

Report

Survey of bullous pemphigoid disease in northern Iran

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Abstract

Background Bullous pemphigoid is an autoimmune subepidermal blistering skin and mucous membrane disease that usually occurs in elderly people. This study was done to determine clinical features, paraclinical findings, incidence of mucosal lesions, prognosis, course of the disease, and mortality rate of patients with bullous pemphigoid.

Method Retrospective descriptive study that reviews the existing files of 122 patients with bullous pemphigoid referred to dermatology clinics of Ghaem and Imam Reza hospitals in Mashhad, Iran, from 1995 to 2010.

Result The majority of patients were aged between 60 and 79 years, and 53% of them were women. The major prodromal lesions were erythematous and urticarial (36.8%) and eczematous lesions (32.7%); 84.3% of patients complained of pruritus, and mucosal lesions were observed in 31.1% of patients (all in the oral mucosa). The most frequent concurrent diseases with pemphigoid were hypertension and diabetes mellitus.

Conclusion Clinical features, paraclinical findings, incidence of mucosal lesions, prognosis, course of the disease, and mortality rate of bullous pemphigoid in the Khorasan region were approximately similar to results from other regions.

Introduction

Bullous pemphigoid (BP) is an acquired autoimmune blistering disease that generally presents with subepidermal blisters in the elderly and is characterized by linear deposits of IgG and/or C₃ along the epidermal basement membrane zone. Autoantibodies to hemidesmosome-associated proteins, BP antigens 1 and 2 (BP 230 and BP 180 respectively), are the main cause of the disease. It occurs throughout the world and is the most frequent immunobullous disease in western Europe. The incidence of BP is estimated to be 6–7 cases per million population per year in France and Germany and 30 cases per million per year in central UK.¹

Skin lesions that characterize the disease include large, tense bullae on normal or erythematous skin, which often appear after a prodromal phase (urticarial prodrome or eczematous prodrome).

The disease has different clinical variants and sometimes is completely localized.^{1–3} Studies show that the incidence rate of BP is increasing.⁴ Since in our country the number of patients who have blistering diseases, in particular BP, is remarkable, it was necessary to obtain

some information about the clinical situation and other epidemiological aspects of this disease. Nasiri *et al.*⁵ studied 17 patients in Tehran, but we have no data related to this disease in Khorasan (north of Iran); therefore, this survey was conducted to determine the epidemiological characteristics, clinical features, frequency of mucosal lesions, prodromal symptoms and signs, and studying laboratory findings of patients with BP who were referred to dermatology clinics at the Ghaem and Imam Reza hospitals in Mashhad from 1995 to 2010.

Patients and methods

This descriptive survey was a cross-sectional study on 140 patients who were referred to dermatology clinics at the Ghaem and Imam Reza hospitals in Mashhad, Iran, between 1995 and 2010, and whose disease was confirmed as BP by histopathology and direct immunofluorescence examination. The necessary information, including age, gender, existence of mucosal lesions, prodromal signs, description of blistering lesions, laboratory findings (cell blood count), existence of associated diseases, malignancies, history of drug use before initiation of the disease, the course of disease and the method

of treatment, relapse cases, and mortality rate were derived from the files and listed in a form. Exclusion criteria were any failure to complete patients' files. SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA), was used in all statistical procedures. We used chi-squared or the Fisher's exact test.

Results

We reviewed the files of 140 patients with BP in Khorasan, Iran. Only 122 patients' files entered the study due to incomplete files. The mean age of our patients at the time of diagnosis was 69 years with a range from 19 to 115 years of age. Over 78% of patients were older than 60 years of age. The average age of onset was 74 for men and 65 for women. Fifty-three percent of patients were women.

The frequency of lesions at the time of admission is shown in Table 1. In the course of hospitalization, large and tense blisters were seen in 100% of patients; 84.3% of patients had pruritus.

Blistering lesions in most patients were generalized with predominance of limbs and trunk involvement, and they were limited to limbs in only four cases, and in one case they were limited to the head and face.

Table 2 shows the frequency of mucosal involvement. In laboratory findings, 60.8% of patients had leukocytosis ($WBC > 10\,000/mm^3$), and 54.9% of them had eosinophilia of peripheral blood (the number of eosinophils was more than $500/mm^3$).

The most frequent concurrent disease with BP was hypertension, which was present in 28 patients (22.9%).

Table 1 Frequency of lesions at the time of admission

Type of lesions	No. of patients	%
Bullous lesion	33	27.3
Urticarial lesion	45	36.8
Eczematous lesion	40	32.7
Mucosal lesion	4	3.2

Table 2 Frequency of mucosal lesions

Oral location	No. of patients
Upper gingival mucosa	1
Lower gingival mucosa	0
Upper lip	0
Lower lip	0
Buccal mucosa	18
Tongue	4
Floor of the mouth	0
Hard palate	3
Soft palate	9
Pharynx	3

Sixteen patients (13.1%) had diabetes mellitus. In one patient, rheumatoid arthritis was seen, and another patient had a history of lichen planus. In addition, one case had chronic renal failure, eight had asthma, two had chronic obstructive pulmonary disease, one had epilepsy, two had Parkinson's disease, and one had tuberculosis. Malignancy (malignant brain tumor) was seen in only one patient.

Sixteen patients had a history of drug consumption before initiation of the disease, but there was no history of use of certain medicine or drug category associated with BP. Among the 122 patients studied, only five were treated and followed up as outpatients due to refusal of admission, and the remaining were hospitalized between one and five times; the average duration of patients hospitalization was 27 days. Therapeutic response was achieved by oral prednisolone in 74 patients (60.6%), by immunosuppressive medication along with prednisolone in 40 (32.7%), and by dapsone in eight.

Twenty-two patients (18%) had a relapse and in studying the mortality rate of this sample, there were two deaths (1/6%; a 95-year-old man hospitalized for 7 d, and a 115-year-old man hospitalized for 12 d).

Discussion

BP is a disease of elderly patients. Our study showed that more than 78% of patients were older than 60 years of age, which is the same as previous studies.⁶⁻⁸

The gender distribution in this study was almost equal, but a 2-year prospective investigation in Switzerland showed an apparent predominance in men compared to women.⁹ In Kuwait,⁸ the female to male ratio was 5.1, and in the United States,^{10,11} males and females were nearly equally affected. BP is considered the most common autoimmune blistering disorder in western Europe. In the Middle and Far East, BP appears to be rarer, except in Singapore, and more likely to develop in Indians than Chinese people.¹

Like other studies, in this survey, blisters had appeared after a prodromal phase (urticarial and erythematous lesions or eczematous lesions) in the majority of cases ($36.8 + 32.7\% = 69.5\%$), and most patients had complained of pruritus. As a result, in old patients, with pruritus, eczema, and urticaria, the possibility of this disease should be considered.^{1-3,12,13}

According to the studies by Venning *et al.* and Hodge *et al.*, mucosal involvement is rarely the first symptom of the disease, but during the disease course, mucosal involvement can be seen, which is limited to oral mucosa in most cases, especially the buccal mucosa.^{14,15} Oral lesions were observed in 37% of patients in Kuwait⁸ and 12.8% in Taiwan.⁶ In this study, mucosal involvement

(31.1%) had a lower frequency than the study of Nasiri *et al.*⁵ and in all cases was limited to oral cavity (with predominance of buccal and soft palate mucosa), and mucosal involvement was the first symptom of the disease in only four patients (3.2%).

There are some reports showing that the disease had appeared after exposure to ultraviolet and psoralen + ultraviolet A radiation and the use of some medications (such as furosemide, sulfasalazine, penicillin, penicillamine, local fluorouracil, and antipsychotics).^{16–18} However, none of our patients had a history of consumption of these drugs before initiation of the disease.

In this study, like most studies, blistering lesions were mainly generalized with a predominance of limbs and trunk involvement, and the localized form was only seen in four cases (three were limited to the limbs, and one was limited to the head and face). In available reports, the localized form of the disease was seen mainly in the limbs.^{1,2} The acute phase of pemphigoid is usually accompanied by leukocytosis and eosinophilia, and almost half of the patients have eosinophilia of peripheral blood.^{1–3,6} In our study, leukocytosis and eosinophilia were also present.

In spite of the association of BP and some autoimmune diseases, Taylor *et al.*¹⁹ showed that there is no available evidence confirming the association between this disease and diseases such as pernicious anemia, rheumatoid arthritis, multiple sclerosis, vitiligo, and ulcerative colitis, which are seen along with this disease.

Although there are some available reports showing an increased frequency of malignancy,²⁰ Rzany and Weller and Venning and Wojnarowska showed that there is no accurate evidence on this association, and due to the prevalence of malignancy and BP in old age, this association is more likely to be a coincidence;^{21,22} similarly, in our study, only one case of malignancy was seen. In case control studies, the association of psoriasis, diabetes mellitus, and lichen planus with this disease has been observed.^{1,3,23} Similarly, in this study, seven cases of diabetes were noticed, and one case had a history of lichen planus.

In this study, hypertension was the most frequent concurrent disease (22.9%). However, based on a systematic review by Haghdoost *et al.*,²⁴ the frequency of hypertension is lower than its prevalence among normal Iranian population older than 55 years of age.

In available resources and papers, there were no records on association of this disease with other diseases that were present in this study (asthma, tuberculosis, epilepsy, etc.), and it seems that these findings are coincidental.

In most cases, BP subsides after treatment, but relapse has also been reported^{1,2,6,8}; similarly, in this study, 18%

of patients had a relapse, which in one case was caused by abrupt prednisolone dose reduction.

The mortality rate of this disease is low, but in the active and acute phase, it could be fatal in old and disabled individuals.^{1–3} The rate of mortality in the first year is between 10 and 40%, and it is rather a consequence of drug therapy.²⁵ Colbert *et al.*¹⁰ reported that the first year mortality rate in patients was 10.8% in their study. Two mortality cases were seen in our study, both of them died at the beginning of the disease course and treatment, and more likely the death was due to acute complications of the disease (water and electrolyte disorders), old age, and underlying diseases (in particular, diabetes mellitus).

Conclusion

According to the findings of this study, epidemiological characteristics and clinical features, oral presentations, laboratory findings, and the rate of response of patients to treatment in our area is almost similar to the results of studies in other parts of our country and the world.

Limitation of the study

We did not have any data about antibasement membrane autoantibodies and antigen profile of patients since these test are not performed in northern Iran.

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