4,11} Nguyen et al¹² suggest that nitric oxide synthase plays a significant role in this process. In lesions of this disease, keratinocytes with nitric oxide synthase were found to be present in the epidermis and to be possible targets of CD8+ and CD68+ lymphocytes, which would induce programmed cell death through the release of nitric oxide.^{12,14} Autoantigens previously hidden from the immune system would thus be exposed.

A constant finding and first sign of the disease is the involvement of the oral mucosa. Painful erosions and ulcers affecting this mucosa and spreading to the vermilion border of the lips are characteristic and are very difficult to manage as they are refractory to treatment. Other mucosas, such as the conjunctival, esophageal, genital, and anal, may also be affected.¹⁻¹⁰ Skin lesions are very variable and are characterized by flaccid or tense blisters, associated or not with erosions or lesions similar to multiforme erythema, lichen planus, or graft-versus-host disease.¹⁻¹⁰ This polymorphism of the lesions can be present in a single patient, simultaneously or during the course of the disease.³ In children, it is more common to find a lichenoid dermatitis on the trunk and limbs and this may spread to the face and neck.^{1,2} Palmar-plantar and nail involvement are also frequent.¹⁻¹⁰ Our patients initially presented oral and genital involvement, and this was associated with palmar-plantar lesions in one of them.

The trachea and bronchial tree can be affected directly, producing respiratory failure due to bronchiolitis obliterans caused by autoantibodies against the plakins in the bronchial epithelium and which are responsible for the acantholytic changes.^{3-5,7,10} Bronchiolitis obliterans is present in 30% of cases and can develop within a month or up to a year after diagnosis. It should be suspected in a patient with

Table 1 Criteria of Anhalt et al

- Clinical features: Painful erosions of the mucosa and polymorphic skin lesions associated with a tumor
- Histology findings: Intraepidermal acantholysis, necrotic keratinocytes, vacuolar interface dermatitis
- Direct immunofluorescence: Immunoglobulin G and complement deposits in intercellular spaces of the epithelium and variably along the basement membrane
- Indirect immunofluorescence: Presence of circulating antibodies that target the intercellular zone of stratified and transitional epithelia
- Immunoprecipitation: Serum antibodies against high-molecular-weight antigens: desmoplakin I (250 kd), bullous pemphigoid antigen (230 kd), desmoplakin II and envoplakin (210 kd), periplakin (190 kd), and an unidentified 170-kd antigen

Adapted from Olguin MF, Pénfigo paraneoplásico. *Dermatol Argent* 2009;15(2):97-105.

Table 2 Diagnostic Criteria of Camisa and Helm

Major	Minor
Polymorphic rash on the skin and mucosas	Histological evidence of acantholysis
Associated internal tumor	Direct immunofluorescence of perilesional skin showing intercellular and basement membrane deposits
Characteristic immunoprecipitation test	Indirect immunofluorescence positive in rat bladder
Three major or 2 major and 2 minor criteria should be met.	

Adapted from Kimyai-Asadi A, Jih MH. Paraneoplastic pemphigus. *Int J Dermatol* 2001;40(6):367-72.

progressive respiratory difficulty. We believe that our first patient presented this complication but we were not able to confirm it because of the rapid deterioration. Bronchiolitis obliterans was diagnosed in the second patient through lung function tests and computed tomography of the thorax, which revealed the characteristic findings.

Paraneoplastic pemphigus is diagnosed on the basis of clinical observation, histology findings, and immunology studies. According to the criteria outlined by Anhalt et al in 1990 (Table 1) and subsequently revised by Camisa and Helm, who divided them into major and minor criteria (Table 2), diagnosis requires 3 major or 2 major and 2 minor criteria.¹⁻¹²

The histology findings are as varied as the polymorphic lesions that are observed in these patients. Intraepidermal acantholysis and lichenoid dermatitis with different degrees of keratinocyte necrosis may be observed. This is due to the coexistence of humoral and cytotoxic responses resulting

from an autoimmune reaction against the epithelium.^{1,3,4,9} A lichenoid pattern, as described in our second patient, is seen more commonly in individuals less than 20 years old.¹

The immunologic studies that help confirm the diagnosis are detailed below.

1. Direct immunofluorescence: linear or granular IgG deposits with or without interkeratinocyte complement deposits are observed in the area on or around the lesion. In addition, IgG deposits and complement are often identified in the area of the basement membrane, and this helps to differentiate paraneoplastic pemphigus from other types of pemphigus, in which immunoglobulin deposits are usually found between the keratinocytes but not on the basement membrane.^{3,4,12} It is important to point out that there is a considerable number of false negatives, and multiple biopsies are often required to establish the diagnosis. This may be due to distinct pathophysiological mechanisms of the different types of lesion or to the fact that the biopsy of mucosas often only contains necrotic tissue.^{1,3} Direct immunofluorescence is usually negative in patients with lichenoid lesions, demonstrating the predominance of cellular immunity over humoral in these cases.^{7,3,15} This was the situation in our second patient, who presented a lichenoid variant of paraneoplastic pemphigus with negative direct immunofluorescence.
2. Indirect immunofluorescence: patients with paraneoplastic pemphigus have serum antibodies that react against desmoplakins present in all epithelia (stratified epithelium of monkey esophagus and transitional epithelium of rat bladder). Patients with other types of pemphigus, however, present antibodies that react against antigens only present in stratified epithelia (desmoglein 1 in pemphigus foliaceus and desmoglein 3 in pemphigus vulgaris). Consequently, this method is now considered highly sensitive and specific. However, in a study of 28 patients, Anhalt et al demonstrated that this technique has a sensitivity of 75% and a specificity of 83% because not all patients with paraneoplastic pemphigus have antibodies directed against all the antigens of the complex. Patients who do not have desmoplakin antibodies but do have envoplakin, periplakin, and desmoglein antibodies will not show fluorescence in the transitional epithelium of rat bladder because the latter antigens are not found in this epithelium.^{3,4,12}
3. Immunoprecipitation: this is the main study for confirming the diagnosis. Desmoplakin I (250 kd), bullous pemphigoid antigen (230 kd), desmoplakin II and envoplakin (210 kd), periplakin (190 kd), and an unidentified 170-kd antigen are detected.^{3,4,10,12}

In our first patient, the major and 2 of the minor criteria were met. In the second, we detected 2 major criteria without immunoprecipitation—this test is not available in Spain—and 1 minor criterion with indirect immunofluorescence that was positive in monkey esophagus and negative in rat bladder. As explained in the discussion of indirect immunofluorescence, this could be because not all patients present antibodies that target

all antigens of the complex and because patients without desmoplakin antibodies will not show fluorescence in this epithelium.^{3,4,12}

Diseases to be considered in the differential diagnosis should include those that cause refractory stomatitis, such as erythema multiforme, Steven Johnson syndrome, toxic epidermal necrolysis, pemphigus vulgaris, bullous pemphigoid, lichen planus, radiation dermatitis, and mycotic or herpetic infections.^{3,4} Treatment of paraneoplastic pemphigus can be divided into 2 categories: management of the tumor and management of the autoimmune phenomena. Most patients with benign conditions improve or recover after surgical excision. There is no effective treatment in cases with a malignant tumor and the disease continues to progress despite surgical excision of the tumor and/or chemotherapy.⁴ The prognosis is poor in patients who develop bronchiolitis obliterans.^{2,5,6} High doses of corticosteroids are the treatment of choice for paraneoplastic pemphigus. The concomitant use of immunosuppressant drugs reduces the dose of steroids required and thus limits their adverse effects. The most common combination used is methylprednisone, 1-2 mg/kg/d, and ciclosporin A, 5 mg/kg/d.⁴⁻¹⁰ However, no favorable results have been obtained. The use of plasmapheresis, intravenous gammaglobulin, dapsone, and gold salts has not been effective.^{5,7} Promising results have been published regarding the use of rituximab, an anti-CD20 monoclonal antibody, in cases of paraneoplastic pemphigus and B-cell lymphoma.^{2,5,6}

Paraneoplastic pemphigus has 90% mortality. Death is usually due to complications of the disease or treatment: sepsis, multiorgan failure, gastrointestinal hemorrhage, or respiratory failure resulting from bronchiolitis obliterans.¹⁻¹⁰

Conclusion

Paraneoplastic pemphigus is very rare before 20 years of age and is a disorder with well-defined clinical and histopathological characteristics associated with a benign or malignant lymphoproliferative tumor. The majority of cases in children and adolescents present with a lichenoid pattern associated with Castleman disease. Response to treatment depends on the type of tumor and the presence of complications. Bronchiolitis obliterans is a common and fatal complication. The term paraneoplastic autoimmune multiorgan syndrome has arisen from the demonstration of the involvement of multiple organs, particularly the lungs (often the cause of death), and the presence of autoantibodies that are not limited to the known antigen complex such as antibodies against plectin and desmoglein 1 and 3. Early diagnosis will facilitate finding the occult tumor in cases in which it has not been detected, as well as the early initiation of appropriate treatment.

Conflict of Interest

The authors declare that they have no conflict of interest.

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