



Clinicopathological Features of Patients with Vesiculobullous Diseases Referred to Dermatology Clinic of Afzalipour Hospital, Kerman, Iran

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Abstract

Background: Bullous diseases are classified as autoimmune blistering diseases, hereditary blistering disorders, and blistering diseases secondary to inflammation and physical trauma. This study evaluated clinicopathological features of patients with bullous diseases.

Methods: This is a retrospective cross-sectional study of 88 patients with vesiculobullous diseases referred to the dermatology clinic of Afzalipour hospital in Kerman, Iran. Demographic features of the patients, type of lesions, differential diagnosis, and pathological features (site of skin biopsy, final pathological diagnosis, type of inflammatory cells, and direct immunofluorescence results) were recorded. Data were analyzed by chi-square test and independent *t*-test.

Results: Eighty-eight patients (59.1% females and 40.9% males) were evaluated. The mean age of patients was 45.09 ± 20.48 years. Autoimmune blistering diseases, hereditary bullous diseases, and blisters secondary to inflammation and trauma were observed in 79.5%, 11.4%, 6.8%, and 2.3% of the cases, respectively. The most common diseases were pemphigus vulgaris (29.5%) and bullous pemphigoid (21.6%). There was a significant correlation between the type of the disease and the age of patients (P -value = 0.001) and the duration of the disease (0.047).

Conclusions: The most common autoimmune blistering diseases, hereditary bullous diseases, and blisters secondary to inflammation and trauma were pemphigus vulgaris, epidermolysis bullosa, lichen planus, and diabetic bullae/friction blister, respectively.

Keywords: Vesiculobullous Skin Diseases, Clinical, Pathology

1. Background

Bullous diseases are clinically classified as autoimmune blistering diseases, hereditary blistering disorders, and blisters secondary to inflammation and physical trauma. Autoimmune bullous diseases are one of the most important types of acquired blistering diseases with nearly similar clinical features. They lead to mucocutaneous involvement with a high risk of mortality rate in untreated cases (1-3). Dysregulation of the immune system and production of autoantibodies against various target antigens of the skin, such as desmoglein and desmoplakin, have an essential role in the pathogenesis of these diseases (4-6). Autoimmune blistering diseases are categorized according to the blister site (subcorneal, intraspinous layer, suprabasilar, and subepidermal) and Direct Immunofluorescence (DIF) results [including the type of immunoglobulin (Ig) such as IgA, IgG, and IgM, as well as a complement (C3), site (basement membrane zone or intercellular), and pattern (granular, lace-like, or linear)] (7-9). Hereditary blistering disorders, including epidermolysis bullosa (EB), Darier disease, Hailey-Hailey disease, and porphyrias, are caused by mutations in genes involved in synthesizing structural proteins and heme (10).

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2. Objectives

This study evaluated clinicopathological features of patients with vesiculobullous diseases referred to Afzalipour hospital.

3. Methods

This is a retrospective cross-sectional study of 88 cases with vesiculobullous diseases referred to Afzalipour hospital in Kerman, Iran, from September 2014 to December 2020. The inclusion criterion included all patients with vesiculobullous diseases referred to the operating rooms of the dermatology department for a skin biopsy. The exclusion criterion was incomplete patients' records. First, demographic features of the patients (age and sex), clinical features of the lesions (type of skin lesion, duration, and differential diagnosis), and pathological features (site of biopsy, final diagnosis, type of inflammatory cells inside the blister, and DIF results) were collected. Then, the correlation of the final diagnosis with the demographic and clinicopathological features of the cases was evaluated.

3.1. Statistical Analysis

Data were analyzed by SPSS16 (IBM, Armonk, NY, USA). Prevalence, frequency, mean, and standard deviation were used for descriptive analysis. Chi-square and independent *t*-tests were applied to assess the final diagnosis's correlation with demographics and clinicopathological features of the cases. The Ethics Committee of Kerman University approved this study with the ethical code of IR.KMU.AH.REC.1396.1427.

4. Results

Eighty-eight cases (59.1% females and 40.9% males) were enrolled in the study. The mean age of the patients was 45.09 ± 20.48 years (ranging from three months to 89 years). The mean duration of the diseases was 1.27 ± 0.25 years (ranging from two days to 24.33 years).

The skin biopsy sites in descending order were upper limb and trunk (each 30.6%) and head and lower limb (each 27.2%). DIF was performed in 33 patients; IgG, IgA, and mixed deposition of IgG and C3 were reported in 51.5%, 27.3%, and 21.2% of the cases, respectively.

Autoimmune blistering diseases, hereditary bullous diseases, and blisters secondary to inflammation and trauma were observed in 79.5%, 11.4%, 6.8%, and 2.3% of the cases, respectively. Intraepidermal and subepidermal blisters were observed in 36.4% and 63.6% of the cases, respectively. The most common autoimmune blistering diseases, hereditary bullous diseases, and blisters secondary to inflammation and trauma were pemphigus vulgaris (PV), EB, lichen planus (LP), and diabetic bulla/friction blister, respectively. The most common vesiculobullous diseases were PV (29.5%) and Bullous Pemphigoid (BP; 21.6%) (Table

1). Most skin biopsies (43.2%) had three differential diagnoses (ranging from 1 to 6). In most cases, the final diagnosis was consistent with the first differential diagnosis (73.8%). Inflammatory cells were observed in 84.09% of the cases within the blister. The most common inflammatory cells were neutrophils (44.3%) and eosinophils (33%). Lymphocytes and mixed inflammatory cells were observed in 4.5% and 2.3% of the cases, respectively.

The most common clinical features of the lesions were blister (56.8%), papule (18.2%), and vesicle (17%). Erosion, plaque, and pustule were observed in 8%, 3.4%, and 2.3% of the cases, respectively. Most patients were in their third and fifth decades of life (40.9%). There was a significant correlation between the disease type and the patient's age ($P = 0.001$; Table 2). Also, there was a significant correlation between the type of the disease and the duration of the disease ($P = 0.047$; Table 3). The longest duration belonged to BP and Darier disease. There was no significant correlation between the type of the disease and the time of disease onset or gender of the patients (Tables 1 and 3).

5. Discussion

The most common vesiculobullous disease in this study was an autoimmune blistering disease, which was compatible with the Karattuthazhathu study (11). Moreover, the most prevalent intraepidermal and subepidermal bullous diseases were PV and BP, which was in line with other studies (3, 4, 12, 13). Although there was no significant correlation between the type of the disease and gender, most autoimmune blistering diseases were observed in females, compatible with other studies (3, 4, 12, 14-16).

In the present study, the mean age of patients was 45.09 years, which was compatible with other studies (12, 17, 18, 21). The earliest age of disease onset was observed in EB and Darier. The latest age of disease onset belonged to Linear IgA Disease (LAD) and BP. Also, the mean age of disease onset for patients with PV and epidermolysis bullosa acquisita (EBA) was in the fifth decade, which was compatible with Daneshpazhoo and Jowkar studies (3, 13). However, the mean age of disease onset in pemphigus foliaceus (PF) and BP was lower in the current study than in the Jowkar study (fifth to sixth decades vs. sixth to seventh decades, respectively) (13). The age of onset of BP patients was higher in other countries such as Tunisia, Germany, and Kuwait than in the current study (4, 14, 15). In the Kuwait study, the age of onset was higher for EBA, while it was lower for PV (14).

In the current study, the lesions' most and least common clinical features were blister and pustule, respectively. In the study by Deepti, similar to this study, the most common clinical feature was blister; but in contrast to our

Table 1. Prevalence of Vesiculobullous Diseases Based on Sex of Patients

Type of Disease	Total, No. (%)	Male, No. (%)	Female, No. (%)
Pemphigus vulgaris	26 (29.5)	11 (42.3)	15 (57.7)
Bullous pemphigoid	19 (21.6)	8 (42.1)	11 (57.9)
Dermatitis herpetiformis	14 (15.9)	9 (64.3)	5 (35.7)
Pemphigus foliaceus	8 (9.1)	2 (25)	6 (75)
Bullous lichen planus	5 (5.7)	2 (40)	3 (60)
Epidermolysis bullosa	4 (4.5)	2 (50)	2 (50)
Darier disease	3 (3.4)	1 (33.3)	2 (66.7)
Epidermolysis bullosa acquisita	2 (2.3)	0	2 (100)
Hailey-Hailey disease	2 (2.3)	0	2 (100)
Linear immunoglobulin a bullous dermatitis	1 (1.1)	0	1 (100)
Subcorneal pustular dermatosis	1 (1.1)	0	1 (100)
Porphyria	1 (1.1)	0	1 (100)
Diabetic bulla	1 (1.1)	1 (100)	0
Friction blister	1 (1.1)	0	1 (100)
P-value		0.587	

Table 2. Association Between Type of the Disease and Age of the Patients^a

Type of Disease	< 10 Years	10 - 20 Years	21 - 30 Years	31 - 40 Years	41 - 50 Years	51 - 60 Years	61 - 70 Years	71 - 80 Years	81 - 90 Years
Pemphigus vulgaris	1 (3.8)	0 (0)	2 (7.7)	5 (19.2)	6 (23.1)	7 (26.9)	2 (7.7)	1 (3.8)	2 (7.7)
Bullous pemphigoid	0 (0)	0 (0)	2 (10.5)	2 (10.5)	4 (21)	1 (5.3)	6 (31.6)	2 (10.5)	2 (10.5)
Dermatitis herpetiformis	0 (0)	0 (0)	7 (50)	1 (7.1)	1 (7.1)	2 (14.3)	1 (7.1)	2 (14.3)	0 (0)
Pemphigus foliaceus	0 (0)	1 (12.5)	0 (0)	1 (12.5)	1 (12.5)	1 (12.5)	4 (50)	0 (0)	0 (0)
Bullous Lichen planus	0 (0)	0 (0)	3 (60)	1 (20)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)
Epidermolysis bullosa	3 (75)	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)
Darier disease	0 (0)	2 (66.7)	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Epidermolysis bullosa acquisita	0 (0)	0 (0)	0 (0)	1 (50)	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)
Hailey-Hailey disease	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)	1 (50)	0 (0)	0 (0)	0 (0)
Linear immunoglobulin A bullous dermatitis	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subcorneal pustular dermatosis	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Porphyria cutanea tarda	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diabetic bulla	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Friction blister	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
P-value					0.001				

^a Values are expressed as No. (%).

study, the rarest one was papule (23). In the present study, lesions were more commonly observed on the upper limb and trunk, consistent with Tunisia and India studies (4, 17). Also, the most common deposited Ig was IgG, compatible with the Mittal study (18).

In the current study, neutrophils and eosinophils were the most prevalent inflammatory cells inside the blisters, which were observed primarily in patients with DH and BP, respectively ($P < 0.05$). Murthy et al. demonstrated that mixed inflammatory cells and eosinophils were the most frequent inflammatory cells within the blister. In the

Murthy study, similar to the present study, a lack of inflammation in the blister cavity was reported in Darier disease and Hailey-Hailey disease (19). Furthermore, the correlation of clinical diagnosis with histological diagnosis varied between 64.2% and 90.90% (11, 12, 17-22). In the current study, there was a complete agreement between the clinical and final pathological diagnoses, with 73.8% concordance with the first diagnosis.

Table 3. Association Between Type of the Disease and Duration of Disease and the Age of Onset

Type of disease	Duration of Disease (d), Mean \pm SD	Onset of Disease (y), Mean \pm SD
Pemphigus vulgaris	90.31 \pm 43.92	48.62 \pm 4.71
Bullous pemphigoid	938.64 \pm 661.62	51.17 \pm 6.87
Dermatitis herpetiformis	299 \pm 89.62	45.08 \pm 5.79
Pemphigus foliaceus	248 \pm 122.85	49.12 \pm 6.91
Bullous lichen planus	41 \pm 9.53	35.68 \pm 7.66
Epidermolysis bullosa	333.33 \pm 273.88	1.50 \pm 14.20
Darier disease	730	17.50 \pm 0.50
Epidermolysis bullosa acquisita	240 \pm 120	40.34 \pm 2.32
Hailey-Hailey disease	58.40	42
Linear immunoglobulin a bullous dermatitis	120	74.67
Subcorneal pustular dermatosis	365	40
Porphyria cutanea tarda	365	22
Diabetic bulla	4	63
Friction blister	3	23
P-value	0.047	0.136

Table 4. Comparison of the Results with Other Studies

Variables	Present Study	Karattuthazhatha (11)	Sobhan (12)	Pavani (17)	Mittal (18)	Murthy (19)	Pratibha (20)	Kumar (21)	Kumar (22)
Number of cases	88	100	168	42	110	74	55	50	35
Male to female ratio	0.69:1	0.93:1	1:1.15	0.82:1	1:1.15	NS	0.89:1	1.08:1	NS
Mean age	45.09	NS	45.32	47.71	47.1	NS	NS	46.02	NS
Clinicopathological correlation	73.8	87	NS	NS	NS	64.2	90.90	70	NS
Most common diseases (%)	PV (29.5)	PV (36)	PV (78)	BP (38.09)	PV (48.2)	BP (21.6)	PV (49.09)	PV (32)	PV (34.3)

Abbreviations: PV, pemphigus vulgaris; BP, bullous pemphigoid; NS, not stated

5.1. Conclusions

The most common bullous diseases in this study were PV, BP, and DH. Also, LAD was the rarest autoimmune blistering disorder. The most common hereditary bullous disease was EB. There was a significant correlation between the type of disease and the age of the patients and the duration of the diseases, but there was no significant correlation between types of diseases and gender (Table 4).

Footnotes

Authors' Contribution: M.Kh. and M.A. contributed to the study conception and design. Material preparation and data collection were performed by R.A., S.M, F.Gh., N.M., and M.A. M.A. and M.Kh performed the acquisition, analysis, and interpretation of data for the work. M.Kh. and M.A wrote the first draft of the manuscript. All authors revised the final version of the manuscript.

Conflict of Interests: We do not have any conflict of interest.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after its publication.

Ethical Approval: The Ethics Committee of Kerman University approved this study with the ethical code of IR.KMU.AH.REC.1396.1427.

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