Dermatology Practical & Conceptual

Frequency and Correlation of Peripheral and Tissue Eosinophilia with Clinical Manifestations in Patients with Bullous Pemphigoid

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ABSTRACT

Introduction: Bullous pemphigoid (BP) is an autoimmune disease involving the sub-epidermal layer. Eosinophilia may play a role in the pathogenesis of BP.

Objectives: We aimed to investigate the correlation between dermal or peripheral eosinophilia with clinical presentations in patients with BP.

Methods: This cross-sectional study was conducted on 108 BP patients from January 2010 to September 2019. Clinical data were recovered. Skin biopsies were re-evaluated, and the Bullous Pemphigoid Disease Area Index (BPDAI) severity score was calculated. Finally, the relationship between clinical features of BP and dermal or peripheral eosinophilia was analyzed.

Results: A total number of 108 patients were included in this study. Thirty-five were excluded due to our exclusion criteria. Finally, data from 73 patients were analyzed. Fifty-seven point five percent of the population was female. There was a significant direct correlation ($r = 0.33$) between BPDAI severity score and tissue eosinophilia ($P = 0.03$). No significant relationship was found between BPDAI severity score and peripheral eosinophilia ($P = 0.52$). There were significant positive correlations between tissue eosinophilia with absolute serum eosinophil count ($P = 0.002$; $r = 0.49$) and percentage ($P < 0.0001$; $r = 0.89$).

Conclusions: This study revealed significant relationships between tissue eosinophilia and BP severity. These findings could be useful in clinical practice. The possible role of eosinophils in BP clinical features should be considered as a promising help for better diagnosis and treatment.

Introduction

Bullous pemphigoid (BP) is an autoimmune bullous disease [1] more prevalent in the elderly with higher morbidity and mortality [2]. BP occurs due to immunological responses against hemi-desmosomal proteins responsible for dermo-epidermal cohesion [3]. Lesions mostly present on the lower abdomen, inner surface and flexors of the thighs, and forearms, localized or generalized. Mucosal involvement is rarely seen [4]. The metacognitive characteristics and biological properties of eosinophils suggest a potential role in the onset or progression of BP [5]. Eosinophilic infiltration of the dermis is one of the crucial early events in the development of bullous lesions in BP [6]. Previous studies on the histopathological features of the lesions revealed the presence of extracellular eosinophil granules, degranulated eosinophils, and free granule proteins throughout the upper dermis or at the dermo-epidermal junction [7,8]. Peripheral eosinophilia has been reported in 50-60% of patients with BP and is associated with disease severity [9]. However, the relationship between peripheral eosinophilia and clinical presentations, and also the presence of tissue eosinophilia has not been studied in BP patients.

Objectives

This study aimed to investigate the possible relationship between peripheral and tissue eosinophilia and clinical manifestations in patients with BP to provide more insight into the disease mechanism.

Methods

Study Design

This cross-sectional study was conducted among BP patients hospitalized in Al-Zahra Hospital, a referral center for dermatological disease in Isfahan, Iran, from January 2010 to September 2019. The study was approved by the ethical committee of Isfahan University of Medical Sciences (Ethical code: IR.MUI.MED.REC.1399.250).

Inclusion Criteria

All patients with a definite diagnosis of BP by an expert dermatologist were included in the study. The diagnosis of BP was based on suggestive clinical features, subepidermal blister formation with dermal eosinophilic infiltration on histopathological evaluations, and linear IgG and/or C3 deposits along the dermo-epidermal junction by direct immunofluorescence [10].

Exclusion Criteria

Patients with (I) incomplete documents, (II) hospitalization for less than 24 hours, and (III) peripheral eosinophilia related to other medical conditions (i.e. atopic dermatitis, asthma, other allergic conditions, parasitic diseases, and hyper-eosinophilic syndrome) were excluded from the study.

Studied Variables

The files of hospitalized patients were reviewed. Age, sex, pregnancy, site of involvement, hospitalization duration, concomitant diseases, past drug history, treatment protocol, and the serum eosinophil count were recruited from the medical records.

The Bullous Pemphigoid Disease Area Index (BPDAI) severity score was calculated for each patient. BPDAI is an index assessing cutaneous and mucosal involvement with a total score [11]. This index quantifies the size and number of the lesions altogether. In addition, the affected areas of the skin are weighted based on BPDAI with more emphasis on limbs and less on the face or scalp. The higher scores are attributed to worse conditions.

The slides of skin biopsies were also re-evaluated by a blinded skilled dermatopathologist for histopathological findings including subepidermal blister, C3, IgG, tissue inflammation, peripheral eosinophilia, and dermal eosinophilia. The presence or absence of a cleft was registered.

Tissue inflammation was assessed at grade 0 = 0%, grade 1 < 25%, grade 2 = 25% to 50%, grade 3 = 50% to 75%, and grade 4 > 75%, based on the proportion of light microscopic fields containing inflammatory cells. Four fields of ×40 power of each slide were evaluated, each field was divided into four quadrants (each 25%), and the tissue inflammation was scored based on the presence of inflammatory cells in each quadrant [12]. Finally, the average percentage in the four fields was considered as the final tissue inflammation score.

Dermal eosinophilia was also scored as grade 0 = 0%, grade 1 < 25%, grade 2 = 25% to 50%, grade 3 = 50% to 75%,

and grade 4 > 75% [13]. Eosinophils were counted among the inflammatory cells and then the percentage was calculated in the same four fields of ×40 power. The average percentage in the four fields was considered the final dermal eosinophilia score.

Peripheral eosinophilia is defined as the serum eosinophil count higher than 500 eosinophils per microliter. Peripheral eosinophilia (serum eosinophilia) was graded as mild (500-1500 eosinophils per microliter), moderate (1500-5000 eosinophils per microliter), and severe (more than 5000 eosinophils per microliter) [14].

Statistical Analysis

The data were analyzed using the Statistical Package for Social Science (SPSS) version 24 for Windows. Descriptive statistics (frequencies, percentages, means, and standard deviations) were used for each item to describe the sample characteristics. Independent t-test, one-way ANOVA, chi-square, and Spearman-Pearson correlation test were performed. A multivariate linear regression test was also used to investigate and eliminate the effect of confounding factors affecting the severity of the disease. P-value < 0.05 was considered as the significance threshold.

Results

A total number of 108 patients were included in this study. Thirty-five were excluded due to our exclusion criteria. Finally, data from 73 patients were analyzed. Among them, 45 patients had complete available histopathological data; 57.5% of the population was female. The mean age was 72.1 years. None of the patients were pregnant. Hypertension was the most frequent medical history and 46.6% of patients had histories of cardiovascular drug consumption.

One patient had BP lesions without blisters and one had localized BP. Limbs and trunk were the most frequent sites of involvement. The mean hospitalization duration was 11 days. Topical corticosteroids, systemic corticosteroids, and topical burrows were the most common treatment protocols among the patients. The most common histopathological findings were subepidermal blisters and positive C3 in a linear pattern in the slide samples. The most common grade of tissue eosinophilia was grade 1. Analysis of patient characteristics between males and females is summarized in Table 1.

Our results showed that patients with mucosal involvements had significantly lower serum eosinophil count (P = 0.02). Our study also showed that patients with higher grades of tissue eosinophilia had significantly higher grades of serum eosinophil count (P < 0.01) and also higher serum eosinophil percentage (P < 0.0001) (Table 2).

There was a significant correlation between BPDAI severity score and tissue eosinophilia grade (P = 0.03; r = 0.33). Although, there was no significant correlation between BPDAI severity score and peripheral eosinophilia grade (P = 0.52; r = 0.76). There was also a significant relationship between dermal inflammation and serum eosinophil count (r = 0.95; P < 0.0001) and serum eosinophil percentage (r = 0.46; P = 0.003) (Table 3).

Investigating the relationship between disease severity and other clinical and histopathological factors, only a significant relationship was observed between the duration of the disease and the severity of the disease, but the designed regression model was not statistically significant (Co-efficient of determination [R2] = 0.06, F =1.53, degrees of freedom [df] = 3, P-value >0.05).

In the regression model of patients medications, after the entering of anti-neoplastic drugs and oral corticosteroids into the model, the model was statistically significant and only the dose of corticosteroids was still statistically inversely related to the severity of the underlying disease (R2 = 0.11, F = 4.5, df = 2, P-value = 0.01). In the regression model of mucosal involvement and disease severity, after the inclusion of facial and trunk bullous involvement factors in the model, the model was statistically significant and no statistically significant relationship was observed between the severity of the disease and trunk and facial bullous involvement (R2 = 0.1, F = 3.99, df = 2, P-value = 0.02). In the regression model of peripheral and tissue eosinophilia involvement, the tissue eosinophilia grade (P = 0.001) and severity of tissue inflammation (P = 0.04) had significant relationships with the severity of the disease (Table 4).

Conclusions

In this study, analysis of clinical and histopathological findings revealed a direct and significant relationship between BP severity and tissue eosinophilia, despite peripheral eosinophilia. Furthermore, a significant direct correlation was found between tissue eosinophilia and serum absolute eosinophil count and percentage.

Eosinophils may play a significant role in the pathogenesis of BP. Some serial histological observations in the studies support this hypothesis, such as eosinophilic dermal infiltration, the presence of degranulated eosinophils, extracellular eosinophilic granules, and free granular proteins in the lesions. Therefore, eosinophils infiltration may initiate and later the degranulation process may progress the formation of bullous lesions in BP [6].

There are some studies evaluating the association between BP severity and related clinical and histopathological factors [15,16]. A recent prospective study was performed on 27 patients with newly diagnosed BP. This study reported that there is a correlation between dermal eosinophilia and tissue inflammation severity. Also, a significant direct

Table 1. Characteristics of the Study Population.

Variable	Total (N = 73)	Male (N = 31)	Female (N = 42)	P-Value
Age (years)				
Mean (SD)	72.1 (15.17)	70.81 (13.31)	73.10 (16.52)	0.53
Median (min-max)	76 (26-97)	72 (43-91)	76 (26-97)	
Past medical history N (%)				
Hypertension	33 (45.2)	10 (30.3)	23 (69.7)	0.05
Endocrine disease	28 (38.4)	10 (35.7)	18 (64.3)	0.33
Neurologic disease	16 (21.9)	6 (37.5)	10 (62.5)	0.57
Hyperlipidemia	7 (9.6)	0 (0.0)	7 (100)	0.01
Malignancy	3 (4.1)	2 (66.7)	1 (33.3)	0.77
Others	24 (32.9)	11 (45.8)	13 (54.2)	1
Past drug history N (%)				
Cardiovascular	34 (46.6)	14 (41.2)	20 (58.8)	0.81
Diabetes	12 (16.4)	4 (33.3)	8 (66.7)	0.53
Neurologic	11 (15.1)	6 (54.5)	5 (45.5)	0.51
Others	10 (13.7)	1 (10.0)	9 (90.0)	0.03
Site of involvement N (%)				
Limbs	72 (98.6)	32 (44.4)	40 (55.6)	1
Trunk	66 (91.7)	29 (43.9)	37 (56.1)	0.69
Mucus membrane	36 (49.3)	16 (44.4)	20 (55.6)	0.91
Acral	23 (31.5)	11 (47.8)	12 (52.2)	0.8
Head and neck	19 (26)	7 (36.8)	12 (63.2)	0.59
Hospitalization duration (days)				
Mean (SD)	11 (7.48)	10.16 (6.50)	11.69 (8.20)	0.39
Median (min-max)	9 (1-44)	9 (1-30)	10 (4-44)	
Treatment protocol N (%)				
Topical CS	69 (94.5)	30 (43.5)	39 (56.5)	1
Systemic CS	67 (93.1)	29 (43.3)	38 (56.7)	1
Topical Burrow	66 (90.4)	29 (43.9)	37 (59.1)	1
Topical antibiotic	61 (83.6)	29 (47.5)	32 (52.5)	0.2
Antihistamine	58 (79.5)	27 (46.6)	31 (53.4)	0.39
Systemic antibiotics	43 (58.9)	19 (44.2)	24 (55.8)	0.94
Antineoplastic	35 (47.9)	16 (45.7)	19 (54.3)	0.81
Histopathologic Finding N (%)				
Subepidermal blisters	35 (79.5)	16 (45.7)	19 (54.3)	0.71
C3	27 (79.5)	10 (37.0)	17 (63.0)	0.70
IgG	33 (75.0)	12 (36.4)	21 (63.6)	0.56
C3+IgG	24 (55.8)	9 (37.5)	15 (62.5)	0.55
Tissue eosinophilia N (%)				
Grade 1	23 (45.8)	8 (34.8)	15 (65.2)	0.45
Grade 2	13 (31.0)	5 (38.5)	8 (61.5)	
Grade 3	5 (11.9)	3 (60.0)	2 (40.0)	
Grade 4	1 (2.4)	1 (100)	0 (0.0)	

CS = corticosteroid; SD = standard deviation.

relationship between the disease severity and serum eosinophil is reported [10].

Another case-control study on 225 patients with BP investigated the association between peripheral eosinophilia and BP clinical manifestations. It reported that patients with BP with serum eosinophilia were significantly older and had higher palmoplantar involvement. Patients with BP with a normal eosinophil count were younger and presented more

Table 2. Serum Eosinophil Count, Percentage, and BPDAI Severity Score Based on Different Variables.

Variable		Serum eosinophil count	P-Value	Serum Eosinophil Percentage	P-value	BPDAI Severity Score	P-value
Sex							
Male		1113.5±974.86	0.44	30.6±25.1	0.15	42.3±29.68	0.62
Female		1412.1±2426.15		21.3±17.15		40.6±30.44	
Site of involvement							
Mucous	yes	947.8±1011.97	0.02	27.7±20.66	0.52	39.3±30.29	0.42
	no	1560.7±2278.69		23.5±21.86		43.4±29.83	
Past medical history							
Autoimmune disease	yes	899.7±499.36	0.6	19.7±16.58	0.16	45.8±27.9	0.51
	no	1487.1±2235.73		28.8±23.27		38.5±31.11	
Hypertension	Yes	1113.5±974.86	0.31	20.3±17.4	0.17	44.2±27.78	0.31
	No	1412.1±2426.15		29.1±23.32		38.9±31.76	
Hyperlipidemia	Yes	1459.1±540.23	0.42	25.4±21.96	0.99	43.8±31.95	0.81
	No	1220.7±1849.54		25.3±21.4		41.1±29.94	
Malignancy	Yes	1303.3±1268.13	0.76	22.5±22.9	0.63	40.7±32.38	0.58
	No	1228.8±1885.05		26.1±20.97		41.5±29.48	
Neurologic disease	Yes	1303.3±1268.13	0.61	17.4±20.21	0.50	58.3±16.07	0.31
	No	1228.8±1885.05		25.9±21.4		40.6±30.23	
Histopathologic findings							
Subepidermal blister	Yes	1364 ±2177.73	0.75***	25.2±19.26	0.92*	49.6±30.36	0.24
	No	770±309.39		25.9±29.00		36.7±30.86	
C3	Yes	1428.3±2604.77	0.19***	24.5±19.6	0.19*	46.0±33.23	0.56***
	No	1006.6±515.21		35.5±28.51		58.7±26.44	
IgG	Yes	1331.9±2326.14	0.66***	25.2±21.88	0.31*	47.6±32.25	0.96***
	No	1014.8±474.4		33.8±23.28		49.8±30.25	
C3+IgG	Yes	1448.4±2795.72	0.32***	23.1±20.20	0.47*	41.9±33.09	0.19***
	No	980.3±494.69		31.0±24.12		59.4±25.10	
Peripheral eosinophilia	Yes	1445.7±1880.36	<0.0001***	25.0±21.12	0.8*	42.9±30.53	0.48***
	No	309.7±111.02		27.4±23.72		33.5±26.37	
Tissue eosinophilia grade	1	714.3 ±364.30	<0.01****	10.5±6.01	<0.0001**	37.0±26.98	0.08****
	2	1176.5±415.24		34.6±7.61		61.4±30.4	
	3	1092.6±533.4		63.7±3.79		62.8±34.19	
	4	13200		83.7		-	
Dermal inflammation	Mild	911.9 ±551.13	0.95****	13.0±17.02	0.14**	50.5±31.42	0.86****
	Moderate	964.5±469.64		25.0±20.38		43.1±23.38	
	Severe	1849.1±3295.53		31.8±22.41		47.8±29.36	

BPDAI = Bullous Pemphigoid Disease Area Index.

frequently with atypical clinical manifestations [6]. Although, we observed no significant relationship between age and eosinophilia.

In 1983, Bushkell et al, reported a peripheral serum eosinophilia in patients with BP. They declared that peripheral blood eosinophilia was a common finding in their patients and BP should be included in the differential diagnosis of cutaneous bullous lesions with eosinophilia [17].

An animal model has suggested that eosinophils can mediate tissue injury in patients with BP by providing a relation between immunoglobulin-E auto-antibodies and skin blistering. As a result, higher tissue inflammations could be associated with higher BP severity [18].

An experimental study also demonstrated the overexpression of Thelper-2 cytokines like interleukin-31 on the injured skin of BP patients [19].

Table 3. Relationships Between Quantitative Variables Related to BPDAI Severity.

Variable		Hospitalization Duration	Serum eosinophil count	Serum Eosinophil Percentage	BPDAI Severity Score
Age	r	–0.11	–0.09	–0.289	0.008
	P	0.34	0.45	0.06	0.945
Hospitalization duration	r	1	–0.03	0.003	–0.21
	P	-	0.77	0.984	0.08
Peripheral eosinophilia grade	r	–0.09	0.15	0.15	0.76
	P	0.42	0.30	0.30	0.52
Tissue eosinophilia grade	r	–0.04	0.49	0.89	0.33
	P	0.80	0.002	<0.000	0.03
Dermal inflammation	r	–0.01	0.95	0.46	0.22
	P	0.95	<0.0001	0.003	0.06

BPDAI = Bullous Pemphigoid Disease Area Index.

Table 4. Regression Model Analyses.

Model		Standardized beta Coefficients	t	P-Value	95% Confidence Interval for Beta	
					Lower Bound	Upper Bound
1	Constant		3.04	0.003	19.87	95.88
	Age	-0.02	-0.22	>0.05	-0.52	0.42
	Sex (female/male)	-0.02	-0.16	>0.05	-15.73	13.28
	Hospitalization duration	-0.25	-2.11	0.03	-2.00	-0.05
2	Constant		6.86	0.0001	45.51	82.83
	Oral prednisolone	-0.26	-2.33	0.02	-29.38	-2.33
3	Constant		5.45	0.0001	40.71	87.62
	Facial bullous lesion (yes/no)	-0.22	-1.93	0.05	-31.39	0.457
	Trunk bullous lesion (yes/no)	-0.19	-1.68	>0.05	-45.88	3.934
4	Constant		1.45	>0.05	-9.72	57.37
	Tissue eosinophilia grade	0.61	3.65	0.001	16.25	57.40
	Peripheral eosinophilia grade	0.21	1.45	>0.05	-4.67	28.06
	Tissue inflammation grade	-0.35	-2.08	0.04	-22.52	-0.24
	Presence of subepidermal blister (yes/no)	0.12	0.88	>0.05	-11.56	29.11
	C3 (positive/negative)	0.05	0.35	>0.05	-13.07	18.54
	IgG (positive/negative)	0.31	1.86	>0.05	-1.73	38.04

Although, Wakugawa et al, suggested that eotaxin and interleukin□5 contribute to the blister formation but no correlations were reported between tissue eosinophilia and BP severity [20].

There are also a number of reports about BP and hyper-eosinophilia. A recent report in 2023, was a 16-year-old girl with generalized aggressive bullous lesions diagnosed as BP which was unresponsive to low dose prednisolone. More investigations revealed BP associated with hyper-eosinophilic syndrome. Finally, the patient was treated with high dose corticosteroid [21].

Our study supports the possible association between histopathological markers like tissue hyper-eosinophilia and clinical findings severity in patients with BP. The limitations of this study are a restricted study population, unknown potential confounders, and also, we had inferior level of evidence compared to prospective studies. Therefore, more studies with larger populations are suggested.

In conclusion, our study showed a significant correlation between histopathological findings in BP (such as tissue eosinophilia) and the disease severity. In conclusion, the possible role of eosinophils in BP clinical features should be considered as a promising help for better diagnosis and treatment.

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