REVIEW ARTICLE

Pathology

JUVENILE PEMPHIGUS VULGARIS: AN INSIGHT.

KEY WORDS: Pemphigus Vulgaris, Autoimmune disease, Immunoglobulin, Erosion, Bullae

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ABSTRACT

Pemphigus Vulgaris is an autoimmune disorder that presents with painful mucocutaneous blisters and erosions. On the skin, they are flaccid bullae or erosions, and on the mucosa, they present as erosions. This disease is rare but is devastating to those who have it; it also is related—perhaps genetically—to other autoimmune conditions. This is to say that a patient can develop Pemphigus Vulgaris if they have thyroiditis or diabetes mellitus. A biopsy is needed to obtain histopathological evidence of the breakdown of intercellular connections due to the autoimmune attack on components of desmosomes, which are responsible for intercellular integrity above the basement membrane. When these desmosomes are attacked, loss of connection ensues, and the cells break apart at these connections; this leads to fluid buildup, seen grossly as bullae. Pemphigus Vulgaris (PV) is a chronic autoimmune blistering disease of the skin and mucous membranes. Most cases occur in adults; cases in children are rare. This article describes the clinical presentations and treatment responses of three children with PV, as confirmed according to histology and indirect immunofluorescence studies. In all three cases, oral prednisone used in conjunction with mycophenolate mofetil (MMF) resulted in complete clinical remission, during which all pharmacotherapy was successfully discontinued. Pemphigus Vulgaris is a serious and infrequent disease in children. Its timely diagnosis and treatment allow 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, Treatment of the disease is difficult and sometimes unsafe. For decades, the mainstay of treatment has been glucocorticoids followed by other drugs. Unfortunately, these drugs are systemically absorbed, and the side effect profile can be unfavorable. In the past several years, however, more innovative treatments have emerged that may help ease the cost and safety burden to patients. This review highlights the major points about Pemphigus Vulgaris, its pathophysiology, and its treatment

INTRODUCTION:

Pemphigus Vulgaris (PV) is an acquired autoimmune disease in which IgG antibodies target desmosomal proteins to produce intraepithelial, mucocutaneous blistering. Desmoglein (Dsg) 3 is the major antigen but 50–60% of patients have additional antibodies to Dsg1, the antigen in pemphigus foliaceus (PF).[1,2,3] The underlying antibody profile is a major determinant of the clinical phenotype of PV.[4,5] The mortality of PV was 75% on average before the introduction of corticosteroids (CS) in the early 1950s.[6] This figure may be an underestimate due to lack of diagnostic criteria, the inclusion of all subtypes of pemphigus, and inclusion of other blistering disorders, such as bullous pemphigoid, which have a better prognosis. However, not all cases of PV have such a dismal prognosis. Studies differentiating according to clinical phenotype have shown lower mortality in patients with predominantly mucosal PV (1–17%) compared with those with mucocutaneous PV (34–42%).[7,8]

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. The awareness of its distinctive characteristics allows an adequate diagnostic approach and a timely treatment, which influences the prognosis.[9,10,11] 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 foliaceous, immunoglobulin A (IgA) pemphigus, and paraneoplastic pemphigus[9,10]. According to their age of appearance, they are classified as congenital and acquired. The acquired ones are sub-classified in infectious, inflammatory, and secondary to physical and autoimmune agents.[9-14] 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.[12, 15, 17-21] 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 firm linear pressure on normal skin, is characteristic but not pathognomonic. The peripheral increase of the blister size when pressing it vertically or the Asboe-Hansen sign is another possible manifestation[11,22-26]. 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 the involvement of the palate, gums, and occlusal plane. The nasal and conjunctival mucous membranes are frequently affected.[15,16,20] Patients with PV usually present a significant deterioration of the general condition secondary to extensive cutaneous/mucosal involvement, difficulty in 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.[15, 19-22] 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.[11, 15, 17] the objective of this study is to describe the clinical characteristics of a 2-year-old child with PV, an uncommon form of the autoimmune blistering disease in children, and to review its diagnostic and therapeutic approach.

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.[11, 16] 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.[22] Genetic and environmental factors have been associated with 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.[12,15, 21-26] In this case, the definitive diagnosis was established after one month of illness.The wide variety of blistering diseases most prevalent at this age and the lack of knowledge of this entity may 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.[27] 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 concerning 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.[28] 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.[16] 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 the patient serum to demonstrate the presence of circulating antibodies against a hemidesmosome antigen that is 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.[12,15,19,20] 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 %[12,22,26,29] Prolonged corticosteroid treatment is usually required thus side effects are very common. This has encouraged the search for adjuvant treatments with immunomodulators 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.[18, 22, 26, 30] 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.[13,15,16,22,26] In the long term, better results have been reported in children than in adults, as long as treatment is started early or promptly.[12] The importance of long-term follow-up of patients is highlighted 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.[15]

A CASE PRESENTATION:

- A 09-year-old male patient reported to our hospital with the chief complaint of itching on his oral cheek mucosa and neck region and further on detailed clinical examination he got diagnosed with allergic reaction lesions on left oral cheek mucosa and left neck and back also over the left shoulder with Vesico bullous, clear fluid-filled lesion. Treatment is done as per guidelines of pemphigus management. The patient's condition improved and the lesions started to heal, oral lesions got cured completely after treatment, but the patient discontinued the follow-up after few months due to his poor financial status.

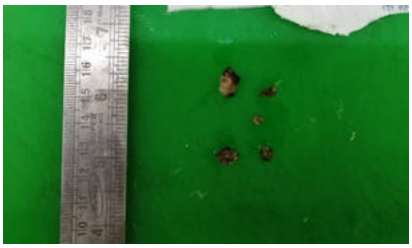

Fig. 1 Biopsy received- from the lesion

Fig. No. 2, 3, 4: histological presentation of lesion: 1 – Intraepithelial blister with a single layer of basal cells recovering the conjunctive tissue and lymphoplasmacytic inflammatory infiltrate with eosinophils 2 –Ulcered area with grouped acantholytic cells with degenerative alterations, 3 – View of the inferior area of epithelial blister and suprabasal slit showing tiny area with rare basal cells still attached to the conjunctive tissue.

TREATMENT

Before the advent of systemic corticosteroids, PV was fatal.[31,32,33,34] Use of systemic corticosteroids has reduced the mortality of PV to 30% from 70% to 100%.[32,35,36] Although PV remains a potentially fatal disease, newer treatments have reduced mortality to less than 5 %. There has been some controversy over optimal systemic management of pemphigus in the pediatric population.[37] Treatment of juvenile PV with steroids alone can have significant consequences in children, from its effects on physical appearance, susceptibility to infection, and nutrition. The reported frequency of side effects of therapy in children with the use of steroids and immunosuppressants is higher than in adults, with growth retardation, sepsis, and death being the most notable.[35, 37] Treatment is aimed at reducing antibody production and suppressing local inflammation to induce remission. Reported remission rates in old and new studies of PV treatment are approximately 30% (10). Factors that may predict treatment response and remission include disease severity at the time of diagnosis, early response to treatment, and levels of indirect immunofluorescence and ELISA titers (10), but because of the infrequency of pemphigus and the paucity of controlled trials in PV, there are currently no Food

and Drug Administration-approved therapies for PV and the treatment guidelines available lack strength of evidence.[31, 32,34,37,38]

Systemic corticosteroids are the mainstay of treatment, whereas immunosuppressive agents are used as adjuvant therapy for their corticosteroid-sparing effects.[31, 34] The primary goal is to control the disease with the lowest possible dose of corticosteroids, keeping in mind that mucosal lesions are the most recalcitrant to therapy.[31,39] Prednisone is used in doses of 1 to 2 mg/kg per day, with 40 to 60 mg/day being the typical starting dose.[31,35] Control of disease activity is marked according to the time that new lesions cease to form and old lesions begin to heal.[40] Once control is achieved, steroids can be tapered, and an adjunctive immunosuppressant may be added. We have initiated systemic steroid-sparing therapies early to reduce systemic steroid exposure and steroid-related toxic effects.[41]

Osteoporosis, slow linear growth, and rebound exacerbation of disease upon tapering typically preclude long-term use of systemic steroids in children.[42] A systemic medication with a favorable risk-benefit ratio would be a welcome addition to the therapeutic armamentarium for pediatric patients. It appears that MMF may be one such candidate.[42]

Examples of immunosuppressant drugs used in the treatment of PV include MMF, azathioprine, cyclophosphamide, and cyclosporine.[31] of these, MMF seems to be the most promising, although evaluation of any adjuvant therapy is difficult because of small sample sizes and the lack of well-controlled studies.[35, 39, 43] MMF is a fermentation product of Penicillium stolonifera.[43] Once ingested, it is hydrolyzed to mycophenolic acid, the active form of the drug, which inhibits eukaryotic inosine monophosphate dehydrogenase.[41-45] The effects of this enzyme inhibition include preferential inhibition of proliferating B and T lymphocytes and prevention of the formation of antibodies and cytotoxic T cells.[31,39,43,44] MMF undergoes hepatic metabolism and renal excretion but has demonstrated no hepatotoxic or nephrotoxic effects.[41] The rate of hepatic drug metabolism seems to be inversely proportional to age, so younger children will require higher relative doses of MMF than older children and adolescents.[42] The most common reported side effect of MMF is gastrointestinal distress, occurring in 10% to 30% of patients.[31,41-43] Less common side effects include hepatotoxicity, which can be severe; genitourinary symptoms; hematologic aberrations; and neurologic symptoms. Malignancies and lymphoproliferative disorders have not been reported in children receiving MMF alone.[42] The adverse effects, if present, are usually observed at a dose of 3 g/day, and discontinuation is usually unnecessary.[41] Latent viral infections can be activated in response to therapy with immunosuppressant therapy, including cases of progressive multifocal leukoencephalopathy as well as BK virus-associated nephropathy. Live vaccines should be avoided while patients are receiving MMF. MMF is also teratogenic and has a Pregnancy Category D rating.[46]

For more than a decade, MMF has been successfully used as an immunosuppressant in adults and children undergoing solid organ transplantation.[42,44] In addition, there are several reports in the literature demonstrating the safety, efficacy, and utility of MMF adults and children for various cutaneous diseases, including pemphigus, pemphigoid, severe atopic dermatitis, dermatomyositis, and psoriasis.[41] Strowd et al achieved 89% complete remission when they used a therapeutic ladder consisting of MMF and prednisone in 18 patients with PV. Edge et al.[41] described the use of MMF in 12 patients with dermatomyositis recalcitrant to traditional therapies. Ten of twelve patients displayed significant improvement within 8 weeks of initiating MMF, with few adverse effects.[41] Rouster-Stevens et al[45] performed a retrospective review of 50 children with juvenile dermatomyositis who received MMF after failing to respond to conventional therapies. Disease activity scores for muscle and skin had significantly improved after 12 months. The drug was well tolerated, with the most common side effect being infection, but none of them was serious or required hospitalization.[45] A retrospective analysis that Heller et al. performed examined 14 children with severe atopic dermatitis (AD) treated with MMF as monotherapy at New York University (NYU) between August 2003 and August 2006. Their analysis demonstrated that MMF at a dose of 30 to 50 mg/kg per day is safe, well-tolerated, and effective for the treatment of severe pediatric AD, with more than half of the patients in their series achieving complete clearance within 3 months of starting therapy.[42] In one of the larger randomized controlled trials using MMF in adults with PV, Beissert et al.[36] compared responses to prednisone and MMF with those to prednisone and placebo. Although there were no significant differences between the proportions responding to treatment (69.0% vs 63.9%, respectively), those who received MMF had faster and more durable responses at 3 and 6 months. In our series, all three patients were able to achieve durable clinical remission through the use of prednisone and MMF. Although several reports have indicated a favorable role for MMF in pemphigus, some reports have not indicated as much benefit from using MMF. In a multicenter nonblinded study by Beissert et. al.[47] involving 33 patients with PV and nine with pemphigus foliaceus, patients were randomized to receive prednisone and azathioprine or prednisone and MMF. MMF was not found to be superior to azathioprine. In another report by Chams-Davatchi et al.[48] prednisone in conjunction with several adjunct therapies was examined, and azathioprine was found to be superior to pulse cyclophosphamide and MMF.

CONCLUSION:

Clinicians need to be aware of the existence of juvenile PV because the early diagnosis may have prognostic implications. It is known from treating adults that earlier intervention is associated with greater rates of clinical remission. Pemphigus Vulgaris should be a consideration in children with chronic erosive mucous membrane disease. Our experience with children with PV treated with combination therapy using prednisone and MMF indicates that children can tolerate these treatments well. There is emerging evidence in support of MMF as a safe and effective treatment for juvenile PV and other chronic cutaneous diseases. Combination therapy with corticosteroid and MMF may be effective at achieving durable clinical remission in juvenile pemphigus.

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