



## Pemphigus vulgaris in pediatrics: a case report

### Pénfigo vulgar en pediatría a propósito de un caso

Ana Laura Casuriaga Lamboglia<sup>a</sup>, Agustina Minut Gubitosi<sup>b</sup>,  
Claudia Guebenlián Bakerdjian<sup>c</sup>, Gustavo Giachetto Larraz<sup>a</sup>

<sup>a</sup>Pediatrician. Spanish Association, Montevideo, Uruguay

<sup>b</sup>Former resident of Pediatrics, Spanish Association. Montevideo, Uruguay

<sup>c</sup>Dermatologist. Spanish Association. Montevideo, Uruguay

Received: 2-5-2018; Approved: 2-7-2018

#### Abstract

**Introduction:** pemphigus vulgaris is a serious and infrequent disease in children. Its timely diagnosis and treatment allows modifying its prognosis. The objective is to describe its clinical characteristics, and the diagnostic and therapeutic approach of this uncommon autoimmune blistering disease in children. **Clinical case:** 2-year-old male patient, previously healthy. He initially presented generalized dermatosis with maximum lesion areas at the umbilical region, limbs and genitals; characterized by blisters, some denuded, and of easy bleeding, without mucosal involvement nor fever. Bullous impetigo was diagnosed and topical and systemic antibiotic treatment was started, showing no clinical improvement. He developed extension of the lesions with oral and anal mucosal involvement. The histologic and direct immunofluorescent study of lesions and perilesional skin confirm the diagnosis of pemphigus vulgaris. The patient started treatment with corticosteroids and immunomodulatory agents with good clinical response. **Conclusions:** Due to the similarity with other more prevalent infectious and inflammatory diseases, a high index of suspicion is required in order to avoid delays in the diagnosis and the start of treatment. In patients with blisters with an unexpected clinical evolution, it is necessary to conduct a joint evaluation with a dermatologist and to assess the opportunity of performing a biopsy of the lesion and perilesional skin for histological study and direct immunofluorescence, which will allow diagnostic confirmation.

#### Keywords:

Blistering diseases;  
pemphigus vulgaris;  
pediatrics

## Introduction

Acquired blistering diseases in children are a diagnostic challenge due to the etiological heterogeneity and its clinical manifestations. According to the etiopathogenic mechanism they are classified as infectious, inflammatory, and secondary to physical and autoimmune agents<sup>(1-3)</sup>. The awareness of its distinctive characteristics allows an adequate diagnostic approach and a timely treatment, which influences the prognosis<sup>(1-3)</sup>.

Acquired autoimmune forms are uncommon in children. From the histopathological point of view, two types are distinguished: the intraepidermal and the subepidermal. Pemphigus vulgaris is an intraepidermal blistering disease. Other intraepidermal forms include pemphigus foliaceus, immunoglobulin A (IgA) pemphigus, and paraneoplastic pemphigus<sup>(2,3)</sup>. According to their age of appearance, they are classified as congenital and acquired. The acquired ones are sub-classified in infectious, inflammatory, secondary to physical and autoimmune agents<sup>(3-6)</sup>.

Pemphigus vulgaris (PV) is a chronic, rare and severe autoimmune blistering disease with cutaneous-mucosal involvement. Its incidence is estimated at 0.1-0.5% of cases per 100,000 people per year. It is exceptional in children<sup>(4,7,9-13)</sup>. It is characterized by the appearance of superficial thin-walled blisters on healthy skin and/or mucosa, which extend progressively and rupture easily, leaving large exposed areas. Nikolsky sign, this is to say the epidermal detachment caused by a firm linear pressure on normal skin, is characteristic but not pathognomonic. The peripheral increase of the blister size when pressing it vertically or Asboe-Hansen sign is another possible manifestation<sup>(3,14-18)</sup>.

Skin lesions predominate in the urogenital, palpebral, anus, hands, face, neck, thorax and feet. In more than 60% of cases, the disease begins in the oral cavity with involvement of the palate, gums and occlusal plane. The nasal and conjunctival mucous membranes are frequently affected<sup>(7,8,12)</sup>.

Patients with PV usually present a significant deterioration of the general condition secondary to extensive cutaneous/mucosal involvement, difficulty in the fluids and food intake, and protein and electrolyte losses. Local and systemic infectious complications are common due to the loss of skin integrity and the immunosuppressive effects of the drugs used in its treatment<sup>(7,11-14)</sup>.

Diagnosis in children is often difficult due to the low prevalence of the disease and the wide variety of differential diagnoses. Its confirmation requires a biopsy<sup>(3,7-9)</sup>.

The objective of this study is to describe the clinical characteristics of a 2-year-old child with PV, an

uncommon form of autoimmune blistering disease in children, and to review its diagnostic and therapeutic approach.

## Clinical case

A previously healthy 2-year-old boy who consulted due to the sudden and progressive appearance of blisters in the umbilical region, upper and lower limbs and genitals, some of which were denuded with easy bleeding, without mucosal involvement or fever (Figure 1). Bullous impetigo was diagnosed and treated with oral administration of trimethoprim-sulfamethoxazole was started. On the tenth day of treatment, there was no improvement and, in addition, small erosions appeared in the oral mucosa. In the lesions exudate culture, he developed methicillin-sensitive *Staphylococcus aureus*, therefore it was indicated cefradine through oral route for 10 days.

At one month of follow-up, new blistering lesions appeared on the face, trunk, limbs and genitals, intensely painful erosions on the anal mucosa, and greater oral mucosa involvement with multiple erosions that made feeding difficult; he also presented dysphonia. The examination showed crusted lesions on lips with positive Nikolsky sign (Figures 2 and 3). Probable toxicodermia, Stevens-Johnson Syndrome type was suggested, laboratory tests were requested: hemogram, C-reactive protein, liver tests, and renal function that did not show alterations. There was no bacterial development in the blood culture. The serology for human immunodeficiency virus was negative, and the study of lymphocyte populations and immunoglobulin levels were normal.

The patient was referred to a dermatologist, where a lesional and perilesional skin biopsy was performed. The histology with hematoxylin and eosin staining showed a vesicular lesion, with suprabasal blister and persistence of basal cells attached to the basal layer (row of tombstone image). Necrobiotic tissue and fibrinous exudates comprising acantholytic cells were observed in the top of the blister and lymphomononuclear infiltrates in the dermis with frequent eosinophils. Direct immunofluorescence (DIF) showed linear intraepidermal intercellular fluorescent deposition of Immunoglobulin G (IgG) and complement fraction C3. According to the findings of the immunofluorescence biopsy, the diagnosis of PV was made.

Prednisolone through oral route was initiated at 1.5 mg/kg/day with fast improvement of lesions (Figures 4 and 5). After one month he relapsed, therefore azathioprine was added at 3 mg/kg/day through the oral route. The patient received both drugs for three months, then they were progressively decreasing until the suspension



**Figure 1.** Blister lesions evolved denuded.



**Figure 2.** Crusted lesions on lips.

one year after starting the treatment. After five months without treatment, he had a mild relapse that led to a restart of prednisolone and azathioprine. In the last follow-up visit, two years after the debut of the PV, the patient was four years old, asymptomatic and in a plan of progressive decrease of the medication.

### Discussion

PV is a rare disease in children. In 1955, the first case in pediatric age was reported. Since then, approximately 50 new cases have been reported to date<sup>(3,8)</sup>.

PV is an autoimmune disease characterized by the production of autoantibodies against specific proteins of the skin and mucous membranes, which causes the separation between keratinocytes or acantholysis. The rupture of intercellular junctions is mediated by IgG antibodies which act against desmoglein-3, affecting the structure of desmosomes<sup>(14)</sup>. Genetic and environmental factors have been associated in its etiopathogenesis. An association between PV and certain antigens of the major histocompatibility complexes class II has been observed. Drugs, hormones, physical agents (radiation and burns) and some viruses (Epstein Barr, Cytomegalovirus, Herpesvirus 8) have been associated with probable immune stimuli<sup>(4,7, 13-18)</sup>.



**Figure 3.** Extensive blister lesions on the back, positive Nicolsky sign.



**Figures 4 and 5.** Appearance of the lesions 72 hours after the start of treatment with corticosteroids.

In this case, the definitive diagnosis was established after one month of illness. It is possible that the wide variety of blistering diseases most prevalent at this age and the lack of knowledge of this entity explain the diagnosis delay. The initial characteristics of the skin lesions and the absence of mucosal and systemic involvement led to the approach of bullous impetigo. However, two elements should have warned of differential diagnoses. On the one hand, the lack of improvement with an adequate empirical antibiotic therapy, and on the other hand, the appearance of lesions in the oral mucosa, since bullous impetigo does not describe mucosal involvement<sup>(19)</sup>. The finding of *Staphylococcus aureus* in the exudate of lesions must have been interpreted as a possible contaminant. It was a strain susceptible to methicillin and therefore also susceptible to trimethoprim-sulfamethoxazole. It is important to interpret the results of laboratory tests in relation to the evolution of clinical manifestations.

Subsequently, when mucosal involvement was extended and in addition to the general condition involvement, probable toxicoderma of the Stevens-Johnson Syndrome type was raised. The diagnosis of toxicoderma is clinical and exclusionary. In this case, the suspicion was based on the history of exposure to drugs recognized as causative agents, such as sulfonamides and cephalosporins. However, the characteristics of the lesions and the absence of fever distanced this diagnostic approach. In Stevens-Johnson Syndrome, the eruption begins with maculopapular erythematous lesions that in their evolution present purple coloration and then become blisters. That was not the evolution in the patient<sup>(20)</sup>.

It is highlighted that although the clinical manifestations of autoimmune blistering diseases in children are similar to those of adults, the low prevalence of this disease in children causes delays in diagnosis due to the lack of sensitization and therefore clinical suspicion. In addition, in their initial phases, these autoimmune dermatoses can mimic other more common processes in the pediatric age, such as occurred in the analyzed case<sup>(8)</sup>.

The diagnosis of PV requires biopsy as it is confirmed by histological study and direct immunofluorescence. The histopathological study is characterized by the presence of intraepidermal blisters containing eosinophils and perivascular superficial and deep inflammatory infiltrates. Direct immunofluorescence (DIF) generally reveals linear intraepidermal intercellular IgG and C3 depositions.

Indirect immunofluorescence (IFI) uses patient serum to demonstrate the presence of circulating antibodies against a hemidesmosome antigen that are present in 70% of cases. The skin biopsies should include the edge of the ampulla or integral vesicle to observe

the level of formation of the lesion with hematoxylin and eosin staining and that in this pathology acquires the characteristic aspect of a row of tombstones. For DIF, a sample of the perilesional skin adjacent to the blister lesions will be obtained<sup>(4,7,11,12)</sup>.

Regarding treatment, the use of systemic steroids has changed the prognosis of the disease. Before its use, the mortality was close to 75% and then it was reduced to figures close to 6%<sup>(4,14,18,21)</sup>.

Prolonged corticosteroid treatment is usually required thus side effects are very common. This has encouraged the search for adjuvant treatments with immunomodulators in order to reduce the dose and duration of corticosteroids. There is little scientific evidence on the comparative efficacy of different immunomodulators. Despite this, good results have been reported with the use of azathioprine in children<sup>(10,14,18,22)</sup>.

Patients with mild and moderate forms who have a fast response to treatment are more likely to achieve complete remission. Suspension of treatment is based on prolonged clinical remission and IFI findings<sup>(5,7,8,14,18)</sup>. In the long term, better results have been reported in children than in adults, as long as treatment is started early or promptly<sup>(4)</sup>.

The importance of long-term follow-up of patients is highlighted in order to monitor the evolution of the disease, the adverse effects of the indicated treatments as well as the progressive reduction of the drugs to the minimum doses sufficient to keep the patient asymptomatic<sup>(7)</sup>.

## Conclusions

Pemphigus vulgaris is a severe autoimmune blistering disease, rare in pediatrics, therefore its diagnosis requires a high rate of suspicion to avoid delay in treatment and improve prognosis. Given the similarity with other exanthematic diseases of higher prevalence, it is necessary when there are diagnostic doubts in cases of unexpected evolution, re-evaluate the clinical manifestations with the specialist and perform lesional and perilesional skin biopsy with histological study and direct immunofluorescence to confirm the diagnosis.

It is important to report new cases of pemphigus vulgaris in children in order to characterize their behavior and response to treatment in this age.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World

Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

### Financial Disclosure

Authors state that no economic support has been associated with the present study.

### Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

### References

- Dinulos J, Carter J. Differential diagnosis of vesiculobullous lesions. En: Harper J, Orange A, Prose N. Harper's Textbook of Pediatric Dermatology. 3era Ed. Hoboken. Editorial Wiley Blackwell 2011: 954-63.
- Mascaró JM. Enfermedades ampollas no hereditarias. *Protoc diag ter Pediatr*. 2014;23-8.
- Schmidt E, della Torre R, Borradori L. Clinical features and practical diagnosis of bullous pemphigoid. *Immunol Allergy Clin North Am*. 2012;32:217-32.
- Paller AS, Mancini AJ. Bullous disorders in childhood. En: Hurwitz Clinical Pediatric Dermatology. A Textbook of Skin Disorders of Childhood and Adolescence. 5ta Edición. Edimburgo. Elsevier 2016;317-33.
- Catacora J. Enfermedades Ampollares: Bases de Diagnóstico y Tratamiento. Fundación Instituto Hipólito Unanue. *Revista Diagnóstico*. 2004;43(4):170-17.
- Baselga Torres E. Enfermedades ampollas hereditarias. *Protoc diag ter Pediatr*. 2014;15-22.
- Herrera López I, Miranda J. Pénfigo Vulgar. Criterios actuales. *Revista Habanera de Ciencias Médicas* 2009;8(5): 45-51.
- Arranz Sánchez D, Corral de la Calle M. Pénfigo vulgar en la Infancia. *Med Cutan Iber Lat Am* 2007;35(1):22-4.
- De la Cueva P, Hernanz J. Enfermedades ampollas. *An Pediatr Contin*. 2007; 5 (6): 373-7
- Salman A, Tekin B, Yucelten D. Autoimmune Bullous Disease in Childhood. *Indian J Dermatol*. 2017; 62(4):440-52.
- Baliña G, Cividino G, Fernández R, Lespi P. Penfigoide ampollar de la Infancia. *Arch argent pediatr* 1999; 97(2):280-2.
- Alemán N, Moya A, Lugo R. Pénfigo vulgar en la infancia. Presentación de un paciente. *Medicentro* 2009;13(3):1-5.
- Gilberto Nunes L, Moresco R, Marley G, Cristina B, Matesanz P. Pénfigo vulgar-Caso clínico. *Avances en odontoestomatología*. 2005;21(4): 189-93.
- Sánchez-Pérez J, García-Díez A. Pénfigo. *Actas Dermosifiliogr*. 2005;96(6): 329-56.
- Korman N. Bullous pemphigoid. *J Am Acad Dermatol* 1987;16(5):907-24.
- Korman N. Pemphigus. *J Am Acad Dermatol* 1988;18:1219-38.
- Bello C, Mondaca L, Navarrete C, González S. Pénfigo vulgar tipo cutáneo. Caso clínico. *Rev Med Chile* 2013;141:525-30.
- Ensinck G, Casanueva E, Sguassero Y, et al. Infecciones de piel y partes blandas en pediatría: consenso sobre diagnóstico y tratamiento. *Arch Argent Pediatr* 2014; 112(1):96-106.
- Telechea H, Speranza N, Giachetto G, Pérez C. Síndrome de Stevens Johnson: una Enfermedad habitualmente producida por medicamentos. *Arch Pediatr Urug* 2008;79(3):229-34.
- Alba Álvarez-Abella, Sara Martín-Sala, Ignasi Figueras Nart y Anna Jucgla. Tratamiento de los pénfigos. *Piel*. Barcelona: Elsevier. 2012: 90-7.
- Korman N. New immunomodulating drugs in autoimmune blistering diseases. *Dermatol Clin*. 2001;19(4):637-48.
- Vinay K, Kanwar AJ, Sawatkar GU, Dogra S, Ishii N, Hashimoto T. Successful use of rituximab in the treatment of childhood and juvenile pemphigus. *J Am Acad Dermatol*. 2014; 71(4):669-75.