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Research Article

Evaluation of Comorbidities in Patients with Autoimmune Bullous Diseases: A Retrospective Study

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Abstract

Objectives: The purpose of the present study was to define the accompanying diseases of patients with autoimmune bullous diseases (ABDs).

Methods: One hundred forty-two patients with ABD who were followed up in the dermatology and venereology inpatient clinic of Şişli Hamidiye Etfal Training and Research Hospital between January 1999 and December 2015 were enrolled in the study. Age, gender, and accompanying diseases of the participants were recorded and compared with the healthy subjects.

Results: Eighty patients with pemphigus, 62 patients with pemphigoid, and 217 healthy subjects were included in the study. The pemphigoid group had a statistically significant higher prevalence of hypertension, diabetes mellitus, coronary artery diseases, cataract, malignancy, dementia, Alzheimer's disease, Parkinson's disease, and cerebrovascular events relative to the pemphigus and control groups ($p<0.01$, $p<0.01$, $p=0.001$, $p<0.01$, $p=0.02$, $p=0.008$, $p=0.001$, $p=0.001$, and $p<0.01$, respectively). The prevalence of asthma, benign prostatic hyperplasia, and cataract was higher in the pemphigus group than in the controls ($p=0.02$, $p=0.04$, and $p=0.02$, respectively).

Conclusion: To the best of our knowledge, this is the first study comparing accompanying diseases between controls and patients with pemphigus and pemphigoid. It is disputable whether the diseases mentioned occur due to some common pathophysiological pathways or coexist just coincidentally. We believe that it is important to evaluate accompanying diseases in patients with ABD.

Keywords: Comorbidity; diabetes mellitus; hypertension; pemfigoid; pemfigus; vesiculobullous skin diseases.

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Autoimmune bullous diseases (ABDs) are a group of diseases characterized by vesiculobullous lesions in the mucosa and/or skin as a result of the development of autoantibodies against some target antigens present in the skin.[1, 2] ABDs are divided into two main classes as intraepidermal and subepidermal ABDs depending on the level of bullae formation. The main event in intraepidermal ABDs is acantholysis, which is the separation of keratinocytes from autoantibodies developed against desmogleins, which are the intercellular adhesion molecules. Intraepidermal ABDs form the pemphigus group diseases.

Subepidermal ABDs consist of the pemphigoid group diseases and dermatitis herpetiformis (DH). In pemphigoid group disease, target antigens are localized in the dermoepidermal junction, whereas in DH, the target antigen is epidermal transglutaminase.[1, 3]

In the literature, there are many studies investigating the association of ABDs with other diseases, mainly autoimmune

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diseases and malignancies.[4] Although there are studies investigating the diseases associated with ABDs in Turkey, we have not encountered a study comparing healthy controls with ABDs and patients with pemphigus and pemphigoid groups among themselves as for these comorbidities.

The aim of the present study was to evaluate the comorbidities of patients with ABD hospitalized and treated in our clinic and to compare them with the healthy controls and pemphigus and pemphigoid groups. We believe that the identification of the diseases associated with ABDs will provide the conduction of necessary screening tests and, thus, may be a guide in early diagnosis and treatment.

Methods

A total of 142 patients with ABD who were hospitalized and treated in Şişli Hamidiye Etfal Training and Research Hospital, Department of Dermatology and Venereology during January 1999–December 2015 and 217 and healthy controls were included in the study. The patients' data were retrospectively analyzed from the epicrizes and patient files. The diagnosis of the patient was made based on the clinical features of the patient and histopathological and direct immunofluorescence examination results of the lesion. The patients were divided into two groups as the pemphigoid and pemphigus groups.

Sociodemographic characteristics of the patient and control groups, such as age and gender, and additional diseases were recorded. The ages at the time of the first diagnosis and the accompanying diseases were also recorded. Thus, comorbidities that will be developed secondary to the drugs used in the treatment of ABDs were prevented. The control group consisted of patients who were admitted to the dermatology outpatient clinic with tinea pedis without any other autoimmune or inflammatory skin disease. Patients with ABD were compared with both the control group and the pemphigus and pemphigoid subgroups in the ABD group as for the presence of comorbid diseases. Statistical analysis was made using the Statistical Package for the Social Sciences for Windows version 17.0 (SPSS, Chicago, IL, USA). Descriptive statistics were expressed as mean±standard deviation, numbers, and percentages. Mann–Whitney U test was used for statistical analysis. Kruskal–Wallis test was used to determine the difference (if any) between the groups. Categorical data were compared by chi-square test. Correlations were evaluated using Spearman correlation analysis. A p value <0.05 was considered as statistically significant.

The study was approved by the ethics committee of Şişli Hamidiye Etfal Training and Research Hospital (approval date and code: 05/24/2016-677). A summary of this article was submitted as an oral presentation in the 26th National Dermatology Congress organized in 2016 in Antalya, Turkey.

Results

A total of 142 patients with ABD and 217 healthy controls were included in the study. Of the patients with ABD, 80 had pemphigus, and 62 had pemphigoid group diseases. The patients in the pemphigus group had pemphigus vulgaris (PV) (n=73), pemphigus foliaceus (PF) (n=5), pemphigus vegetans (Pvej) (n=1), and IgA pemphigus (n=1). Of the 62 patients with pemphigoid, the patients had bullous pemphigoid (BP) (n=59), mucosal membrane pemphigoid (MMP) (n=1), and pemphigoid due to vaccination (n=1). Patients with DH, linear IgA dermatosis, and acquired epidermolysis bullosa (AEB) who had been followed up in our clinic were excluded from the study.

When the mean ages of the pemphigus, pemphigoid, and control groups were evaluated, the mean age of the pemphigoid group was significantly higher than that of the other two groups (51.06±17.99, 71.71±14.56, and 53.57±19.27 years, respectively; p<0.01). The pemphigus, pemphigoid, and control groups were not significantly different in terms of gender distributions (p=0.103). Hypertension (HT) was present in indicated percentages of the patients in the pemphigus (15%), pemphigoid (51.6%), and control groups (19.8%). The frequency of HT in the pemphigoid group was significantly higher than that in the pemphigus and control groups (p<0.01).

The incidence of diabetes mellitus (DM) was 8.8% in the pemphigus, 32.3% in the pemphigoid, and 5.9% in the control groups. The incidence of DM was significantly higher in the pemphigoid group than in the pemphigus and control groups (p<0.01). The frequency of disease in the pemphigoid group was significantly higher than that in the pemphigus and control groups in terms of coronary artery disease (CAD) (11.3%, 3.8%, and 55.5%, respectively; p=0.001). The incidence of internal organ malignancies was 3.8% in the pemphigus, 6.5% in the pemphigoid, and 0.05% in the control groups. This rate was significantly higher in the pemphigoid group than in the pemphigus and control groups (p=0.02).

When the neurological diseases were examined, the frequency of dementia, Alzheimer's disease, Parkinson's disease, and cerebrovascular event (CVE) was significantly higher in the pemphigoid group (p=0.008, p=0.001, p=0.001, and p<0.01, respectively). The frequency of asthma, cataract, cholelithiasis, appendectomy, and benign prostatic hyperplasia (BPH) in the pemphigus group was statistically significantly higher than that in the control group (p=0.02, p=0.02, p=0.007, p=0.03, and p=0.04,

Table 1. Comparison of the pemphigus, pemphigoid, and control groups

	Groups			
	Pemphigus (n=80) %	Pemphigoid (n=62) %	Control (n=127) %	p
HT	15	51.6	19.8	[a]**<0.01**
DM	8.8	32.3	5.9	[a]**<0.01**
CAD	3.8	11.3	5.5	[a]**0.001**
Thyroid disease	3.8	8.1	1.8	[a]**0.6**
Asthma	7.5	3.2	1.4	[a]**0.08**
HL	5	3.2	3.7	[a]**0.98**
Cataract	2.5	7.9	0	[a]**<0.01**
Cholelithiasis	6.3	4.8	0.9	[a]**0.03**
Appendectomy	3.8	0	0.5	[a]**0.04**
Vitiligo	1.3	0	0.5	[a]**0.59**
Malignancy	3.8	6.5	0.5	[a]**0.02**
Depression	0	1.6	0.5	[a]**0.42**
Dementia	0	0.9	0	[a]**0.008**
Alzheimer	0	1.4	0	[a]**0.001**
Parkinson	0	1.4	0	[a]**0.001**
Psychosis	0	1.6	0	[a]**0.09**
CVE	0	14.5	0.9	[a]**<0.01**
IBD	1.3	0	0	[a]**0.18**
Parathyroid	1.3	0	0.9	[a]**0.7**
BPH	0	3.2	5.1	[a]**0.12**
Anemia	0	0	0.9	[a]**0.52**
Skin cancer	0	0	1.8	[a]**0.37**
Gender				
Female n (%)	49 (61.3)	38 (61.3)	78 (61.4)	[b]**0.103**
Male n (%)	31 (38.8)	24 (38.7)	49 (38.6)	

[a]Kruskal–Wallis test; [b]Pearson chi-square test; HT: Hypertension; DM: Diabetes mellitus; CAD: Coronary artery disease; HL: Hyperlipidemia; CVE: Cerebrovascular event; IBD: Inflammatory bowel disease; BPH: Benign prostatic hyperplasia.

Table 2. Intergroup comparisons

	Groups		
	Pemphigus–pemphigoid p	Pemphigus–control p	Pemphigoid–control p
HT	[a]<0.01	[a]0.84	[a]<0.01
DM	[a]<0.01	[a]0.4	[a]<0.01
CAD	[a]0.008	[a]0.86	[a]0.001
Thyroid disease	[a]0.87	[a]0.34	[a]0.51
Asthma	[a]0.41	[a]0.02	[a]0.34
HL	[a]0.87	[a]0.98	[a]0.86
Cataract	[a]0.13	[a]0.02	[a]<0.01
Cholelithiasis	[a]0.72	[a]0.007	[a]0.04
Appendectomy	[a]0.13	[a]0.03	[a]0.59
Vitiligo	[a]0.38	[a]0.46	[a]0.59
Malignancy	[a]0.07	[a]0.92	[a]0.009
Depression	[a]0.26	[a]0.54	[a]0.34
Dementia	[a]0.11	[a]1	[a]0.008
Alzheimer	[a]0.048	[a]1	[a]0.001
Parkinson	[a]0.048	[a]1	[a]0.001
Psychosis	[a]0.26	[a]1	[a]0.06
CVE	[a]<0.01	[a]0.39	[a]<0.01
IBD	[a]0.38	[a]0.1	[a]1
Parathyroid	[a]0.38	[a]0.8	[a]0.45
BPH	[a]0.11	[a]0.04	[a]0.54
Anemia	[a]1	[a]0.4	[a]0.45
Skin cancer	[a]1	[a]0.29	[a]0.35

[a]Mann–Whitney U test; HT: Hypertension; DM: Diabetes mellitus; CAD: Coronary artery disease; HL: Hyperlipidemia; CVE: Cerebrovascular event; IBD: Inflammatory bowel disease; BPH: Benign prostatic hyperplasia

respectively). Diseases seen in patients with ABD and their distribution among groups and the comparison of these diseases in binary groups are summarized in Tables 1 and 2, respectively.

Discussion

A total of 142 patients with ABD who were hospitalized and treated in our clinic between 1999 and 2015 were included in the study. These cases had been most frequently diagnosed as PV (n=73) and BP (n=59) in compliance with literature findings. The most frequently reported ABD was PV, followed by BP in many studies.[5–7] In studies conducted in Turkey, in support of the literature, PV has been reported as the most frequently seen ABD, followed by BP.[1, 7–9] Similarly, in our study, the frequency was 51.4% for PV and 41.5% for BP.

Pemphigus is a rare disease group characterized with intraepidermal vesicles and bullae and has subtypes, such as vulgaris, foliaceus, erythematosus, vegetant, herpetiformis, paraneoplastic, and IgA pemphigus according to the level of epidermal detachment. PV is the most common type.[10] In our study, the most frequent PV (n=73) was detected in the pemphigus group, followed by PF (n=5), Pvej (n=1), and IgA pemphigus (n=1). Although pemphigus can be seen in all age groups, it is frequently diagnosed between 40 and 60 years old.[11] Demircioğlu et al.[12] and Akbaş et al.[9] reported that the age of onset is 52 years in pemphigus similar to our results (51.4 years).

Studies investigating the comorbidities of patients with pemphigus are available, but these studies are mostly focused on a single group of diseases. There are studies investigating the association of autoimmune diseases, mainly thyroid diseases and neoplasms with pemphigus. In a study of 295 patients with pemphigus, the most common accompanying diseases of pemphigus were reported

as DM, HT, hypothyroidism, solid organ malignancies, heart diseases, and asthma, and an increased risk of hypothyroidism, IBD, and diabetes was demonstrated in patients with pemphigus compared with the general population.[13] In the same study, a psychiatric disorder (21 depression, two anxiety, and four psychoses) was reported in 27, and vitiligo in one patient.[13] Michailidou et al.[14] reported the presence of thyroid diseases, allergic reactions, and candida in PV cases. Akbaş et al.[9] indicated that thyroid diseases, HT, DM, and CAD are the most common concomitant diseases in patients with pemphigus in Turkey. In our study, the most common comorbid diagnoses in patients with pemphigus were HT, DM, asthma, cholelithiasis, and hyperlipidemia.

The incidence of asthma, cholelithiasis, cataract, appendectomy, and BPH was statistically higher in the pemphigus group than in the control group. We have not enough data to explain a physiopathological mechanism common to both pemphigus and these diseases. At the same time, a small number of patients with these diagnoses do not allow us to talk about a definite relationship between pemphigus and the aforementioned diseases.

Pemphigoid group diseases are a group of diseases characterized with subepidermal bullae, BP, linear IgA disease, DH, and AEB.[11] BP is the most common subepidermal ABD.[11] BP is characterized by BP antigens 1 and 2 (BPAG1 and BPAG2) in the structure of IgG against two basal membrane proteins.[15] The incidence of BP increases with age, and it is most commonly seen in the elderly population >70 years old.[11] In the present study, of the 62 patients with pemphigoid, 59 were diagnosed as BP, one as MMP, and one had developed pemphigoid secondary to vaccination. The onset of manifestations of BP was reported in patients >65–70 years old.[16] In studies conducted in Turkey, different ages for the onset of BP were reported by Akbaş et al.[9] 78 years, Erdoğan et al.[17] 71 years, and Uzun et al.[10] 64 years, whereas in our study, the mean age of the pemphigoid group was 71.7 years. There are many studies investigating neurological and psychiatric disorders and comorbidities such DM and malignancy with BP.[18–22] In a recent study, heart failure and DM were found to be more frequent in patients with BP than in the control group. There was no statistically significant difference in HT, hyperlipidemia, atrial fibrillation, and CAD.[23] In the study of 77 patients with BP in Portugal, two neurological diseases as CVE and dementia in patients with BP were found to be statistically more frequent than in the control group.[15] In the study of 122 patients with BP in Iran, the most common comorbidities were HT (22.9%) and DM (13.1%).[24] Akbaş et al.[9] reported that they observed the coexistence of HT, DM, thyroid diseases, and various neurological diseases in patients with BP in Turkey. The association of BP with neurological diseases is an accentuated issue. There are studies reporting the association of BP with various neurological diseases, such as dementia, CVE, Parkinson's disease, and multiple sclerosis.[25–28] Although the association of BP with malignancies is still controversial, publications that examine this issue are not scarce in number.[22, 29–31] It is still not known whether the coexistence of malignancy and BP is due to the presence of a common physiological pathway or to the more frequent occurrence of both diseases in the older age group.[32] In our study, the most common diseases in the pemphigoid group were HT, DM, neurological diseases, and CAD. When the pemphigoid group was compared with the control and pemphigus groups, HT, DM, CAD, neurological diseases, malignancies, and cataract were statistically significantly more frequently seen in the pemphigoid group. The incidence of HT, DM, CAD, Alzheimer's disease, Parkinson's disease, and CVE was higher in the pemphigoid group than in the pemphigus and control groups, whereas the incidence of cataract, cholelithiasis, malignancy, and dementia was significantly higher in the pemphigoid group than in only the control group. The occurrence of BP in the elderly population and the high prevalence of medical comorbidities in this population may explain the coexistence of these diseases; however, it is still open to research whether or not some common pathways are involved in their pathogenesis. In our study, the most frequent diseases in both pemphigus and pemphigoid groups were HT and DM. HT, DM, neurological diseases, and malignancies were statistically significantly more common in the pemphigoid group than in the control and pemphigus groups. Asthma, cataract, cholelithiasis, appendectomy, and BPH were statistically significantly more common in the pemphigus group than in the control group. The definition of the relationship between these diseases and ABD may guide the treatment and the follow-up of the disease.

The retrospective design of the study is the limitation of the study. The data on the comorbidities were obtained from patients' files and in some cases comorbidities were recorded based on the patients' declarations.

To the best of our knowledge, no studies are available comparing pemphigus and pemphigoid groups with each other and with the control group in terms of concomitant diseases. Further studies are needed to understand whether some diseases are more common in patients with pemphigoid and pemphigus due to the development of these diseases through common pathophysiological pathways, or it is purely coincidental.

Disclosures

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