Characterization of cellular infiltration in polymorphic eruption of pregnancy and pemphigoid gestationis in histopathological examinations

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Conflicts of interest: None to declare

Background: Pregnancy-specific dermatoses represent a group of pruritic skin diseases unique to pregnancy and the most common types are polymorphic eruption of pregnancy and pemphigoid gestationis. It is difficult to obtain a histopathological diagnosis for polymorphic eruption of pregnancy and pemphigoid gestationis in the lack of immunofluorescence because of their similar clinical presentation, particularly in the absence of bullous eruptions. We assessed the potential correlation between cellular cutaneous infiltration and a diagnosis of polymorphic eruption of pregnancy or pemphigoid gestationis.

Methods: This retrospective analysis was conducted at King Khalid University Hospital (Riyadh, Saudi Arabia) using biopsy-based data collected from 1999–2014. The study group included 29 patients with polymorphic eruption of pregnancy and 24 patients with pemphigoid gestationis.

Results: Three skin biopsy reports were excluded due to a strong history of atopy to rule out any possibility of atopic eruption of pregnancy. We performed a histopathological study of 50 patients. The data analysis revealed significant eosinophilic cell infiltration along the dermoepidermal junction and the tagging of eosinophils along the basal layer in biopsies from pemphigoid gestationis.

Conclusion: We observed significant eosinophilic cell infiltration along the dermoepidermal junction and the tagging of eosinophils along the basal layer, which may support a diagnosis of pemphigoid gestationis in the absence of direct immunofluorescence.

Keywords: dermatoses of pregnancy, pemphigoid gestationis, polymorphic eruption of pregnancy, pruritus

Received: 30 May 2016
Accepted: 25 June 2016

Iran J Dermatol 2016; 19: 73-78

INTRODUCTION

Pregnancy-specific dermatoses represent a group of pruritic skin diseases unique to pregnancy. The current classification by Ambros-Rudolph et al. includes four entities: pemphigoid gestationis (PG), polymorphic eruption of pregnancy (PEP), atopic eruption of pregnancy (AEP), and intrahepatic cholestasis of pregnancy (ICP) [1]. Among these classifications, PEP and PG are the most challenging for histopathological diagnosis given the lack of immunofluorescence due to similar clinical presentation, particularly in the absence of bullous eruptions. Polymorphic eruption of pregnancy or Pruritic Urticarial Papules and Plaques of Pregnancy (PUPPP) is the most common pregnancy-related skin disorder with an incidence rate of approximately 1:160–1:200 [2]. The

pathogenesis of PEP remains unknown. It has been suggested that the activation of the skin immune system characterized by an increased number of dendritic cells and activated T cells in the lesional skin contributes to the pathology of PEP [3]. Skin infiltrates of macrophages and eosinophils have been also described in the affected tissue [2,4,5]. The histopathology varies with the stage of the disease, but in general, AEP is characterized by perivascular lymphohistiocytic infiltration with frequent eosinophils and dermal edema and negative direct immunofluorescence (DIF) [6-8]. Pemphigoid gestationis is a rare and intensely pruritic autoimmune skin disorder that only occurs in association with pregnancy. The incidence of PG is roughly 1 in 60,000 pregnancies [9]. There has been some evidence that the deposition of immune complexes plays a major role in complement activation, which leads to chemoattraction and degranulation of eosinophils, resulting in tissue damage and blister formation [6]. The classic histological picture reveals superficial and deep perivascular lymphohistiocytic and eosinophilic infiltration. Direct immunofluorescence shows a linear deposition of IgG and C3 complement at the basement membrane antigenic zone [10,11]. C3 has been reported in up to 100% of the cases, and IgG has been observed in 25–50% of the cases [11]. Here, we performed a detailed histopathological study of a series of AEP and PG patients to identify certain histopathological features that might help to differentiate AEP from PG in the absence of DIF.

PATIENTS AND METHODS

We designed a retrospective study using biopsy-based data collected from 1990–2014 at King Khalid University Hospital (Riyadh, Saudi Arabia). This study was approved by the Institutional Review Board. All of the patients had clinical features of PEP or PG documented by histopathological features. We collected and analyzed the biopsies of 29 patients with PEP and 24 patients with PG. All histopathology reports were reviewed by a dermatopathologist. We conducted a histopathological analysis of the biopsies that included epidermal and dermal changes and DIF. We graded parakeratosis, spongoisis, and papillary edema as present or absent, and graded inflammatory cells on a visual analogue scale ranging from 0–3 (mild, moderate, rich). We derived frequency and percentage and analyzed the data using the version 22 of IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). The results are presented as numbers and percentages. We investigated correlations using the chi-square test and z test of proportions to determine significant differences in the percentage between two populations. P values less than 0.05 were considered significant.

RESULTS

Three biopsies were excluded from polymorphic eruption of pregnancy due to a strong history of atopy to rule out any possibility of atopic eruption of pregnancy. We analyzed 50 cases, and the primary skin biopsy features are summarized in Tables 1 and 2 and Figures 1 and 2.

Epidermal changes: There was no significant difference in the presence of parakeratosis and spongoisis between the two diseases. However, the percentage positivity of eosinophilic cells infiltrated to the dermoepidermal junction (DEJ) was significantly higher in PG than PEP (P<0.001). (Table 1 and Figures 1-2).

Dermal inflammatory infiltrate: There was no

Table 1. Epidermal characteristics in pemphigoid getationis versus polymorphic eruption of pregnancy.

Epidermal characteristics	Pemphigoid gestations (n=24) (%)	Polymorphic eruption of pregnancy (n=26) (%)	*P*
Parakeratosis			
Negative	18 (75.0)	18 (69.2)	0.652
Positive	6 (25.0)	8 (30.8)	
Spongiosis			
Negative	7 (29.2)	10 (38.5)	0.490
Positive	17 (70.8)	16 (61.5)	
Eosinophilic infiltration of DEZ			
Negative	3 (12.5)	26 (100)	<0.001
Positive	21 (87.5)	0 (0.0)	

Table 2. Dermal inflammatory infiltrates in pemphigoid getationis versus polymorphic eruption of pregnancy.

Characteristics	Pemphigoid gestations (n=24) (%)	Polymorphic eruption of pregnancy (n=26) (%)	*P*
Perivascular lymphocytes			
Negative	0 (0.0)	3 (11.5)	0.325
Mild infiltrations	24 (100)	7 (26.9)	
Moderate infiltrations	0 (0.0)	15 (57.7)	
Rich infiltrations	0 (0.0)	1 (3.8)	
Plasma cell			
Negative	23 (95.8)	26 (100)	0.293
Positive	1 (4.2)	0 (0.0)	
Histiocytes			
Negative	16 (66.7)	21 (80.8)	0.254
Positive	8 (33.3)	5 (19.2)	
Mast cells			
Negative	21 (87.5)	26 (100)	0.062
Positive	3 (12.5)	0 (0.0)	
Neutrophils			
Negative	18 (75.0)	24 (92.3)	0.094
Positive	6 (25.0)	2 (7.7)	
Eosinophils			
Negative	1 (4.2)	-	0.547
Mild infiltrations	5 (20.8)	20 (76.9)	
Moderate infiltrations	12 (50.0)	2 (7.7)	
Rich infiltrations	6 (25.0)	4 (15.4)	
Papillary edema			
Negative	-	10 (38.5)	0.510
Mild	17 (70.8)	13 (50.0)	
Moderate	6 (25.0)	3 (11.5)	
Severe	1 (4.2)	0 (0.0)	
Direct immunofluorescence			
Negative	0 (0.0)	26 (100)	<0.001
Positive	24 (100)	0 (0.0)	
C3 antibody			
Negative	1 (4.2)	26 (100)	<0.001
Weakly positive	6 (25.0)	0 (0.0)	
Moderately positive	12 (50.0)	0 (0.0)	
Strongly positive	5 (20.8)	0 (0.0)	

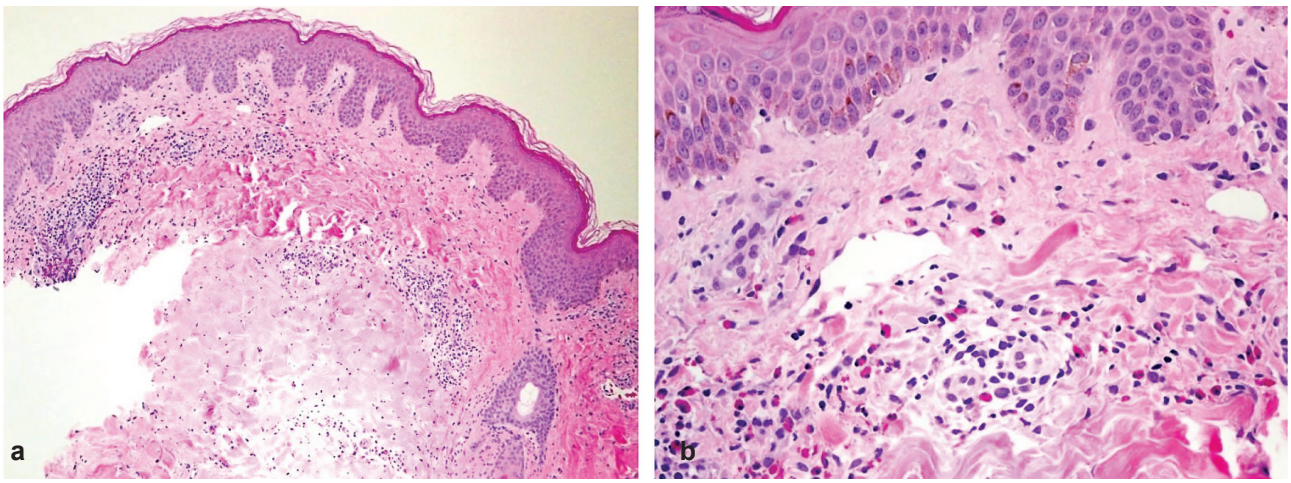

Figure 1. 1.a. Low power shows epidermal acanthosis and spongiosis with underlying perivascular and interstitial infiltration in polymorphic eruption of pregnancy (H&E, 100×). **1.b.** Higher power reveals perivascular and interstitial eosinophilic infiltration. No eosinophils are present at the dermoepidermal junction in polymorphic eruption of pregnancy (H&E, 400×).

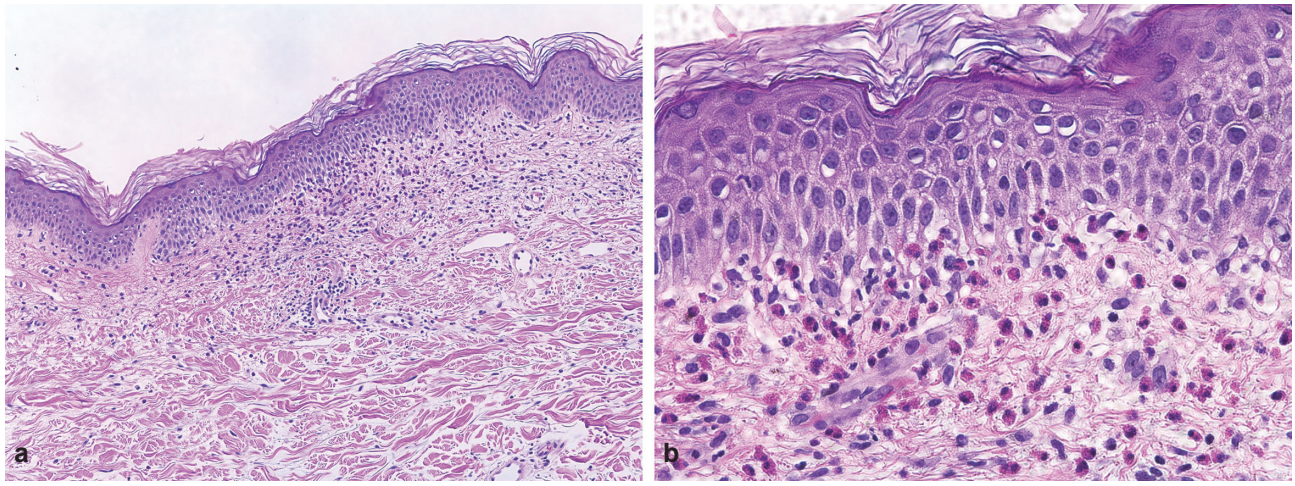

Figure 2. 2.a. Low power shows epidermal spongiosis with underlying infiltration mainly around dermoepidermal junction in PG (H&E stain, 200×). **2.b.** Higher power reveals eosinophilic infiltration at the dermoepidermal junction in PG (H&E, 400×).

significant difference in perivascular infiltration of lymphocytes between PG and PEP (P=0.325). All biopsies exhibited mild-to-moderate dermal perivascular lymphocytic infiltration. Eosinophilic infiltration tended to be milder in PEP compared to PG which had more moderate eosinophilic infiltrations. (Table 2) There was no significant infiltration of other cells. (Table 2)

Papillary edema and DIF: PG showed a significant papillary edema and positive DIF (P<0.001) (Table 2 and Figures 3).

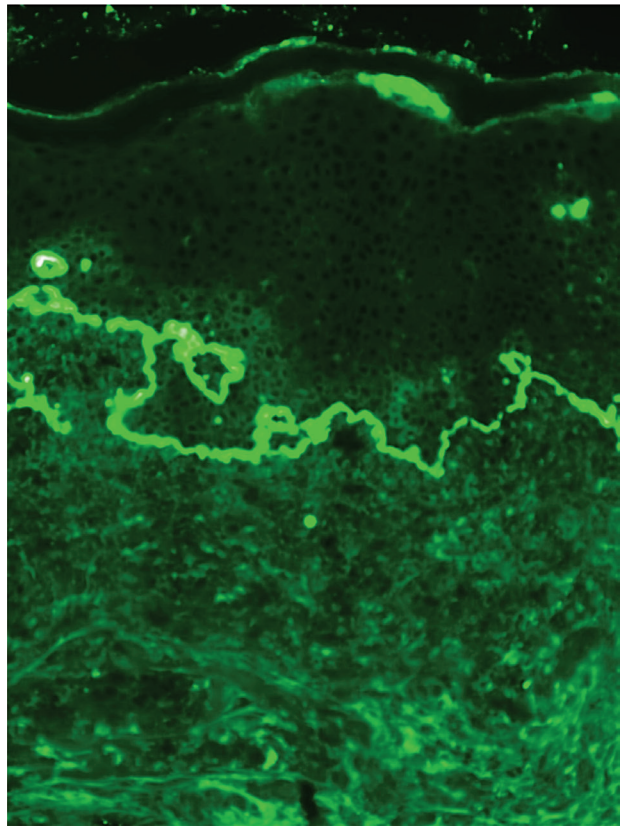

Figure 3. Direct immunofluorescence (DIF) study shows C3 positivity at the basement membrane zone (DIF, 200×).

DISCUSSION

The specific dermatoses of pregnancy represent a group of pruritic skin diseases with considerable overlapping clinical and histopathological features. Polymorphic eruption of pregnancy is the disease most often clinically confused with PG; both can present with urticarial papules and plaques and have always posed a challenge to dermatologists and pathologists. Given the absence of bullous eruptions of PG and a lack of DIF, the histological findings of PEP are similar to those of PG [12]. Recent studies have demonstrated the utility of anti-C4d or anti-C3d antibodies to differentiate between PEP and PG [13]. The results of these studies have shown the potential utility of C4d routine immunohistochemistry in the formalin-fixed paraffin-embedded tissue for distinguishing PEP from PG. Despite this important achievement, we still need to identify certain histopathological features that can differentiate between these diseases, particularly in centers lacking access to DIF and anti-C4d.

Frequent epidermal changes—including spongiosis and parakeratosis—have been reported in PEP as late histopathological manifestations [7,14]; eosinophilic spongiosis has been reported in PG [15].

In our study, parakeratosis was documented in less than 30% of PEP and PG patients. On the other hand, spongiosis was documented in more than 60% of patients of both groups, which may reflect the early skin biopsies obtained from our patients.

We noted moderate to rich eosinophilic infiltration and tagging of eosinophils along the basal layer in 75.0% of PG patients; these features were frequently less observed (23.1%) in PEP patients. These findings support the idea of the active participation of eosinophils in generating cutaneous lesions in pemphigoid-group disorders [16] via the deposition of toxic cationic proteins [17]. This finding of eosinophilic spongiosis may be used as a histopathological clue for diagnosing PG.

A sub-epidermal split and C3 deposits in DIF of peri-lesional skin as a linear deposition along the basement membrane zone (BMZ) are gold standards to differentiate between PEP and PG [1,7,15,18]. In our study, we found DIF positivity in 100% of our PG patients and complete DIF negativity in 100% of our PEP patients. A large fraction of our patients (95.8%) had C3, and one patient had a weak linear deposit of IgM along the BMZ. Two patients had positive deposition of IgG along with C3. These results are comparable to those of previous studies.

Dermal inflammatory cells that preferentially infiltrate lymphocytes and eosinophils play a key role in the entire pathogenesis of PEP and PG [8,16,17]. We noted a perivascular infiltrate of lymphocytes and, to a lesser extent, histiocytes in both diseases. We confirmed the general infiltration pattern of lymphocytes and histiocytes, but we did not observe lymphocytic vasculitis in PEP, which has been reported in approximately 27% of PEP patients in other studies [8]. A variable number of scattered eosinophils were present in all patients in both groups, but were prominent in the PG group. It has been speculated that mast cells are involved in the pathogenesis and early onset of PEP [19]. In our study, we could not find any mast cells in the PEP group, and only 12.5% of the PG group exhibited mast cells. Based on these results, it is unlikely that mast cells play any role in the pathogenesis of either PEP or PG. We did not find any significant infiltration of neutrophils or plasma cells in either group. The prebullous stage of PG is characterized by edema of the upper and middle dermis [7], and the early stage of PEP exhibits prominent dermal edema in approximately 18% of the cases [8]. In our study, dermal edema was documented in over 90% of PG-group patients and a little more than 50% of PEP-group patients.

Direct immunofluorescence is crucial for a definitive diagnosis of PG. If DIF is not available, a clinicopathologic correlation is crucial to differentiate between PEP and PG. Our study highlighted the significance of eosinophilic cell infiltration and the tagging of eosinophils along the basal layer to support a diagnosis of PG.

Acknowledgements

The authors acknowledge the support they received from Deanship of Scientific Research, King Saud University, Riyadh, Saudi Arabia.

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