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Evaluation of 62 bullous pemphigoid patients

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Abstract
Bullous pemphigoid (BP) is an acquired autoimmune disease often manifesting with subepidermal bullae. Autoantibodies against hemidesmosomes constitute the main cause of BP. In this study, we aimed to evaluate the clinical and histopathological characteristics of BP patients and to discuss them in light of the studies conducted in Turkey and around the world. The retrospective study included 62 patients that were diagnosed with BP in our clinic between 2005 and 2017. Diagnosis of BP was established based on clinical, histopathological, and DIF microscopy findings. Age, gender, duration of disease, presence of pruritus, peripheral eosinophilia, significant histopathological findings, history of smoking, and family history were recorded for each patient. Patients under 18 years of age were excluded from the study. The 62 patients comprised 24 (38.7%) men and 38 (61.3%) women with a median age of 72.0 years. The male-to-female ratio was 1.5. The median age at disease onset was 67.0 (range, 50-75) years and the median duration of disease was 1.0 (0.5-3.0) years. Of the 62 patients, 35 (56.5%) had a history of smoking and mucosal involvement was found in 27 (43.5%) patients. BP is a disease of the elderly and more common in women than in men. Oral mucosa should be an integral part of the physical examination in BP patients. Pruritus is a significant clinical symptom and eosinophilia is an important laboratory marker in the diagnosis of BP, particularly in patients with difficult diagnosis.

Keywords: Bullous pemphigoid, smoking, pruritus

Introduction

Bullous pemphigoid (BP) is an acquired autoimmune disease that often manifests with subepidermal bullae and is characterized by linear deposition of immunoglobulin G (IgG) and/or C3 along the epidermal basement membrane zone. Autoantibodies against hemidesmosomes constitute the main cause of BP. BP mostly affects the elderly and is more common in women than in men. Moreover, it is a common disease around the world and also the most common immunobullous disease in Europe [1].

Bullous pemphigoid (BP) may start with pruritus in the prodromal stage, which may last for several days to several months. Classical BP is characterized by tense, hemorrhagic bullae of 1-3 cm diameter that appear on erythematous skin. BP mostly involves the axillae, groins, legs, and lower abdomen. The bullae in BP typically heal without scars after becoming eroded and crusted areas. Skin or mucosal lesions are often not life-threatening, but mortality rate is relatively higher in the elderly [2].

Diagnosis of BP is based on clinical features, direct immunofluorescence (DIF) microscopy, and presence of circulating autoantibodies. Laboratory tests can be normal in 10% of the patients [3].

Bullous pemphigoid (BP) is a self-limiting disease which may last from several months to a few years. BP may relapse in some patients during the first year of treatment. The primary step in the treatment of BP is to stop the provoking drug and treat underlying malignancy, if identified any. Mainstay treatment of BP includes immunosuppressive drugs, mostly including topical corticosteroids [2,4].

In this study, we aimed to evaluate the clinical and histopathological characteristics of BP patients and to discuss them in light of the studies conducted in Turkey and around the world.

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Material and Methods

The retrospective study included 62 patients that were diagnosed with BP in our clinic between 2005 and 2017. Diagnosis of BP was established based on clinical, histopathological, and DIF microscopy findings. Typical histopathological features of BP included subepidermal splitting and mixed inflammatory infiltrate, whereas typical DIF microscopy pattern was linear deposition of IgG and/or C3 along the epidermal basement membrane zone. Patients with nonbullous BP, those that could not be diagnosed histopathologically, and patients under 18 years of age were excluded from the study. Age, gender, duration of disease, presence of pruritus, peripheral eosinophilia, significant histopathological findings, history of smoking, and family history were recorded for each patient. The study was conducted in accordance with the Helsinki Declaration and was initiated after an approval was obtained from the local ethics committee.

Statistical Analysis

Data were analyzed using SPSS for Windows version 17.0 (SPSS Inc. Co, Chicago, IL, USA). Normal distribution of data was tested using histogram plots and the Kolmogorov–Smirnov test. Descriptive statistics were expressed as median and percentiles (25-75).

Results

The 62 patients comprised 24 (38.7%) men and 38 (61.3%) women with a median age of 72.0 years. The male-to-female ratio was 1.58. DIF microscopy indicated C3 deposition in 12 (19.4%), C3 + IgG deposition in 30 (48.4%), IgG deposition in 6 (9.7%), and no deposition in 14 (22.6%) patients. Although no comorbidity was found in 28 (45.2%) patients, brain tumor was found in 1 (1.6%), diabetes mellitus (DM) in 12 (19.4%), hypertension (HT) in 11 (17.7%), and cerebrovascular diseases (CVDs) in 10 (16.1%) patients. Of the 62 patients, 27 (43.5%) patients were using less than 3 drugs, 19 (30.6%) were using 3-5 drugs, 4 (6.5%) were using more than 5 drugs, and 12 (19.4%) had no drug history. The bullae were localized in the extremities + body in 21 (30.6%), extremities only in 35 (56.4%), and body only in 6 (9.7%) patients. Of the 62 patients, 35 (56.4%) had a history of smoking and mucosal involvement was found in 27 (43.6%) patients. The most common drugs used in the treatment of BP were systemic steroids (n= 36; 58.1%), followed by topical steroids (n=19; 30.6%), topical antibiotics (n=3; 4.8%), intravenous immunoglobulin (IVIG) (n=2; 3.2%), and dapsone (n=1; 1.6%). Pruritus was present in 51 (82.3%), treatment-related complications occurred in 2 (3.2%), and eosinophilia occurred in 25 (33.9%) patients. The skin lesions manifested with bullae in 10 (16.130%), polymorphic lesion in 25 (40.322%), eroded plaques in 1 (1.613%), eroded-ulcerated lesions in 1 (1.613%), and vesicular bullae in 25 (40.322%) patients. The median age at disease onset was 67.0 (range, 50-75) years and the median duration of disease was 1.0 (0.5-3.0) years (Table 1, Table 2).

Table 1. Demographic, laboratory, and clinical characteristics - 1

		n	%
	Male	24	(38.7)
	Female	38	(61.3)
Age (years)		72.00	(54.00-78.00)
DIF findings	C3 deposition	12	(19.4)
	C3 + IGG deposition	30	(48.4)
	IGG deposition	6	(9.7)
	No deposition	14	(22.6)
Comorbidity	None	28	(45.2)
	Brain tumor	1	(1.6)
	DM	12	(19.4)
	HT	11	(17.7)
	CVD	10	(16.1)
Drug usage	None	12	(19.4)
	Less than 3 drugs	27	(43.5)
	3-5 drugs	19	(30.6)
	More than 5 drugs	4	(6.5)
Lesion site	Extremities + Body	21	(30.6)
	Extremities	35	(56.4)
	Body	6	(9.7)
Smoking	No	27	(43.5)
	Yes	35	(56.5)
Mucosal involvement	No	35	(56.5)
	Yes	27	(43.5)

HT: hypertension; DM: Diabetes mellitus; for quantitative variables, median was used in lieu of n value and percentiles (25-75) were used in lieu of %.

Table 2. Demographic, laboratory, and clinical characteristics - 2

		n	%
Drugs	Dapsone	1	(1.6)
	IVIG	2	(3.2)
	Systemic steroids	36	(58.1)
	Topical antibiotics	3	(4.8)
	Topical steroids	19	(30.6)
Pruritus	No	11	(17.7)
	Yes	51	(82.3)
Treatment complications	No	60	(96.8)
	Yes	2	(3.2)
Eosinophilia	No	41	(66.1)
	Yes	21	(33.9)
Lesions	Bullae	10	(16.130)
	Polymorphic lesion	25	(40.322)
	Eroded plaques	1	(1.613)
	Eroded-ulcerated lesions	1	(1.613)
	Vesicular bullae	25	(40.322)
Age at disease onset (years)		67.0	(50.0-75.0)
Duration of disease (years)		1.0	(0.5-3.0)

For quantitative variables, median was used in lieu of n value and percentiles (25-75) were used in lieu of %.

Discussion

The results indicated that BP is a disease of the elderly and mucosal involvement can be commonly seen in BP patients. Although BP can be seen at any age, it mostly affects patients older than 60 years of age [2,3]. Banihashemi et al. [1] reported that more than 78% of their patients were aged over 60 years and Försti et al. [5] reported a mean age of 77 years for their patients. In our patients, mean age was 72 years, which was consistent with the literature.

Bullous pemphigoid (BP) is more common in women than in men. However, a study conducted in Switzerland [6] reported that there was a male preponderance in their BP patients and another study that was conducted in USA [7] reported that the male-to-female ratio was similar. Nevertheless, a study conducted in Kuwait [8] revealed that BP was five times more common in women than in men among their patients. In our study, the female-to-male ratio was 1.58, which confirms the hypothesis that autoimmune diseases are more common in women than in men.

Mucosal involvement in BP can be seen in 10-30% of the patients. Akay et al. [9] reported that mucosal involvement was present in 12.9% and Ekiz et al. [10]. reported that mucosal involvement was found in 17.2% of their patients. In our study, mucosal involvement was present in 43.5% of the patients, which was remarkably higher than the rates reported in previous studies. Both our study and the previous studies indicate that mucosal involvement should be taken care of during the physical examination of BP patients.

Bullous pemphigoid (BP) typically manifests with vesicles and bullae that appear on erythematous skin. Esmaili et al. [11] and Banihashemi et al. [1] both evaluated BP in Iranian patients and reported that bullae were detected in 97.5% and 27.3% of the patients, respectively. In our study, bullae accompanied by vesicles or bullae alone were detected in 56.4% of the patients, which was a median rate between the rates reported by other studies.

Pruritus is known to be a significant clinical symptom in BP patients. Yazici et al. [12] detected pruritus in 73%, Akay et al. [9] detected in 77.4%, Ekiz et al. [10] detected in 82.8% , and Pascal et al. [4] detected in 93% of the patients. In our study, pruritus was detected in 82.3% of the patients, which suggests that pruritus is a significant clinical symptom in BP patients.

Peripheral eosinophilia and elevated serum total immunoglobulin E (IgE) levels have been implicated in some BP patients (2). Esmaili et al. [11] found peripheral eosinophilia in 30.3% , a Taiwanese study [13] found in 22.1%, and Kizilyel et al. [14] found in 13.2% of the patients. In our study, peripheral eosinophilia was detected in 33.9% of the patients. Taken together, all these rates implicate that peripheral eosinophilia can be a supportive diagnostic marker of BP, particularly in patients with difficult diagnosis.

Smoking is a significant factor for the development of BP. A history of smoking was detected in 24% of the patients in the study by Akarsu et al. [15] and in 23.6% of the patients evaluated by Alexandre et al. [16]. However, in our study, 56.5% of the patients had a history of smoking, which was higher than the rates reported by other studies. All these rates implicate that smoking is an aggravating factor for BP.

Bullous pemphigoid (BP) is a chronic disease with varying duration of disease. Sophan et al. [17] reported that the mean duration of disease was 2.1 months, Ekiz et al. [10] reported a mean duration of 15.4 months, and Yazici et al. [12] reported a mean duration of 9.8 months for their patient series. In our study, the mean duration of disease was 1 year, which was consistent with the literature.

Coexistence of BP with various diseases has been reported in numerous studies. These diseases mainly include neuropsychiatric

disorders, tumors, DM, HT, and autoimmune diseases [2,3]. Kibsgaard et al. [18] evaluated 98 patients with BP and reported that 70 patients were accompanied by cardiovascular diseases, 37 patients by neurologic disease, 15 patients by DM, and 14 patients by cancer. Similarly, Kizilyel et al. [14] evaluated 46 patients with BP and revealed that 28 patients had HT, 21 patients had CVD, 17 patients had DM, and 4 patients had cancer. In our study, 12 patients had DM, 11 patients had HT, 10 patients had CVD, and 1 patient had tumor. Although these rates were similar to those reported in the literature, the only difference was that the incidence of cancer in our patients was relatively lower.

Factors that facilitate BP in genetically predisposed individuals are various. These are drug intake (eg, furosemide, enalapril, ıbuprofen, ampicillin, sulfonamide), physical agents (eg, ultraviolet, thermal or electrical burns, or surgical procedures), vaccinations (eg, anti-influenza vaccine, tetanus toxoid), diet (eg, gluten), infections (eg, cytomegalovirus, epstein-barr virus, HHV-6, hepatitis B and C viruses, helicobacter pylori, toxoplasma gondii) [19]. In our study, the majority of patients were taking medication. Especially the use of antihypertensive drugs was high. But we could not detect many of the other triggering agents.

Common agents used in the treatment of BP include topical corticosteroids, systemic corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, dapsone, intravenous immunoglobulin, plasmapheresis, rituximab, and omalizumab [2,3,20]. Ekiz et al. [10] reported that 37% of the patients received topical corticosteroids and 34.5% of the patients received systemic corticosteroids. Moreover, Kibsgaard et al. [18] reported that 67.3% of the patients received topical corticosteroids. In our study, 30.6% of the patients received topical corticosteroids and 58.1% of the patients received systemic corticosteroids. These findings implicate that corticosteroids are the mainstay treatment of BP.

Our study was limited in several ways. First, it was a single-center study. Secondly, it had a relatively small patient series. Thirdly, no evaluation was performed for serum IgE levels.

Conclusion

In conclusion, BP is a disease of the elderly and more common in women than in men. Oral mucosa should be an integral part of the physical examination in BP patients. Pruritus is a significant clinical symptom and eosinophilia is an important laboratory marker in the diagnosis of BP, particularly in patients with difficult diagnosis. However, further multicenter, prospective studies are needed to substantiate our findings.

Competing interests
The authors declare that they have no competing interest

Financial Disclosure
The financial support for this study was provided by the investigators themselves.

Ethical approval
Our study was approved by the local ethics review board.

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