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BRIEF REPORT

Possible Role for Plasmacytoid Dendritic Cells in Pemphigus

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Dear Editor:

Plasmacytoid dendritic cells (pDCs) are a specialized DC population[1]. They display plasma cell morphology and express CD4, CD123, HLA-DR, BDCA-2, and toll-like receptors (TLR)7 and TLR9 within endosomal compartments. pDCs are usually not present in normal skin, but infiltrate the skin in several cutaneous pathologies including inflammatory/autoimmune, infectious, and neoplastic entities[1]. Upon TLR stimulation, pDCs have the ability to secret type I interferons (IFNs) up to 1,000 times more than other cell types as well as proinflammatory cytokines including interleukin (IL)-6 and tumor necrosis factor (TNF)-α[1]. These lead mainly to an antiviral state and contribute to the regulation of the function of other immune cells such as myeloid DC, T-, B- and natural killer (NK) cells. Thus, pDCs provide protective immunity at the skin level by regulated sensing of microbial or self-nucleic acids upon skin damage. However, when excessive sensing of self-antigens occurs, pDCs may participate in an exaggerated self-directed immune responses contributing to the pathogenesis of different inflammatory/autoimmune cutaneous pathologies. Several studies have identified a significant role of pDCs in several inflammatory/autoimmune mucocutaneous disorders including lupus erythematosus (LE), psoriasis, and lichen planus (LP)[1]. However, the role of pDCs in the autoimmune blistering disorders has not been well-explored. Hence, we intend in this study to investigate pDC role in the pemphigus group of the autoimmune blistering skin diseases. This may allow us to uncover part of the underlying pathogenesis of these disorders.

Our institutional review board approved the study (American University of Beirut IRB protocol DER.OA.24). Forty-six pemphigus cases (including 36 pemphigus vulgaris (PV) and 10 pemphigus foliaceus types) and 32 pemphigoid cases (29 bullous pemphigoid and 3 pemphigoid gestationis) as comparison group were retrieved from our database. Only straightforward cases that fit the clinicopathological and immunoflorescence features of the respective autoimmune blistering diseases were included. Immunohistochemical analysis was performed on sections obtained from formalin-fixed, paraffin-embedded tissue using antibodies to BDCA-2 (mouse immuno globulin G1, clone 124B3.13; Dendritics, Lyon, France) and myxovirus resistance protein A (MxA, M143; University of Freiburg, Freiburg, Germany). Anti-BDCA2 antibody is a specific pDC marker[1], while anti-MxA antibody assesses type I IFN production by pDCs, since MxA is well established surrogate marker for local type I IFN production[1]. A semi-quantitative scoring system was used to assess pDC recruitment and MxA expression (Table 1).

Results showed the pDCs to be present in all of the pemphigus cases (n=46) and 72% (n=23) of pemphigoid cases. However, pDCs were significantly more abundant in pemphigus cases (Fig. 1B, E) than in pemphigoid cases (Fig. 1H) with a significantly higher pDC score ($p<0.05$). MxA expression was mostly patchy in both pemphigus (n=44, 96%) (Fig. 1C, F) and pemphigoid (n=23, 72%) cases (Fig. 1I).

Our hypothesis in this study concerning pDCs role in the pemphigus group is based on several observations. First,

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Table 1. pDCs presence and MxA expression in pemphigus versus pemphigoid group (%)

Entity (case no.)	Age (yr)	Gender (ratio)	Frequency of pDC infiltration	pDC score*				MxA score†		
				0	1	2	3	0	1	2
Pemphigus (n=46)	6~81	20 M:26 F	46	0	16	29	1	0	44	2
Pemphigoid (n=32)	47~91	14 M:18 F	23	9	17	6	0	9	23	0
p-value‡	-	-	<0.05	<0.05				<0.05		

pDCs: plasmacytoid dendritic cells, MxA: myxovirus resistance A, M: male, F: female. *BDCA2+ pDC content was scored as percentage of total mononuclear infiltrate: 0 (no positive cells), 1 (1%~10% positive cells), 2 (10%~50% positive cells), 3 (>50% positive cells). †MxA staining was scored as: 0=negative, 1=patchy/weak, and 2=diffuse. ‡Statistical analysis was performed by using the Mann-Whitney test to analyze statistical differences in pDC and MxA scores between the 2 groups. A two-tailed *p*-value of <0.05 was considered statistically significant. Normal skin tissue served as negative control and cutaneous lupus erythematosus served as positive control.

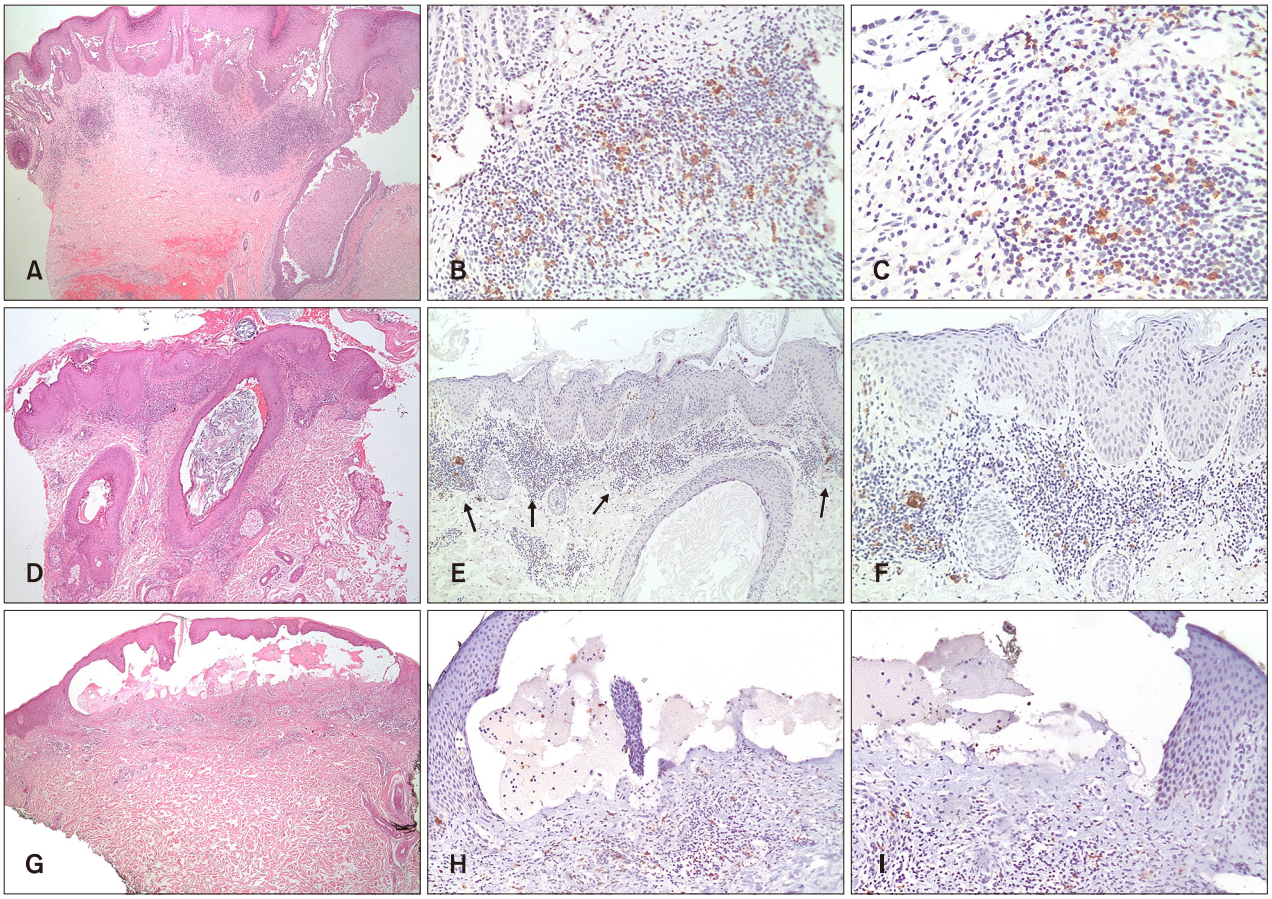

Fig. 1. (A~C) Pemphigus vulgaris. (A) Representative case showing suprabasal acantholysis with underlying dermal inflammatory infiltrate (H&E, ×40). (B, C) BDCA-2 immunostaining highlighted plasmacytoid dendritic cells (pDCs) in a superficial perivascular and interstitial distribution with pDCs making up more than 10% of the inflammatory infiltrate/pDC score of 2 (B: ×100, C: ×200). (D~F) Pemphigus foliaceus. (D) Representative case showing subcorneal acantholysis with underlying dermal inflammatory infiltrate (H&E, ×40). (E, F) BDCA-2 immunostaining highlighted pDCs in a superficial perivascular and interstitial distribution with pDCs making up more than 10% of the inflammatory infiltrate/pDC score of 2 (E: ×100, F: ×200). (G~I): Bullous pemphigoid. (G) Representative case with subepidermal blistering and underlying inflammatory infiltrate (H&E, ×100). (H, I) BDCA-2 immunostaining highlighted scattered pDCs in a perivascular and interstitial distribution with pDCs making up less than 10% of the inflammatory infiltrate/pDC score of 1 (H: ×100, I: ×100).

several reports have described induction of autoimmune blistering disorders following administration of IFN-α, the endogenous local counterpart of which is mainly produced by pDCs[2]. Second, high-titer IFN-α antibodies have been detected in patients with autoimmune blistering disorders[3]. Third, imiquimod, an immunomodulator known to be a potent pDCs activator, and TNF inhibitors, known to be secondary inducers of IFN-α, have been reported to induce autoimmune blistering disorders[4,5]. Fourth, some autoimmune blistering disorders have been associated with viral infections. Since pDCs' mainly function in anti-viral resistance, their involvement in such autoimmune blistering disorders would not be surprising[6]. Finally, autoimmune blistering disorders have been associated with several inflammatory disorders such as LE, LP and psoriasis, in which evidence suggests significant pDC role in their underlying pathogenesis[7].

Our study results support our hypothesis, especially in relation to a possible role for pDCs in pemphigus pathogenesis. While the contribution of the adaptive immune system has been well studied using animal models, the earlier mechanisms that contribute to the initial production of autoantibodies and loss of tolerance have not been well investigated[7,8]. One study demonstrated that, in the presence of Dsg3, NK cells interact with CD4+ T cells in the perilesional skin and peripheral blood of PV patients leading to the production of several cytokines, with especially high IL-6 levels. IL-6 is a pleiotropic cytokine important in the pathophysiology of inflammation and autoimmune disorders such as its role in the production of anti-DNA and chromatin autoantibodies in LE[8]. However, the contribution of pDCs, which can also secret IL-6, was not explored in this study[8]. In another study investigating the local inflammatory infiltrate in Darier's disease and using 14 PV cases as a comparison group, the authors reported the presence of CD123+ pDCs in low percentages (<5%) in PV cases[9].

The results of our study and the known multifaceted immunological functions of the pDC indicate a possible role of this cell in the autoimmune blistering disorders, especially pemphigus group[1]. Especially with NK cells which have been implicated in the early pathogenic steps of PV pathogenesis, pDCs have been shown to have bidirectional interaction[10]. There is evidence that NK cells, upon cell-to-cell contact, promote pDC maturation and strongly enhance pDC production of IFN-α, TNF-α, and IL-6. On the other hand, pDCs can efficiently promote NK cell activation. In addition, several studies have shown that pDCs are critical for antibody responses through their role in promoting plasma cell differentiation from naive and memory B cells[1]. Actually, pDCs have been shown to induce plasma cell differentiation through the sequential action of type I IFNs and IL-6[10]. This thus makes their possible role in the induction of autoantibodies in the autoimmune blistering disorders unsurprising.

The authors recognize that a relatively small number of cases have been studied and that the study is performed at only one point during the course of these autoimmune blistering disorders. Hence, these observations are considered preliminary.

In summary, we have shown that pDCs are recruited into the skin lesions of the autoimmune blistering disorders, with significantly higher content in the pemphigus group. Their consistent presence speaks in favor of an important role of these cells in their pathogenesis, possibly in the initial mechanisms leading to autoantibody production.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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Factors Determining Treatment Response to Cryotherapy for Foot Warts

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Dear Editor:

Different clinical and biologic factors, such as disease duration, infection site, and lesion size, are associated with the treatment response to cryotherapy of cutaneous warts[1-3]. However, published data on the predictive factors of cryotherapy in the treatment of cutaneous warts showed inconsistent results[3,4]. In addition, the majority of previous studies have not controlled for confounding variables[1-4], or have included warts located in different anatomical sites[1,2]. Thus, we aimed to investigate the factors affecting the treatment response to cryotherapy in foot warts using multivariable analysis.

We reviewed the medical records of patients having foot warts and who started cryotherapy at the SMG-SNU Boramae Medical Center from February 2016 through January 2018. All patients were followed until we confirmed that their warts completely disappeared, until they were lost to follow-up, or until February 2, 2018 (date of scheduled data extraction), whichever arrived earlier. Age, sex, disease duration, infection site (toe, sole, and periungual), number of lesions, the maximum diameter of lesions, and recurrent status (primary infection vs. re-infection) were obtained from the medical records of the initial visits. Treatment intervals, the number of cryotherapy sessions, and treatment outcomes (cleared vs. persistent) were obtained. A patient with clearance was considered a patient who no longer had visible warts and had sustained normal skin color and skin lines for at least 4 weeks after the last cryotherapy. A responder was defined as a patient having complete clearance of warts within after 6 cryotherapy sessions[5]. The study protocol was approved by the Institutional Review Board of the SMG-SNU Boramae Medical Center (approval number: 30-2017-30) and the requirement for informed consent was waived.

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