CASE REPORT

Pemphigus vegetans induced by use of enalapril *

Pênfigo vegetante induzido por uso de enalapril

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Abstract: Pemphigus Vegetans was first described as a variant of Pemphigus Vulgaris in 1876 by Neumann. In 1889, Hallopeau described a patient with pustules and vegetating plaques, suggesting that it would be a variant of Pemphigus Vegetans of Neumann. Both types of Pemphigus Vegetans are characterized by the development of vegetating plaques especially on skin folds (axillae, groin, perianal region). The authors present and discuss a case of Pemphigus Vegetans with an unusual clinical presentation lacking involvement of mucous membrane and flexor surfaces in an elderly female patient, associated with the use of enalapril as possible trigger factor. Clinical and histological diagnosis were suggestive of Pemphigus Vegetans of the Hallopeau type.
Keywords: Autoimmunity; Enalapril; Pemphigus

Resumo: Pênfigo Vegetante foi primeiramente descrito como uma variante do pênfigo vulgar, em 1876, por Neumann. Em 1889, Hallopeau descreveu um paciente com pústulas e placas vegetantes, e sugeriu ser uma variante do Pênfigo Vegetante de Neumann. Ambos os tipos de pênfigo vegetante são caracterizados pelo desenvolvimento de placas vegetantes, especialmente, em dobras (axila, inguinal, perianal). Os autores apresentam e discutem um caso de Pênfigo Vegetante com uma clínica incomum, com ausência de acometimento de mucosas e áreas de flexão, em paciente idosa, associado ao uso de enalapril como possível desencadeador. Diagnóstico clínico e histológico sugestivos de Pênfigo Vegetante tipo Hallopeau.
Palavras-chave: Autoimunidade; Enalapril; Pênfigo

INTRODUCTION

Pemphigus is a group of autoimmune diseases that affect the skin and sometimes the mucous membrane, having as common characteristic the presence of intraepidermal blisters that occur by acantholysis.[1,2]

Pemphigus Vegetans is an uncommon form of Pemphigus Vulgaris that comprises between 1 and 2% of cases. It is considered a benign variant that usually affects younger patients. The pathogenesis should consider genetic, immunological and environmental factors.[2]

The clinical presentation is characterized by the onset of flaccid pustules that break and are replaced by exulcerative areas involved by vegetation forming plaques of verrucous and hyperpigmented aspect. The lesions usually begin on the oral mucosa and evolve affecting flexor surfaces and intertriginous areas.[2]

CASE REPORT

A 78-year-old female patient, born and resident in Laguna-SC, had a pustulous lesion on an erythematous base that had started 4 months before on the

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right malar region, with progressive growth and formation of a yellow crust with a verrucous aspect. She had several treatments for bacterial infection, without results. The lesion progressed increasing in size and disseminating over the entire face in the last month, without affecting the mucosae (Figures 1 and 2), in addition to two verrucous lesions, one with 1cm diameter on the back and one with 2cm on the left shoulder. The patient was referred to our service.

PPH: primary pulmonary hypertension (she is using atenolol and enalapril, the latter for 6 months) and arrhythmia. She denies other diseases and has no other complaints.

SPH: secondary pulmonary hypertension – she resides in her own house, alone, has no pets, the house has an ample backyard and there are lots of mosquitoes.

The conduct followed was to perform an incisional biopsy and the sample was sent to the laboratory for histopathology, immunology and culture testing.

Anatomopathological tests showed suprabasal acantholysis with epithelial hyperplasia and presence of eosinophil and neutrophil microabscesses (Figures 3 and 4).

Direct immunofluorescence revealed by microscopy negative IgA, IgM and C3, as well as positive granular IgG along intercellular spaces (Figure 5).

Bacterial culture was positive for *Staphylococcus aureus* and negative for mycoses.

The laboratory tests were normal, except for moderate leukocytosis.

The test results associated to the patient's clinical picture confirmed the diagnosis of Pemphigus Vegetans of the Hallopeau type.

A treatment with oral prednisone 60mg/day and tetracycline 500mg was started, 2x/day due to bacterial contamination. Because of the high dose of corticosteroids, the therapy included use of albendazol e calcium replacement for eradication of possible infection by *Strongyloides Stercoralis*. The use of enalapril was also suspended.

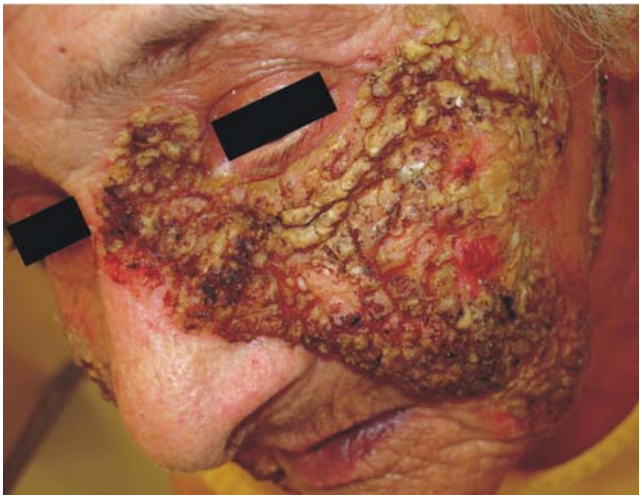

Figure 2: Pemphigus Vegetans - vegetating plaque on the face

After one month of treatment the patient had significant regression of lesions and the prednisone dose was gradually decreased. The topical use of salicylate vaseline 5% (Figure 6) was also associated.

DISCUSSION

Pemphigus is the general name of a set of autoimmune pathological entities, characterized by formation of intraepithelial bullous lesions on the skin and mucosae.[1] These bullous occur by acantholysis (loss of adhesion between epithelial cells of the Malpighian layer).[2] The auto-antibodies act on desmo-

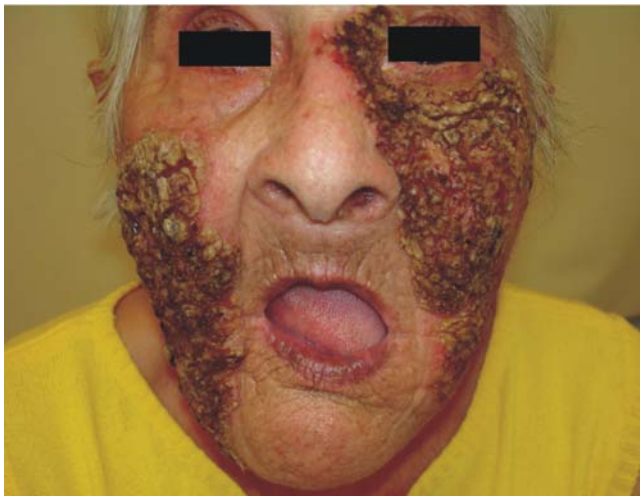

Figure 1: Pemphigus Vegetans – vegetating plaque on the face, without affecting the oral mucous membrane

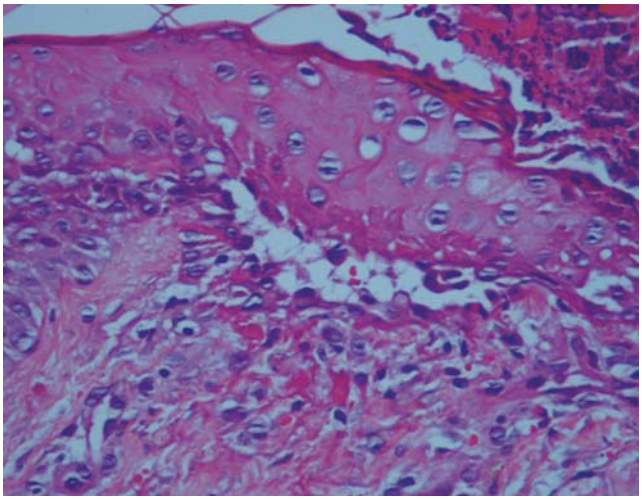

Figure 3: Pemphigus Vegetans. Anatomopathological finding: suprabasal acantholysis and epithelial hyperplasia

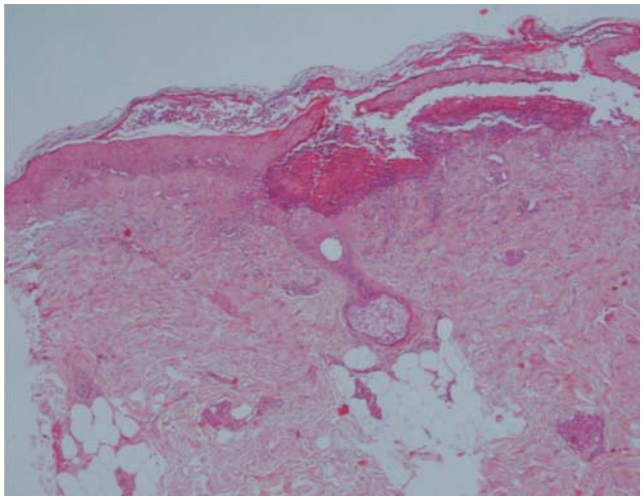

Figure 4: Pemphigus Vegetans. Anatomopathological findings: suprabasal acantholysis with epithelial hyperplasia and presence of eosinophil and neutrophil microabscesses

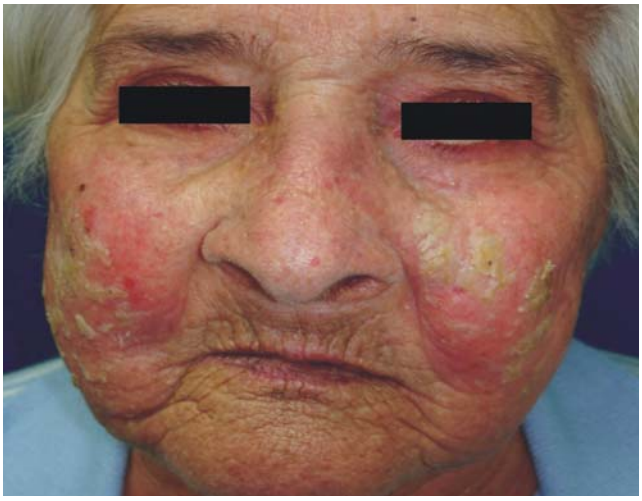

Figure 6: Pemphigus Vegetans. Marked improvement of lesions after 1 month of treatment

somes, promoting loss of intercellular adhesion.[1]

Pemphiguses are classified into different clinical and etiopathogenic variants, the most common of which are pemphigus vulgaris and pemphigus foliaceus. The less frequent forms are drug-induced, herpetiform, paraneoplastic and IgA pemphiguses.[2]

Pemphigus vulgaris is an intraepidermal bullous disease that affects the skin and mucous membranes that is potentially fatal. Its distribution is universal, but it is more common among the Ashkenazi Jews.[3] Immunogenetic studies demonstrate increased incidence of HLA-DR4 (in Ashkenazi Jews) or DRw6 (in other ethnic groups).[4] Around 90% of pemphigus vulgaris patients have oral involvement, and around 50 to 70% of patients begin the symptom complex with ulcerative lesions on the oral mucosa. Pemphigus vulgaris affects equally men and women

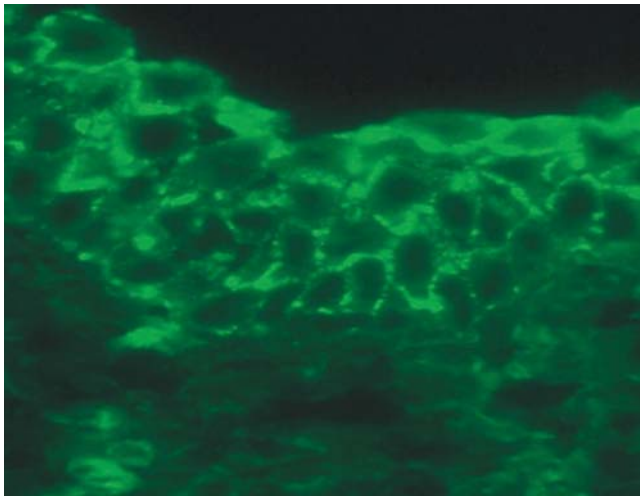

Figure 5: Pemphigus Vegetans. Direct immunofluorescence: positive granular IgG deposit along intercellular

but occurs mainly in patients who are between the fourth and sixth decades of life; however, individuals of any age may be affected, including children and newborns of mothers who have pemphigus vulgaris.[4,5,6]

Pemphigus Vegetans was (PV) first described as a variant of pemphigus vulgaris in 1876, by Neumann. In 1889, Hallopeau described a patient with pustules and vegetating plaques, suggesting that it would be a variant of PV of Neumann. Both types of pemphigus vegetans are characterized by the development of vegetating plaques, especially in skin folds (axilla, inguinal, perianal).[7] They tend to affect younger patients.

Even though both types of PV are characterized by vegetating plaques in skin folds, the first lesions are different. The Neumann type begins with lesions similar to pemphigus vulgaris, that is, ephemeral blisters that during the repair process become vegetating. The Hallopeau type, in contrast, begins with pustules in groups, mainly in flexor surfaces, where an actual vegetation grows.[8,9]

The second difference between the two types is the response to therapy and prognosis. The course of the pemphigus vegetans of Neumann is similar to pemphigus vulgaris but with worse prognosis. The Hallopeau type is more benign, has few relapses and generally maintain remission. The use of dapsone is an alternative to the systemic treatment with corticosteroids, with or without immunosuppressants for the Hallopeau type.[7,8]

The third difference is the histopathological exam. The bullous lesions of the PV of Neumann demonstrate intraepidermal blister and suprabasal acantholysis identical to pemphigus vulgaris. The early lesions of PV of the Hallopeau type show mode-

rate suprabasal acantholysis, many intraepidermal microabscesses with acantholytical epidermal cells, and innumerous eosinophils (eosinophilic microabscesses). In both types, vegetating plaques are characterized by evident acantholysis, extensive papillomatosis and patent eosinophilia.[7]

Some episodes of pemphigus induced by use of angiotensin-converting enzyme (ACE) inhibitors have been reported. In most reports the drug involved was captopril. It has been proposed that the sulfhydryl group in captopril is responsible for pemphigus induction as it interferes in keratinocyte adhesion. As for enalapril, which does not include the sulfhydryl group, there are less than ten cases caused by its use reported in the literature.[7]

Histopathologically, the initial lesions of pemphigus vulgaris and pemphigus vegetans demonstrate suprabasal acantholysis. PV also exhibits epidermal hyperplasia, papillomatosis and intraepidermal eosinophilic microabscesses. Histopathology is different in pemphigus vegetans as it presents eosinophilic response, microabscess formation and vesiculation extension.

The immunofluorescence found in PV is indistinguishable from pemphigus vulgaris. Direct immunofluorescence demonstrates IgG and C3 deposits on the surface of keratinocytes and indirect immunofluorescence reveals IgG circulation.

The diagnosis may be compromised by the varied clinical presentation.[10] Differential diagnosis should be used with chronic infections and Hailey-Hailey disease.[8]

Systemic corticosteroid is the treatment of choice. However, the addition of immunosuppressants such as cyclosporine and azathioprine may be necessary even as corticosteroid use saver. Patients with the Neumann type have a course similar to pemphigus vulgaris, requiring larger doses of corticosteroid, with relapse and remission phases. Patients with PV of the Hallopeau type have little or no relapse and generally respond to smaller doses of corticosteroids.[10]

The publication of this case is important for the rarity of the disease, manifested in this case with an uncommon clinical presentation, with absence of mucosae and flexor surfaces involvement, as well as the more advanced age of the patient, associated with the use of enalapril as a possible trigger factor. It also brings to mind the importance of using differential diagnosis in day-to-day outpatient clinic activities, aiming at changing the treatment when the patient is not responsive to the first prescribed. ❑

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