



# Bullous dermatosis in the southeastern of Turkey: A study of 125 cases

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## Abstract

**Aim:** Autoimmune bullous diseases occur when antibodies against proteins such as desmosomes and hemidesmosomes cause separation in the skin. Detailed epidemiological studies examining these diseases are limited in our country. We aim to contribute to the demographic, clinical, and treatment data on bullous diseases from an important geographic region of our country.

**Materials and Methods:** The data of 125 cases who were followed up with a diagnosis of bullous disease between 2006 and 2019 were evaluated retrospectively. Socio-demographic characteristics, diagnoses, age and duration of disease onset, clinical findings, accompanying systemic diseases, treatments given, and side effects related to treatment were recorded.

**Results:** 57.6% of the patients (72 people) were diagnosed as pemphigus, 31.2% (39 people) bullous pemphigoid (BP), 8% (10 people) dermatitis herpetiformis (DH), 3.2% (4 people) linear Ig A dermatosis (LAD). BP patients were found to be significantly older than the other patients ( $p = 0.002$ ). While pemphigus, BP, and LAD were more common in women, 70% of DH patients were men. Malignancy was detected in 2.8% of pemphigus patients and 5.1% of BP patients. Accompanying autoimmune disease was found in 9.7% of pemphigus patients, 17.9% of BP patients, and 20% of DH patients. The only systemic steroid was used in 20.8% of pemphigus patients, and azathioprine as a conventional agent was used in 76.4% with systemic steroid. Rituximab was started in patients who did not respond to therapy. The systemic steroid was used in 35.9% of BP patients, and azathioprine with systemic steroid was used in 43.6% of BP patients. Doxycycline was added to the treatment in 41% of the patients. Rituximab was used in 5 (12.8%) patients.

**Conclusion:** Since our study is the first data obtained on bullous diseases from the southeastern Anatolia region, it is useful for the literature in terms of providing a basis for future studies.



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## Introduction

Autoimmune bullous diseases occur when antibodies against proteins such as desmosomes and hemidesmosomes cause separation in the skin. They are divided into intraepidermal and subepidermal according to the level of separation. Intraepidermal autoimmune bullous diseases consist of pemphigus vulgaris, pemphigus foliaceus, pemphigus erythematosus, etc. subtypes. Bullous dermatoses with subepidermal separation can be classified as bullous pemphigoid, cicatricial pemphigoid, dermatitis herpetiformis, linear Ig A dermatosis, etc. [1].

Our university is one of the leading centers where bullous dermatosis patients are diagnosed and followed up in southeast and eastern Anatolia. We retrospectively evaluated the demographic, clinical, and treatment characteristics of these cases. We aim to contribute to the data on bullous diseases from an important geographic region of our country.

## Material and Methods

The data of 125 patients who were followed up with the diagnosis of bullous dermatosis between 2006 and 2019 in the Department of Dermatology of İnönü University were evaluated retrospectively. Ethics approval was taken from the local institutional Ethics Committee. Patients

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who were followed regularly in our bullous dermatosis outpatient clinic and diagnosed with bullous dermatosis by clinical, histopathological, and direct immunofluorescence (DIF) methods were included in the study. Patients who could not be followed up because they did not come to the polyclinic control and whose data could not be accessed were excluded from the study. Socio-demographic characteristics, diagnoses, age and duration of disease onset, clinical findings, accompanying systemic diseases, treatments given, and side effects related to treatment were recorded. During the study, the Helsinki Declaration principles were followed.

The compatibility of numerical data to normal distribution was examined by the Shapiro-Wilk test and median, minimum and maximum values were used as descriptors. Comparisons of the two groups were made using the Mann-Whitney U test. In comparing more than two groups, the Kruskal-Wallis test and then the Conover pairwise comparison method was used. The distribution of categorical variables was shown in numbers and percentages. Depending on the assumptions, Fisher's exact chi-square, Pearson's exact chi-square, or continuity-corrected chi-square tests were used for comparisons. The two-sided significance level was accepted as 0.05 in all tests.

## Results

55.6% of the patients included in the study were female and 44.4% were male. The mean age of the patients was 52.6 years. The patients were followed up for an average of 29 months, with a minimum of 1 month and a maximum of 168 months. 57.6% of the patients (72 people) were diagnosed as pemphigus, 31.2% (39 people) BP, 8% (10 people) DH, 3.2% (4 people) linear Ig A dermatosis (LAD). The mean age at the time of diagnosis was 56 in pemphigus patients, 80 in BP patients, 55 in DH patients, and 35 in LAD patients. When we compared the mean age at the time of diagnosis, BP patients were found to be significantly older than the other patients ( $p = 0.002$ ). While pemphigus, BP, and LAD were more common in women, 70% of DH patients were men. The socio-demographic data of the patients are shown in Table 1.

While 43.2% of the patients followed up with the diagnosis of pemphigus showed mucous, 36.1% mucocutaneous involvement, 20.8% were followed only with cutaneous involvement. Only cutaneous involvement was observed in 74.4% of BP patients. Mucosal involvement was not observed in any of the patients followed up with a diagnosis of DH and AD (Table 1).

Among the pemphigus subtypes, pemphigus vulgaris was the most common (80.5%), followed by pemphigus foliaceus (9.7%). The pemphigus subtypes seen in the patients are summarized in Table 2.

Malignancy was detected in 2.8% of pemphigus patients and 5.1% of BP patients. CLL was found in two pemphigus patients, breast and colon cancer in two BP patients, respectively, and laryngeal cancer and basal cell cancer in two duhring patients, respectively (Table 3).

Accompanying autoimmune disease was found in 9.7% of pemphigus patients, 17.9% of BP patients, and 20% of DH patients. The most common autoimmune disease was diabetes mellitus (9.6%). Apart from this, thyroid disease

and rheumatoid arthritis were detected in one patient. Additionally, HBV was accompanied in 4.8% of the patients (Table 3).

Transglutaminase was positive in 40% of the patients with DH, and antigliadin antibody was positive in 40%. Celiac was accompanied in three of the ten patients. No patient was diagnosed with gastrointestinal lymphoma.

The only systemic steroid was used in 20.8% of pemphigus patients, and azathioprine as a conventional agent was used in 76.4% with systemic steroid. Rituximab was started in patients who did not respond to systemic steroid and adjuvant therapy. 36.1% of the pemphigus patients received rituximab treatment and 30% of them received prophylaxis. In a child patient, intravenous immunoglobulin treatment was administered, but rituximab was administered at a dose appropriate to the lymphoma protocol (375 mg/m<sup>2</sup> weekly dose), as he was unresponsive. After two cycles of rituximab, the patient went into remission. Plasmapheresis was applied in one of the patients in addition to adjuvant therapy.

The systemic steroid was used in 35.9% of BP patients, and azathioprine with systemic steroid was used in 43.6% of BP patients. Doxycycline was added to the treatment in 41% of the patients. Rituximab was used in 5 (12.8%) patients, but no prophylaxis was given to any patient. Two of the patients taking rituximab developed side effects related to the drug. Treatment was discontinued due to the development of anaphylaxis in one of the pemphigus patients. Another patient died due to severe lung infection after rituximab.

All Duhring and LAD patients were successfully treated with dapson. Local wound care was applied for cutaneous and mucosal lesions in all patients.

When the mean duration of systemic steroid use of BP and pemphigus patients was compared, it was found there was a significant difference ( $p = 0.000$ ). Systemic steroids were used for an average of 78 months in pemphigus patients and 51 months in BP patients. It was found that the mean duration of systemic steroid use was longer in pemphigus patients who took rituximab than those who did not ( $p = 0.004$ ).

19.2% of the patients were using cigarettes and 2.4% were using alcohol. There was no significant difference between smoking and mucous involvement ( $p = 1.000$ ). It was observed that smoking was significantly more common in patients with DH compared to other groups ( $p = 0.007$ ). There was no difference in alcohol use ( $p = 0.518$ ).

There was no difference in the age of onset of the disease in pemphigus patients who smoke ( $p = 0.982$ ). No significant difference was found between smoking pemphigus patients (29 months) and non-users (37 months) in terms of the duration of systemic steroid use ( $p = 0.226$ ) and the requirement for Rituximab prophylaxis ( $p = 0.592$ ).

## Discussion

The incidence of bullous dermatoses varies by geographic region [1]. While the most common bullous dermatosis in Europe is BP, it is pemphigus in our country. This may be due to the high rate of the elderly population in European countries. In our study pemphigus disease was the

**Table 1.** Socio-demographic data of the patients are shown.

		Groups				Total
		Pemphigus	Bullous pemphigoid	Duhring	Lineer IgA	
Sex	Female (%)	40 (55.6%)	26 (66.7%)	3 (30%)	3 (75%)	72 (57.6%)
	Male (%)	32 (44.4%)	13 (33.3%)	7 (70)	1 (25%)	53 (42.4%)
Average age at the time of diagnosis		56.04	80.72	55.05	35.38	-
Involvement	Mucous (%)	31 (43.1%)	5 (12.8%)	0 (0%)	0 (0%)	36 (28.8%)
	Cutaneous (%)	15 (20.8%)	29 (74.4%)	10 (100%)	4 (100%)	58 (46.4%)
	Mucocutaneous (%)	26 (36.1%)	5 (12.9%)	0 (0%)	0 (0%)	31 (24.8%)
Cigarette	Smoking (%)	12 (16.7%)	6 (15.4%)	6 (60%)	0 (0%)	24 (19.2%)
	Not smoking (%)	60 (83.3%)	33 (84.6%)	4 (40%)	4 (100%)	101 (80.8%)
Alcohol	Using (%)	3 (4.2%)	0 (0%)	0 (0%)	0 (0%)	3 (2.4%)
	Not using (%)	69 (95.8%)	39 (100%)	10 (100%)	4 (100.0%)	122 (97.6%)
Total		72	39	10	4	-

**Table 2.** Pemphigus subtypes

	Frequency	Percent
Pemphigus vulgaris	58	80.5
Foliaceus	7	9.7
Vejetans	1	1.4
Erythematousus	3	4.2
Paraneoplastic	2	2.8
Ig A pemfigus	1	1.4
Total	72	100

most common bullous dermatosis similar to other studies conducted in Turkey [2, 3]. The incidence of BP increases with age.

The frequency of BP increases 300 times over the age of 90 was shown [4]. Similar to pemphigus, BP is more common in women [5, 6]. It has been suggested that genetic, hormonal, and environmental factors may cause predisposition in women [2]. DH is more common in young adults and has been shown to occur twice as often in men [7]. LAD has been shown to occur frequently in the 60s [8]. However, the average age of our patients at the time of diagnosis was 35.

In our study, malignancy was detected in 2.8% of pemphigus patients and 5.1% of BP patients. Studies are showing the incidence of hematological malignancies and solid organ tumors in BP patients is increased [9]. Although some authors argue that this relationship is due to age [10], it has been shown BP regresses after the treatment of the underlying malignancy [9]. In our study, following the literature, association with solid organ cancers was observed in BP patients.

Patients with accompanying malignancy in which intraepidermal separation is demonstrated should be evaluated in terms of paraneoplastic pemphigus diagnostic criteria. The specific immune-precipitation pattern in serum in paraneoplastic pemphigus and PV patients can be differentiated by demonstrating intracellular storage in rat bladder epithelium on DIF and indirect immune fluorescence [11]. In a study on cancer prevalence in patients with

pemphigus, the incidence of malignancy was reported as 5% and 0.61% in the control group [12]. In another study conducted in Turkey, it was shown cancer accompanied pemphigus patients at a rate of 3.8% [13]. In our study, CLL was detected in two pemphigus patients. However, these patients did not meet the paraneoplastic pemphigus criteria. When the frequency of malignancy was compared in pemphigus patients and BP patients, no significant difference was observed between them ( $p = 0.612$ ).

Caproni et al. showed antibodies against tissue transglutaminase correlated with gastrointestinal involvement [14]. In our study, tissue transglutaminase was found to be positive in all patients with celiac symptoms. While the prevalence of celiac in DH patients was 12.6% [15] in the United States, 15% in France [16], and 18% in Spain [17], this rate was shown as 40% in our study. In another study conducted in Turkey, the prevalence of celiac was reported as 37.5% [18]. We think that this difference is since the disease is affected by geographical region and environmental factors.

The frequency of gastrointestinal lymphoma is increased in DH patients compared to the normal population has been shown. In a review study, gastrointestinal or nodal lymphoma frequency was found as 2% [19]. In our study, no gastrointestinal lymphoma or nodal lymphoma was observed in any of our DH patients. However, one patient had laryngeal cancer and the other had basal cell carcinoma. We think that this is coincident.

Fuertes et al. showed in their study 40% of DH patients were accompanied by autoimmune diseases. They reported thyroid diseases and diabetes mellitus as the most common accompanying diseases [17]. Llamazares et al. reported that 22.2% often accompanied by autoimmune disease [15]. Similarly, we found an accompanying autoimmune disease in 20% of our DH patients.

There are many studies in the literature showing pemphigus is seen together with thyroid diseases such as Hashimoto and Graves, autoimmune diseases such as myasthenia gravis and sjögren [20, 21]. Firooz et al. showed the frequency of type 1 DM and thyroid diseases is higher in their study [22]. In our study, the most com-

**Table 3.** Frequency of autoimmune diseases and malignancies according to bullous dermatosis groups

		Groups				Total
		Pemphigus	Bullous pemphigoid	Duhring	Lineer IgA	
Autoimmune	present (%)	7 (9.7%)	7 (17.9%)	2 (20%)	0 (0%)	16 (12.8%)
	absent (%)	65 (90.3%)	32 (82.1%)	8 (80%)	4 (100%)	109 (87.2%)
Malignancy	present (%)	2 (2.8%)	2 (5.1%)	2 (20%)	0 (0%)	6 (4.8%)
	absent (%)	70 (97.2%)	37 (94.9%)	8 (80%)	4 (100%)	119 (95.2%)
Total		72 (%100)	39 (%100)	10 (%100)	4 (%100)	

mon accompanying autoimmune disease in patients with pemphigus was diabetes mellitus. Although autoimmune disease association has been considered more prominent in pemphigus patients until now, autoimmune disease was detected in 17.9% of BP patients in our case series. In a case-control study conducted in Turkey, the frequency of diabetes mellitus was reported as 8.8% in pemphigus patients, 32.3% in pemphigoid patients, and 5.9% in the control group. Similarly, thyroid diseases were found more common in the BP group [13].

Autoimmune bullous dermatoses can be triggered by drug use, infections, ultraviolet, and stress[23]. In a study, smoking has been shown to have a protective role in the development of pemphigus by Brenner et al. [24]. In other studies conducted in Turkey, not smoking was counted among the triggers in patients with pemphigus [25]. In our study, we showed that smoking does not affect mucosal involvement, disease onset age, or treatment modalities. However, there is not enough data in the literature regarding the effect of smoking on autoimmune bullous dermatoses, and we think that studies on larger case series are needed.

In recent guidelines, rituximab therapy has begun to take its place as first-line therapy in patients with pemphigus [26]. It has been demonstrated that rituximab shortened the duration of systemic steroid use, and prevented systemic steroid-related side effects [27]. In our study, we found that the mean duration of steroid use was significantly longer in patients who received rituximab compared to those who did not. The reason is this; rituximab could only be used in patients who did not respond to systemic steroids and took adjuvant therapy, since the treatment was not paid according to the Health Implementation Notification (SUT) in our country.

The fact that verification and typing tests other than immune fluorescence could not be used in the diagnosis of the cases and the study was carried out retrospectively constitute the most important limitation. However, since our study is the first data obtained on bullous diseases from the eastern and southeastern Anatolia region, it is useful for the literature in terms of providing a basis for future studies.

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