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Epidemiology and Comorbidities of Bullous Pemphigoid: A Retrospective Study

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ABSTRACT

Background: Bullous pemphigoid is the most common autoimmune subepidermal bullous dermatosis which is most commonly seen in the elderly population. Bullous pemphigoid was confirmed to be associated with neurologic and psychiatric disorders; however, it is not associated with malignancies.

Materials and Methods: The aim of this study is to determine the female-to-male ratio and the mean ages of diagnoses; disease durations and comorbidities separately in the female and male Turkish patient groups. In this descriptive study, the patient files of bullous pemphigoid patients who applied to the Istanbul University-Cerrahpasa Faculty of Medicine, Department of Dermatology Blistering Diseases Outpatient Clinic between the years 1999 and 2019 were evaluated retrospectively. The gender, the age at the time of diagnosis, the disease duration and comorbid diseases of each patient were noted.

Results: For the 58 patients included in this study the female-to-male ratio was 1.42. The average age of diagnosis was 73.79 years (15-103 years). The average disease duration was 104.9 months (1-264 months). As for the comorbidities, the most commonly observed ones were, in decreasing frequency, hypertension, diabetes mellitus, coronary artery diseases, chronic kidney disease and osteoporosis.

Conclusion: Bullous pemphigoid has a female predominance and is usually diagnosed during the seventh decade. This study showed an association between bullous pemphigoid and cardiac diseases or diabetes mellitus. However, the results failed to show an association with neurologic or psychiatric diseases. Bullous pemphigoid is not associated with malignancies; similarly, this study did not find a significant prevalence of history of malignant neoplasms in bullous pemphigoid patients.

Keywords: Bullous, Comorbidities, Epidemiology, Pemphigoid

Introduction

Bullous pemphigoid is an autoimmune subepidermal blistering disease that is most commonly seen in the elderly population [1]. It is the most commonly diagnosed autoimmune blistering disease overall. The rise in the incidence of bullous pemphigoid can be explained by three factors: the aging population, the increase in drug-induced cases and the ameliorated diagnosis of the non-bullous forms [2]. Dipeptidyl peptidase-4 inhibitors, a novel drug used in the treatment of diabetes mellitus, are frequent culprits for drug induces cases [3]. Diuretics, antipsychotics and check-point inhibitors used in the treatment of malignancies are also responsible for drug induced cases [2].

Bullous pemphigoid has a wide spectrum of disease presentation. In the non-bullous phase of the disease, the patient complains of generalized pruritus, erythema or urticaria-like lesions. Thebullous phase, presents with tense vesicles or bullae on

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erythematous or healthy skin appearing symmetrically on the lower trunk, flexor aspect of the extremities and the abdomen [4]. The diagnosis of bullous pemphigoid is confirmed by biopsy from the lesions, perilesional direct immunofluorescence, indirect immunofluorescence from the patient's sera and immunoblotting [5].

In the past, the mortality rate of bullous pemphigoid has been reported up to 25% [6]. The first line treatment modalities are systemic and topical corticosteroids. Doxycycline, dapsone, methotrexate, azathioprine, mycophenolic acid, intravenous immunoglobulin, rituximab and omalizumab may be used in patients who cannot tolerate corticosteroids or in refractory cases [2,3,7]. The association of bullous pemphigoid with malignancies has been questioned a lot and it was concluded that the disease is not associated with malignancies overall; however, there is a possible association with hematologic malignancies that has not been confirmed yet [8]. On the other hand, bullous pemphigoid was confirmed to be associated with neurologic and psychiatric disorders [1].

Previous studies have shown an overall female predominance of the disease with mean ages of diagnoses ranging from the 6th decade to 8th decade [1]. The aim of this study is to determine the female-to-male ratio and the mean ages of diagnoses; disease durations and comorbidities separately in the female and male Turkish patient groups.

Materials and Methods

In this descriptive study, the patient files of bullous pemphigoid patients who applied to the Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Dermatology Department Blistering Diseases Outpatient Clinic between the years 1999 and 2019 were evaluated retrospectively. The gender, the age at the time of diagnosis, the disease duration and comorbid diseases of each patient were noted. Only the patients whose diagnosis was confirmed with biopsy and direct immunofluorescence were included in this study. Patients with cutaneous and/or mucosal lesions were included in the patient group. A total of fifty-eight patients met the inclusion criteria.

The approval of Istanbul University-Cerrahpasa Medical Faculty Ethics Committee was obtained before the study was initiated (06/12/2019-186949).

Statistical Analysis

Data analysis was performed with SPSS program. The female-to-male ratio and the mean ages of diagnoses; disease durations and comorbidities overall and separately in the female and male patient groups were determined. The comorbidities were analyzed separately for both genders.

Results

A total of 58 patients were included in this study. There were 34 female patients and 24 male patients. The female-to-male ratio was 1.42. The average age of diagnosis was 73.79 years (15-103 years). The average disease duration was 104.9 months (1-264 months) As for the comorbidities, the most commonly observed ones were, in decreasing frequency, hypertension, diabetes mellitus, coronary artery diseases, chronic kidney disease and osteoporosis. Tables 1 and 2 show the comorbid diseases observed in the female patient group and male patient group respectively.

Table 1. Comorbid diseases observed in female patients

Disease	Number of patients
Hypertension	15
Diabetes mellitus	7
Osteoporosis	3
Alzheimer's diseases	3
Hypothyroidsm	2
Coronary artery disease	2
Valvular diseases	2
Chronic kidney disease	1
Hyperlipidemia	1
Uterine myoma	1
Ovarian cysts	1
Pulmonary hypertension	1
Parkinson's disease	1
Schizophrenia	1
Cerebrovascular accident	1
Hodgkin's disease	1
Gastritis	1
Hemoroids	1

Table 2. Comorbid diseases observed in male patients

Disease	Number of patients
Hypertension	11
Diabetes mellitus	7
Chronic kidney disease	3
Coronary artery disease	2
Arrythmia	1
Osteoporosis	1
Parkinson's disease	1
Seizure disorder	1
Hyperlipidemia	1
Glaucoma	1
Rectum cancer	1
Asthma	1

Thirty-four female patients were included in this study. The average age of diagnosis was 74.94; the oldest patient was 103 years old and the youngest patient was 15 years old. The average disease duration was 105.7 months for females; 264 months the longest and 1 month the shortest. The most commonly observed comorbidities in female patients were hypertension, diabetes mellitus, Alzheimer's disease, osteoporosis, hypothyroidism, coronary artery diseases and heart valve diseases, in decreasing frequency. Eight of the female patients had no comorbid disease.

Twenty-four of the patients were males. The average age of diagnosis for male patients was 72.17 years; 92 years the oldest and 52 years the youngest. The average disease duration for male patients was 97.04 months; 240 months the longest and 9 months the shortest. The most common comorbid diseases were hypertension, diabetes mellitus, chronic kidney disease and coronary artery diseases, again in decreasing frequency. Seven of the male patients had no comorbid disease.

When the female and male patients are compared, the age of diagnosis for male patients is younger than the female patients; and the disease duration is longer in the female patients. Hypertension, diabetes mellitus and coronary artery diseases are common in both genders. On the other hand, Alzheimer's disease, osteoporosis and hypothyroidism are observed more frequently in female patients; and chronic kidney disease is observed more frequently in male patients.

Discussion

This study revealed similar results to the previous studies. In this study the female-to-male ratio was calculated as 1.42. A similar ratio was reported in many studies previously. Kridin and Bergman [9] reported a ratio of 1.41; Cozzani et al. [10] of 1.46; Bernard et al. [11] of 1.48; Gudi et al. [12] and Joly et al. [13] of 1.5; and Langan et al. [14] of 1.59. In alliance with the previous studies, this study has also shown that bullous pemphigoid has a female predominance similar to other autoimmune diseases in general.

Bullous pemphigoid is a disease of the elderly and it was previously reported that the prevalence of bullous pemphigoid in the 9th decade is 300-fold that of the 6th decade. Thus, the incidence increases with age [4]. The average age of diagnosis was found to be 73.79 years for both genders. This result is similar to those reported in the previous literature. Zillikens et al. [15] reported that the average age of diagnosis was 73.7 years. Cozzani et al. [10] reported the average age of diagnosis as 74 years; Bertram et al. [16] as 74.6 years; and Brick et al. [17] as 75 years. Previously, there were only two studies which determined the average age of diagnosis according to genders [18,19]. This study showed that the average age of diagnosis was 74.94 years for female patients and 72.17 for male patients. Serwin et al. [18] reported that the average age of diagnosis was 68.9 years in female patients and 67.3 years in male patients. Similar to Serwin et al. [18], we have also found that the average age of diagnosis was younger in male patients. However, the averages of the diagnosis age in both genders were younger in Serwin et al.'s [18] study. Jung et al. [19] reported that the average age of diagnosis was 73.7 in female patients and 76.1 in male patients. The fact that Jung et al. [19] showed the age of diagnosis was younger in female patients contrasts to our result even though the age averages are closer to our results than that of Serwin et al. [18].

The most commonly observed comorbidities in bullous pemphigoid patients were hypertension in 26 patients (45%), diabetes mellitus in 14 patients (24%), coronary artery diseases in 6 patients (1%), chronic kidney disease in 4 patients (0.7%) and osteoporosis in 4 patients (0.7%). A study that evaluated a Finnish cohort of bullous pemphigoid patients with an average age of 77 years also reported that the most commonly observed comorbidities in bullous pemphigoid patients were hypertension (44%), diabetes mellitus (34%) and ischemic heart diseases (26%). A significant association between bullous pemphigoid and a history of malignancies, diabetes mellitus and chronic obstructive pulmonary disease was found in the Finnish cohort. Furthermore, 46% of the patients had neurologic comorbidities [20]. Only two of the patients in this study had a past medical history of malignancy: one patients had rectum cancer and the other patient had Hodgkin's disease; both of the malignancies were cured at the time of bullous pemphigoid diagnosis. Previously, Atzmony et al. [8] reported that there was no significant association of bullous pemphigoid with malignancies; but a possible association might have existed between hematologic malignancies and bullous pemphigoid. Similarly, we also report that a history of malignancy is insignificant for bullous pemphigoid. Cardiovascular diseases, including hypertension and coronary artery diseases, were reported to co-exist with bullous pemphigoid ranging from 38% up to 70% in several previous studies [21]. The prevalence of cardiovascular comorbidities is 70% in our study as well, in alignment with the previous literature. Another study investigating the comorbidities of bullous pemphigoid patients reported 55.8% of the patients had a neurologic comorbidity, which was significantly more than the control group [22]. The most commonly observed neurologic comorbidities were stroke, seizure disorder, dementia (including Alzheimer's and Parkinson's disease) and multiple sclerosis [1,22]. Three patients in our patient population had Alzheimer's disease, 2 patients had Parkinson's disease, 1 patient had seizure disorder and 1 patient had a history of stroke. Overall, only 1% of our patients had a neurologic comorbidity, which contrasts the literature. Psychiatric comorbidities are also reported to be frequent in bullous pemphigoid patients: most common diseases are schizophrenia, bipolar disorder and personality disorders [1]. Only one patient

had a psychiatric disorder, namely schizophrenia, in our patient population, which again differs from the previous literature.

Conclusion

Bullous pemphigoid is an autoimmune blistering disease with a female predominance which is usually diagnosed during the seventh decade; according to the previous literature and this study. Previous studies have shown that bullous pemphigoid was associated with cardiac diseases, diabetes mellitus, neurologic and psychiatric diseases. Similar to the literature, this study has also shown an association between bullous pemphigoid and cardiac diseases or diabetes mellitus. However, the results failed to show an association with neurologic or psychiatric diseases. Bullous pemphigoid was reported to be not associated with malignancies; similarly, this study did not find a significant prevalence of history of malignant neoplasms in bullous pemphigoid patients.

Ethics

Ethics Committee Approval: The approval of Istanbul University-Cerrahpasa Medical Faculty Ethics Committee was obtained before the study was initiated (06/12/2019-186949).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.A., D.K., T.K.Ü.U., C.M., Z.K., Concept: Ö.A., D.K., T.K.Ü.U., C.M., Z.K., Design: Ö.A., D.K., T.K.Ü.U., C.M., Z.K., Data Collection or Processing: Ö.A., D.K., T.K.Ü.U., C.M., Z.K., Analysis or Interpretation: Ö.A., D.K., T.K.Ü.U., C.M., Z.K., Literature Search: Ö.A., D.K., T.K.Ü.U., C.M., Z.K., Writing: Ö.A., D.K., T.K.Ü.U., C.M., Z.K.

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