Evaluation of cases of pemphigus vulgaris and pemphigus foliaceus from a reference service in Pará state, Brazil*

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Abstract: BACKGROUND: Pemphigusis a bullous, rare and chronic autoimmune disease. There are two major forms of pemphigus: vulgaris and foliaceus. Epidemiological data and clinical outcome in patients diagnosed in the Brazilian Amazon states are still rare.
OBJECTIVES: To study the occurrence of the disease during the study period and analyze the epidemiological profile of patients, the most common subtype of pemphigus, and the clinical evolution of patients.
METHODS: Retrospective analysis of medical records of hospitalized patients with pemphigus foliaceus and pemphigus vulgaris in the period from 2003 to 2010 in Dermatology Service of Hospital Fundação Santa Casa de Misericórdia do Pará, Belém, Northern Brazil.
RESULTS: We found a total of 20 cases of pemphigus during the study period, 8 of which were of foliaceus pemphigus and 12 of vulgaris pemphigus. Pemphigus foliaceus had the predominance of male patients (75%), showed satisfactory clinical evolution, and was characterized by absence of pediatric cases. Pemphigus vulgaris affected more women (66.7%), showed mean hospital stay of 1 to 3 months (50%), and there were three cases of death (25%). The prescribed immunosuppressive drugs included prednisone with or without combination of azathioprine and/or dapsone. Sepsis was associated with 100% of the deaths.
CONCLUSIONS: The occurrence of the disease is rare, there are no familiar/endemic outbreaks in the sample. Evolution is usually favorable, but secondary infection is associated with worse prognosis. The choice of best drugs to treat pemphigus remains controversial.
Keywords: Autoimmunity; Immunosuppressive agents; Pemphigus; Skin diseases, vesiculobullous

INTRODUCTION

Pemphigus is the name of a group of autoimmune pathological entities characterized by the formation of intraepithelial blisters in the skin and/or mucosa. It is histologically characterized by the formation of intraepidermal blisters and by the presence of deposits of immunoglobulin G (IgG) on the surface of keratinocytes. The presence of intraepidermal blisters results in loss of integrity of intercellular fixations caused by acantholysis, which means loss of adhesion between epithelial Malpighi cells. Autoantibodies act in desmosemes leading to loss of intercellular adhesion.[1,2]

The two major clinical forms of this disease are pemphigus vulgaris (PV) and pemphigus foliaceus (PF) – and its variant, endemic *pemphigus foliaceus* (EPF) or Fogo Selvagem – and differ between each other in terms of clinical, histologic, epidemiological and serological characteristics.[3] Less frequent forms include: drug-induced pemphigus, pemphigus herpetiformis, paraneoplastic pemphigus, and immunoglobulinA pemphigus.[4-7]

PV is considered the most common and most severe type of pemphigus and begins with oral lesions appearing as aphtous ulcers or lesions and subsequently affects the skin, with the onset of vesicles and flaccid blisters containing clear or turbid fluid throughout the tegument (Figure 1). In PV, IgG autoantibodies are directed against a group of transmembrane adhesion proteins located in desmosomes and named desmogleins (Dsg), more specifically their subtypes 1 and 3 (cutaneo-mucous form) and 3 (mucous form), which leads to acantholysis in the suprabasal spinous layer.[2,3,8]

PF is characterized by superficial blisters that break easily, eruptions, erythematous areas, crusts, and scales not affecting the mucosa (Figure 2).

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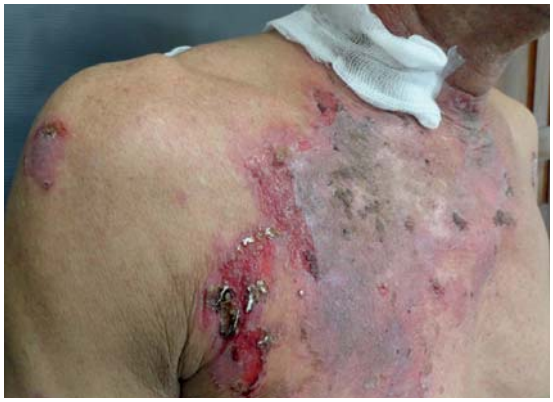

Figure 1: Pemphigus vulgaris. Extensive areas of ulceration, crusting and blisters affecting chest and upper limb

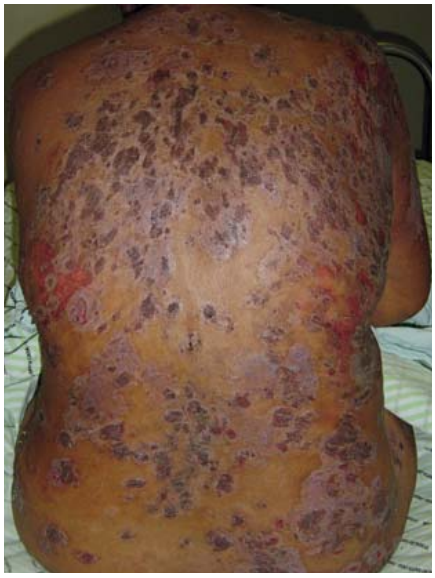

Figure 2: Pemphigus foliaceus. Erythematous-ulcerous-squamous-crusty plaques (like mud splashes) disseminated on patient's back

Intradermal acantholysis occurs in the granular layer. The antigen for PF is known to be Dsg 1, which is highly expressed in the upper spinous layers.[8] PF may be subdivided into two clinical forms: the classical one, also known as Cazenave's disease, which is rare and occurs sporadically throughout the world; and the endemic one (EPF), or Fogo Selvagem, which occurs mainly in South America, especially in rural areas from Southeastern and Midwestern Brazil, and shows a great proportion of familial cases, particularly affecting young adults and children. Evidence indicates that a mosquito of the genus Similium (popularly known as black fly) may the environmental triggering factor for autoimmune response in EPF.[2,9,10]

In the Brazilian Amazon, one of the first effective reports on pemphigus described seven clinical cases diagnosed with PF in Pará state, where several countryside towns had mining areas that attracted a great number of migrants coming from other Brazilian states, especially from the Midwest region. Only one of the reported cases of pemphigus came from Pará state, and the others came from Goiás state, where the disease in acknowledgedly endemic.[11] From 1994 to 2004, 61 histologically confirmed cases of pemphigus were reported at a dermatology referral service in Belém, capital city of Pará state, 30 of which were cases of PF and 31 of PV. Additionally 55.56% of patients presented with the generalized form of the disease.[12]

Other 10 cases of PF in the Brazilian Amazon were reported in Amazon state, including patients from riverside municipalities, but there was no evidence of familial and endemic outbreaks.[13] In the Peruvian Amazon, studies indicate the occurrence of endemic areas of PF and PV, where the disease presents with histopathological, clinical and epidemiological characteristics similar to those described in Brazil.[14,15]

Treatment for pemphigus is primarily performed with systemic corticosteroids and should ideally be prescribed by a physician experienced in immunosupressive therapy at a daily dose of 1 to 2 mg of prednisone per kilo of weight, or the equivalent dose of another corticosteroid. The combination of corticosteroids with imunossupressants (azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) has shown good results in controlling the disease, which allowed to reduce the dose of corticosteroid. When there is an associated bacterial lesion, systemic antibiotic therapy is also implemented. Clinical and laboratory control should be constant, in order to evaluate both disease evolution and undesired effects of corticosteroid therapy. A multiprofessional intervention is recommended to improve the quality of life of pemphigus patients.[10,16-19]

Knowledge on pemphigus has grown considerably in recent years. With the purpose of standardizing scientific definitions on the management of the disease, the International Pemphigus Committee established some criteria to be used in clinical practice.[19] Disease activity is considered controlled when the existing lesions start to heal and the formation of new lesions stops. Therapy remission is defined as the absence of lesions for at least 2 months during minimum therapy, represented either by a dose of prednisone lower than or equal to 10 mg/day or by the use of adjuvant immunosuppresive therapy for at least 2 months. Remission without therapy occurs when patients not using any systemic therapy are free of lesions for at least 2 months. Recurrence occurs when patients develop three or more new lesions per month

that do not heal spontaneously in 1 week. In cases of recurrence or treatment failure, alternative treatments with new combinations may provide some benefit.

The aim of this paper was to evaluate the epidemiological profile and the clinical evolution of patients with PV and PF admitted to a referral hospital for pemphigus cases in Pará state from 2003 to 2010.

PATIENTS AND METHODS

A cross-sectional, observational, descriptive study was conducted based on the direct analysis of the medical records of patients admitted to Hospital Fundação Santa Casa de Misericórdia do Pará (FSCMPA), city of Belém, Northern Brazil from 2003 to 2010 due to histologically confirmed PV and PF. All the 20 cases of pemphigus reported in the dermatology service of the institution during this period were included in the study. Epimiological aspects, disease history, symptomatology, intercurrent diseases, treatment, and clinical evolution were reviewed. The study was approved by the Research Ethics Committee of the institution under decision no. 002/11.

To perform the statistical analysis, categorical variables were compared between themselves based on contingency tables using the Pearson chi-square test. The Fisher's exact test was used when at least one expected frequency was lower than five. Statistical significance was set at p-value below 0.05.

RESULTS

No significant differences were found between patients from PV and PF groups in terms of gender, age, time from onset to diagnosis, length of hospital stay, and evolution. With regard to gender, there was a statistical trend (p = 0.0948) of PF to affect males (75%) and of PV to affect females (66.7%).

The age group most affected by PV was from 22 to 59 years (83.4%), while no pediatric patient, four adult patients (up to 59 years), and four elderly patients (above 60 years) were diagnosed with PF. The time elapsed from the onset of the first signs and symptoms of the disease to the diagnosis was higher than 1 month and lower than 1 year in 75% of cases in patients from both groups.

Length of hospital stay was higher than 1 month and lower than 3 months in 50% of patients from both groups, and a satisfactory evolution (improvement of clinical symptoms) was achieved in most cases (Table 1). Disease recurrence after previous remission was reported in four of the patients discharged with clinical improvement, but they did not require readmission. However, two PV patients and one PF patient required only one readmission, and one PF patient required more than one readmission.

Oral immunosuppressive therapy regimens used to threat these patients included from monotherapy with prednisone to regimens combining steroids with azathioprine or azathioprine and dapsone (Table 2). Clinical support measures, symptomatic treatment specific for each case, and antibiotic therapy for cases of associated secondary infection were also implemented in the management of pemphigus patients.

Four patients from the study sample died, three of which were diagnosed with PV and one with PF, and developed sepsis with infection in different sites at some point of the treatment (Table 3).

DISCUSSION

Epidemiological data on pemphigus are still limited. The worldwide incidence of the disease ranges from 0.75 to 14 cases/1.000.000 inhabitants per year, depending on location, and tends to be higher in countries at lower latitudes.[20,21] PF cases have shown a significant increase over the last century in geographic areas in Brazil and worldwide, due to its endemic form, and have experienced apparent epidemiological changes, which resulted in an increase in the incidence of PV cases even in regions considered traditionally endemic for PF, with the percentage of PV cases reaching 91.15% in a sample of 1,560 pemphigus patients.[22,23]

The incidence of pemphigus cases diagnosed in Pará state has shown to be low, although the presence of these bullous lesions in this region is beyond question. From 1954 to 1970, 15,803 medical records were searched for the bullous lesions studied back then (including cases of PV, PF, Hailey-Hailey pemphigus, and Düring-Brocq dermatitis), showing an incidence of only 1.7 in a total of 1,000 diseases diagnosed. At that time, when all forms of pemphigus were still believed to have a possible endemic involvement, it was stated that "the cases of pemphigus vulgaris [studied] affected patients who have always lived in Belém" and therefore were away from the so-called "pemphigus areas", a term used to refer to the Midwestern region of Brazil, which concentrates the greatest number of cases of EPF.[10,24]

Patients' distribution according to age and gender differs from country to country. In a Thai study, the percentage of females was found to be as twice as high as that of males both in PV and PF patients. However, similar to what was observed in our study, some papers indicate a predominance of females among PV patients and of males among PF patients.[12,15,25,26]

The time elapsed from onset of symptoms and diagnosis was less than 1 month in 20% of PV and PF patients, and between 1 month and 1 year in 75% of

Table 1: Demographic and clinical aspects of 20 pemphigus patients diagnosed between 2003 and 2010

Variables	Type of pemphigus						p-value
	Foliaceus		Vulgaris		Total		
	n	%	n	%	n	%	
Gender							
Female	2	25	8	66.7	10	50	p = 0.0948
Male	6	75	4	33.3	10	50	
Age group							
Under 21 years	0	0	1	8.3	1	5.0	p = 0.1419
22 to 59 years	4	50	10	83.4	14	70.0	
≥ 60	4	50	1	8.3	5	25.0	
Time from the first signs/symptoms to diagnosis							
< 1 month	1	12.5	3	25.0	4	20.0	p = 0.4334
1 month < 1 year	6	75.0	9	75.0	15	75.0	
≥ 1 year	1	12.5	0	0.0	1	5.0	
Length of hospital stay							
Less than 1 month	3	37.5	4	33.3	7	35.0	p = 0.9653
1 - 3 months	4	50.0	6	50.0	10	50.0	
> 3 months	1	12.5	2	16.7	3	15.0	
Evolution							
Satisfactory	7	87.5	9	75.0	16	80.0	p = 0.6186
Death	1	12.5	3	25.0	4	20.0	
Total	**8**	**100**	**12**	**100**	**20**	**100**	

Table 2: Immunosuppressive therapy regimen and time of clinical improvement in 20 pemphigus patients diagnosed from 2003 and 2010

Type of pemphigus	Drug	Mean time of clinical improvement (days)
Vulgaris		
	Prednisone	16
	Prednisone and azathioprine	46.5
	Prednisone and dapsone	44
	Prednisone, dapsone, and azathioprine	36
Foliaceus		
	Prednisone	46.25
	Prednisone and azathioprine	19.5
	Prednisone and dapsone	16
	Prednisone, dapsone, and azathioprine	18

Table 3: Intercurrent diseases related to the four pemphigus patients who evolved to death

Causes of death	n	Percentage
PV + sepsis + septic shock	1	25.0
PV + sepsis + acute renal failure + metabolic disorder + secondary infection	1	25.0
PV + sepsis + multiple organ failure	1	25.0
PF + sepsis + pneumonia	1	25.0
Total	**4**	**100**

PV = pemphigus vulgar; **PF =** pemphigus foliaceus.

patients with both forms of the disease. In most patients, the disease has a gradual onset, with skin lesions evolving for weeks or months. A smaller number of patients present with a more acute onset, with extensive bullous lesions affecting large areas of tegument.[8] Cases of acute systemic involvement are related to the most severe forms of the disease and require more prolonged length of hospital stay.

Although many regimens have been implemented to treat pemphigus, none of them has shown to provide absolute efficacy in controlling the disease. Oral steroids represent the basic choice for the management of pemphigus at any disease stage, and their development in the last century led to a substantial improvement in the survival of all patients.[27] In our study, prednisone was administered in all therapy regimens for PV and PF. Drug dosage was empirically adjusted according to disease severity and reached 2 mg/kg/day as needed.

Mean time that patients used monotherapy with prednisone, from the beginning of treatment to clinical improvement, was 16 days in the PV group and 46.25 days in the PF group. An American study compared the clinical course of patients with different degrees of PV involvement when treated with monotherapy with corticosteroids at prednisone-equivalent doses. As expected, PV patients with moderate severity showed lower mortality rates ($p = 0.045$) compared to those with severe disease, as well extremely lower remission rates.[28]

The disease was controlled by adjuvant therapy with other immunosuppressive agents, which are added as steroid saving agents.[29] The patients of this study received adjuvant therapy with azathioprine and dapsone, or both drugs combined with corticosteroid. Treatment time in PV patients who required a combination of drugs was higher than that of patients receiving steroid monotherapy, which may indicate that this combination was used in cases with more severe disease expression.

In the past, the combination of corticosteroid and azatioprine was believed to represent the cure for pemphigus patients. Evidence on the best therapy regimen is still scarce, but this combination has been considered the most effective steroid saving strategy, since it may have an effect equal to or even higher than that obtained with the treatment with mycophenolate mofetil.[28,30,31] The combination of corticosteroids and azatioprine also showed a greater benefit compared to dexamethasone-cyclophosphamide pulse therapy in the treatment of pemphigus, thus reducing the need for additional therapies.[32,33]

Dapsone, which is currently used as chemotherapeutic agent in many diseases such as Hansen's disease, has been considered to be useful in the treatment of pemphigus, probably because it is able to control antibody levels in pemphigus patients, but this hypothesis requires further confirmation.[27] The rates of overall response to dapsone when it was administered in isolation or in association with corticosteroids or immunosuppressants were 84% in mucous membrane pemphigoid and 81% in bullous pemphigoid. Hemolysis was the most common adverse effect observed.[34] Although dapsone plays a significant role in the treatment of pemphigus, evidence to recommend its use in PV cases is still scarce.[19]

All cases of death from our sample were related, among other comorbidities, to sepsis, which evolved to some of its complicated forms (septic shock, severe sepsis, and organ failure). In these conditions, determining markers to stratify the risk of death for hospitalized patients seems to be useful to improve diagnosis. It was found that PV patients who clinically evolved to severe sepsis or who show laboratory results with high levels of serum lactate (>4mmol/L) represented a potential risk group and may benefit from a more aggressive treatment.[35]

In 1998, pemphigus and other bullous lesions were considered the fourth most common cause of death among all dermatological diseases in the United States.[36] Before the 1940s, when there was the emergence of corticosteroids, PV was almost invariably lethal.[28] Currently, it is difficult to understand the real incidence of mortality for pemphigus because of the small number of studies involving a large sample of patients, the heterogeneous number and size of cohorts, and because it is not always possible to properly distinguish mortality for complications caused by PV from those caused by PF. Anyway, mortality rates range from 3.62% (only PV) to 20% (not distinguishing PV from PF).[37,38]

Studies with large cohorts have been conducted to estimate mortality rates for pemphigus. In Iran, where the disease is highly prevalent, a prospective study with 1,206 patients found mortality rates of 6%, with sepsis representing the main cause of deaths.[39] In Taiwan, a cohort of 853 patients showed a mortality rate of 10.3% and found that, when compared to the general population, pemphigus patients showed a significantly higher risk of death for pneumonia, sepsis, cardiovascular diseases, and peptic ulcer.[40]

CONCLUSIONS

This study allowed to outline some characteristics of pemphigus in Pará state, Brazilian Amazon, during a period of 8 years, showing the evolution of patients from a referral service. The number of cases diagnosed in the state are relatively small compared to other country federal units, and no familial or endemic cases were found. Disease prognosis was predo-

minantly satisfactory, with four cases of death associated with sepsis in the study sample.

The treatment of pemphigus is still a challenging task. The choice for the best regimen for each type of patient, based on the extent of disease, patients' comorbidities, control of side effects, and facility of access to drugs, which may be expensive sometimes, makes treatment options very limited in certain cases.❑

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