Diagnostic Value of Plasmacytoid Dendritic Cells in Differentiating Pityriasis Lichenoides et Varioliformis Acuta From Lymphomatoid Papulosis

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Abstract: Pityriasis lichenoides et varioliformis acuta (PLEVA) and lymphomatoid papulosis (LyP) can often demonstrate clinical and histopathologic overlap. A recent study demonstrated significant plasmacytoid dendritic cell (pDC) recruitment in lesions of PLEVA, whereas another study reported minimal pDC recruitment in lesions of LyP. To confirm the possible diagnostic value of pDCs in differentiating PLEVA and LyP, we compared the presence and distribution of pDCs and myxovirus protein A (MxA) expression (an indirect assessment of pDC activity). In total, 19 cases of PLEVA (16 patients) and 14 cases of LyP (11 patients) were examined using immunohistochemical stains for anti–blood-derived dendritic cell antigen-2 and MxA. Individual semiquantitative scoring systems were used to assess the immunohistochemical results, and a Mann–Whitney test with a subsequent 2-tailed *P* test was performed for statistical analysis. No statistically significant difference in the number of pDCs in both groups was found. However, most PLEVA cases (84%) demonstrated intense and diffuse MxA expression, whereas LyP cases (71%) demonstrated weak patchy staining ($P < 0.007$). Our study suggests that although additional studies may be needed to determine whether pDCs are more relevant to the pathogenesis of PLEVA or LyP, pDC activity through MxA staining may play a role in differentiating PLEVA from LyP and may serve as a platform for additional studies.

Key Words: pityriasis lichenoides et varioliformis acuta, lymphomatoid papulosis, plasmacytoid dendritic cells, MxA, CD303

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INTRODUCTION

In the past few decades, a specialized dendritic cell population with plasmacytoid morphology, known as plasmacytoid dendritic cells (pDCs), has been extensively studied. pDCs are now known to express CD4, CD123, HLA-DR, and BDCA-2,[1,2] along with toll-like receptors (TLR)7 and TLR9 within endosomal compartments.[2] These cells are capable of producing large quantities of type I interferon (IFN)/interferon alpha (IFN-α) against pathogenic agents or danger signals[1] and link innate and adaptive immune systems by controlling the function of myeloid dendritic cells, T cells, B cells, and natural killer cells.[1] In recent studies, myxovirus protein A (MxA), which is transcriptionally upregulated by type I IFN,[3] has also been used to indirectly assess pDC activity.[4]

Although generally lacking from normal skin,[5] pDCs have been demonstrated in several cutaneous pathologies. In addition, pDCs seem to be partially implicated or, at minimum, involved in the pathogenesis and/or evolution of several infections (viral infections including warts,[6] molluscum contagiosum,[7] orf infection,[8] etc), inflammatory/autoimmune (psoriasis,[9] lupus erythematosus,[9] etc.), and neoplastic (melanoma,[2] squamous cell carcinoma,[10] lymphomas,[2] etc.) entities. Some evidence even suggests the microscopic diagnostic utility of immunohistochemical staining for pDCs in the differentiation of cutaneous entities with overlapping features. Currently, the presence of pDCs has been believed to be useful in the differentiation of some lymphocytic scarring alopecias (ie, lichen planopilaris, frontal fibrosing alopecia, and the scarring alopecia of lupus erythematosus [LE]),[11] along with LE and its neoplastic mimickers, both lymphoproliferative (ie, mycosis fungoides and subcutaneous panniculitis-like T-cell lymphoma)[12] and epithelial (ie, squamous cell carcinoma in the case of hypertrophic LE).[13] Similarly, in this study, we sought to differentiate the occasionally, clinically, and histopathologically overlapping entities of pityriasis lichenoides and lymphomatoid papulosis (LyP).

Pityriasis lichenoides is an uncommon dermatosis that includes a spectrum ranging from the acute ulceronecrotic lesions of pityriasis lichenoides et varioliformis acuta (PLEVA) to the more chronic scaly papules of pityriasis lichenoides chronica.[14–16] By contrast, LyP is currently classified in the spectrum of primary cutaneous $CD30^+$ lymphoproliferative disorders and clinically presents as a chronic, recurrent, self-healing papular eruption with a typically waxing and waning course.[14,15,17] In classic lesions of both PLEVA and LyP, histologic characteristics can also aid in the separation of each entity. PLEVA demonstrates epidermal changes including parakeratosis, individually necrotic keratinocytes, and basal vacuolar interface dermatitis overlying a wedge-shaped superficial and deep lymphocytic infiltrate composed of small-sized to medium-sized lymphocytes with extravasated erythrocytes.[18,19] LyP encompasses a variety of histologic types based on pattern (type A wedge, type B band, and type C nodule), location of the infiltrate (type D epidermotropic, type E angioinvasive, and type F folliculotropic), and even chromosomal rearrangement as in the case of LyP

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The authors declare no conflicts of interest.

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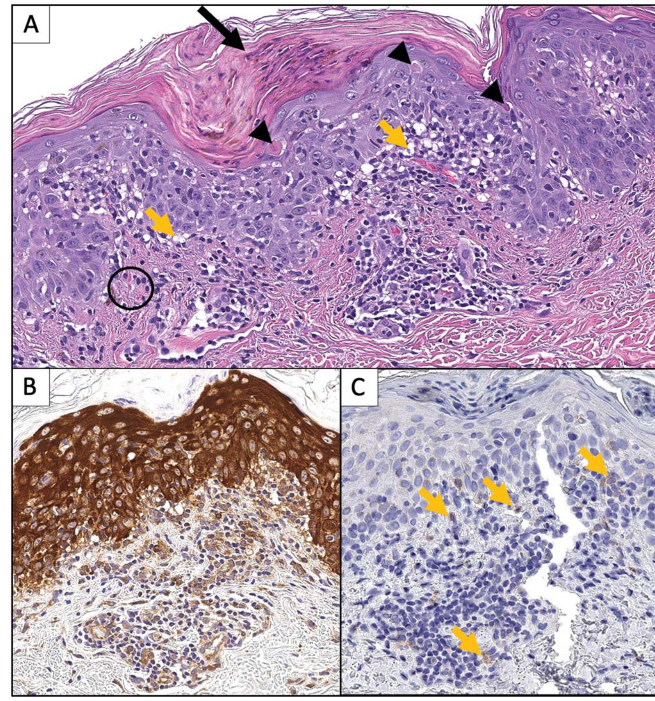

FIGURE 1. A, (H&E, ×200) A case of PLEVA characterized by focal parakeratosis with neutrophils (black arrow), individually necrotic keratinocytes (arrowhead), basal layer vacuolization (yellow arrow), and a perivascular lymphocytic infiltrate with few extravasated erythrocytes (black circle), and both (B) intense (score 2) staining for MxA (×200) and (C) few (score 1) pDCs highlighted by BDCA-2 (CD303) (×200) (yellow arrow).

with DUSP22-IRF4 rearrangement. These LyP types, with the exception of type B and occasionally type D, share the overarching feature of large pleomorphic lymphocytes expressing CD30.[20] However, considerable overlap can exist between PLEVA and LyP clinically, histologically, and immunohistopathologically rendering the differentiation between the 2 entities occasionally difficult.[14,15] A unique PLEVA variant has even been described, which was characterized by a conspicuous CD30^{+} component mimicking LyP.[15]

Recently, a few articles have independently investigated pDC recruitment in PLEVA and LyP. Given that type I IFN has been documented in pityriasis lichenoides and pDCs are known to be the main source of local tissue type 1 IFN,[16] Karouni et al hypothesized that pDCs may play a role in the pathogenesis of pityriasis lichenoides. In their study, they confirmed the presence of active pDCs in the inflammatory infiltrate of all their pityriasis lichenoide cases (n = 20).[16] By contrast, De Souza et al,[17] while studying CD30-positive lymphoproliferative disorders, noted a relatively small number of pDCs in LyP (1%) with most of the inflammatory infiltrate instead composed of CD163-positive M2 macrophages. Given these findings, we undertook this study to compare pDC presence and distribution as well as MxA (myxovirus protein A) expression (surrogate marker of type I interferon production and thus an indirect assessment of pDC activity) in PLEVA versus LyP. We further hoped that these immunohistochemical stains would help to differentiate between these 2 entities.

MATERIALS AND METHODS

This study was approved by the institutional review board (IRB #H-38841). We retrospectively searched our dermatopathology database from January 2015 to April 2019 for diagnoses of "lymphomatoid papulosis" and "pityriasis lichenoides et varioliformis acuta." Only straightforward cases that fit the clinicopathological features of PLEVA (Fig. 1A) and LyP (Fig. 2A–C) were selected, and cases in which the diagnosis was uncertain were excluded from the study. In total, 19 cases of PLEVA (16 patients) and 14 cases of LyP (11 patients) fit our inclusion criteria. pDC presence and distribution (using BDCA-2 as a pDC immunohistochemical-specific marker) as well as MxA expression was evaluated.

Immunohistochemical Analysis

Immunohistochemical analysis was performed on 5-μm-thick sections obtained from formalin-fixed, paraffin-embedded tissue using the following antibodies: BDCA-2 (mouse IgG1, clone 124B3.13, dilution 1:250, Dendritics, France) and MxA (M143, dilution 1:250, University of Freiburg, Germany; Professor Haller). All stained slides were reviewed independently by 2 investigators to ensure consistency of interpretation. pDC content was scored for BDCA-2 and reported as a percentage of the total mononuclear infiltrate: 0 (very rare positive cells), 1 (1%–10% of positive cells), 2 (10%–50% of positive cells), and 3 (>50% of positive cells). In addition, MxA staining was scored as follows: 0 = negative, 1 = weak/patchy staining, and 2 = intense staining. Appropriate positive and negative controls were used.

Statistical Analysis

A Mann–Whitney test was used to analyze for any significant differences in the expression of BDCA-2 and MxA between the compared entities. A 2-tailed P value of <0.05 was considered statistically significant.

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TABLE 1. Comparison of Scoring in the PLEVA and LyP Groups

	PLEVA (n = 19)	LyP (n = 14)	P*
pDC score†			
0	5	4	>0.05 (0.984)
1	12	8	
2	2	2	
3	0	0	
MxA score‡			
0	0	0	<0.05 (0.007)
1	3	10	
2	16	4	

*Statistical analysis through the Mann–Whitney *U* test used to analyze the statistical differences in pDC and MxA scores between the PLEVA and LyP, with a 2-tailed *P* value of <0.05 considered to be statistically significant.

†BDCA-2 (CD303)-positive pDCs were scored as a percentage of the total mononuclear infiltrate: 0 (very rare positive cells), 1 (1%–10% of positive cells), 2 (10%–50% of positive cells), and 3 (>50% of positive cells).

‡MxA staining was scored as follows: 0 = negative, 1 = weak/patchy staining, and 2 = intense staining.

BDCA-2 (CD303), anti–blood-derived dendritic cell antigen-2 (CD303).

RESULTS

Patient Data

Patients with PLEVA had a mean age of 40 years (4–70 years) with a slight female predominance (female to male ratio of 10:6). Lesions were more commonly encountered on the back and right lower extremity. While patients with LyP had a mean age of 43 years (11–70 years) with a female predominance (female to male ratio of 9:2) and the extremities more commonly affected.

BDCA-2-Positive Plasmacytoid Dendritic Cells

Antibodies against BDCA-2 (CD303) were used to detect pDCs. Although all cases demonstrated some degree of BDCA-2 staining (Table 1), 26%–28% of the cases in PLEVA (n = 5, 26%) (Fig. 1C) and LyP (n = 4, 28%) showed only very rare (score 0) (Fig. 2E) dermal staining cells. Most PLEVA (n = 12, 63%) and LyP (n = 8, 57%) cases demonstrated 1%–10% staining (score 1) of the mononuclear infiltrate. Overall, there was no statistically significant difference in the pDC scores between PLEVA and LyP ($P > 0.05$).

Expression of Myxovirus Protein A

In this study, MxA expression was intense and diffuse (score 2) involving the epidermis, dermis, and various adnexal structures (Fig. 1B) in most of the PLEVA cases (n = 16, 84%), whereas LyP showed predominantly weak, patchy (score 1) expression (n = 10, 71%) (Fig. 2D). Using the Mann–Whitney *U* test and a 2-tailed *P* test, these results were found to be statistically significant with a *P* value of <0.05 ($P < 0.007$) (Table 1).

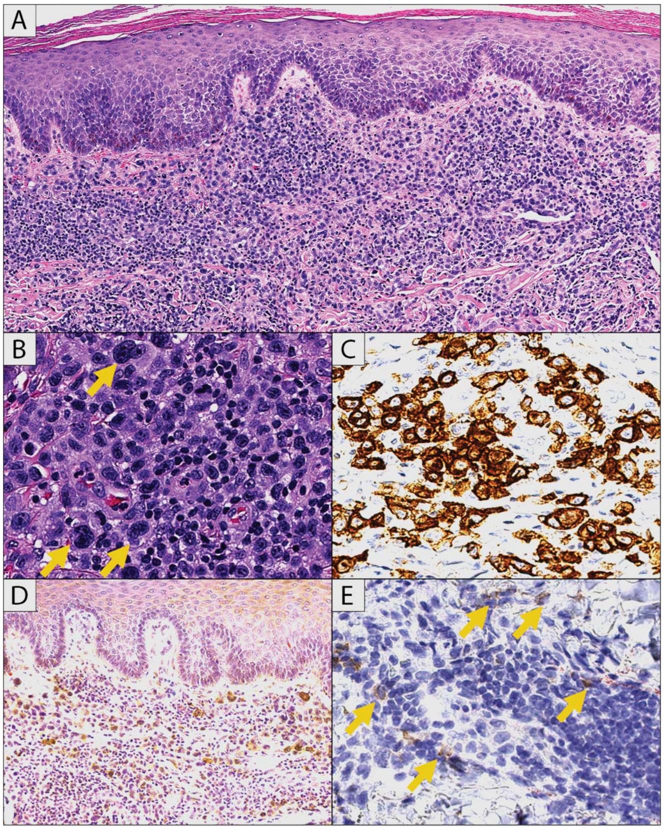

FIGURE 2. A, (H&E, ×100) A case of LyP demonstrating a dense dermal infiltrate composed of (B) (H&E, ×400) medium to large, occasionally multinucleated (yellow arrow), (C) CD30-positive cells (×400). D, Immunohistochemical staining with MxA (×200) is weak/patchy (score 1), and (E) few (score 1) pDCs are highlighted by BDCA-2 (CD303) (×400) (yellow arrow).

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DISCUSSION

Although clinical and histologic similarities between PLEVA and LyP exist, recent studies have indicated that pDCs may provide a way to differentiate these 2 entities. pDCs, initially named natural IFN-producing cells, are a specialized type of dendritic cell with plasma cell morphology that on activation can produce 10–100 times more type 1 IFN, including up to 3–10 pg/cell of IFN-α, when compared with other IFN-producing cells.[21] Type I IFN, through the JAK/STAT pathway, subsequently induces the expression of interferon-stimulated genes, including MxA.[3] Thus, given that pDCs are the main producers of type I IFN in the body[21] and type I IFN induces the transcriptional upregulation of MxA gene expression,[3] MxA has been used as a surrogate or indirect marker of pDC activity.[4]

Plasmacytoid dendritic cells, although typically absent in normal or uninvolved skin,[5] have shown recruitment in response to various stimuli including infectious,[6–8] inflammatory/autoimmune,[3] and neoplastic etiologies.[2,10] Specifically, increased numbers of pDCs and their subsequent type I IFN production have been associated with lichenoid infiltrates, including cutaneous lupus erythematosus (CLE) and lichen planus (LP). An additional study has suggested type I IFN recruitment of effector cells, including CD8-positive T cells, through CXCR3 (a ligand carried in cytotoxic CD8-positive T-cell granules) could act as a mechanism for the chronic inflammation of lichen planus.[22] Similarly, Tomasini et al[23] encountered the lymphoid infiltrate of pityriasis lichenoides to be predominantly composed of CD8-positive cytotoxic T cells (96%) near epidermal keratinocytes. A recent study demonstrating intense and diffuse MxA expression in 80% (n = 4) of their PLEVA cases[16] would further suggest that recruitment of pDCs and subsequent type I IFN recruitment of CD8-positive T cells may have an important role in PLEVA's pathogenesis. By contrast, De Souza et al demonstrated lower numbers of pDCs in LyP when compared with reactive/inflammatory conditions containing CD30-positive cells. Furthermore, the group suggested that in CD30-positive lymphoproliferative disorders, such as LyP, pDCs may be incapable of sensing cancer-related nucleic acids. This dysfunction would in turn lead to a failure in both activation and recruitment of additional pDCs.[17]

In the current study, 100% of our cases demonstrated some degree of BDCA-2 (CD303) immunohistochemical staining, indicating the presence of pDCs. However, only rare dermal cells were present in 26%–28% of the cases of PLEVA (n = 5, 26%) and LyP (n = 4, 28%), whereas most of the remaining cases demonstrating 1%–10% staining of the mononuclear infiltrate. These results were not statistically significant. In contrast, MxA expression, indicative of the presence of activated pDCs producing type I IFN,[3,4,21] as assessed by immunohistochemical staining seemed to show differences between the 2 groups. MxA expression was intense, diffuse, and variably involved the epidermis, dermis, and adnexal structures in 84% of PLEVA cases, whereas demonstrating only weak and patchy positivity in 71% of LyP cases. These results were considered to be statically significant with a P value of <0.007.

Similar MxA staining patterns of the epidermis, adnexal structures, and inflammatory infiltrate have been previously noted in cases of interface dermatitis, including LP[24] and CLE.[25,26] Although uncommonly reported, Vermi et al[26] described, in CLE, that the expression of MxA did not always correlate with pDC density, noting cases with MxA expression and low pDC content. This disconnect between the number of pDCs and MxA expression raises the possibility of either alternative non-pDC sources of type 1 IFN or as is favored in this study, given that an activated pDC can produce 10–100 times more type 1 IFN than other IFN-producing cells,[21] an increase in activated pDCs. The findings in this study also lend support to the idea that activated pDCs are involved in the pathogenesis of PLEVA's lichenoid infiltrate. Specifically, pDCs form type I IFN which then recruits the cytotoxic CD8-positive T cells which, as per Tomasini et al,[23] form most of the lichenoid infiltrate of PLEVA. Our current study results, while adding further credence to the above articles, specifically stress the importance of the identification of activated pDCs (ie, intense MxA expression) in the inflammatory infiltrate as a possible differentiator of PLEVA and LyP.

Overall, this difference in MxA expression (and thus in the activated state of pDCs) between PLEVA (an inflammatory interface skin condition) and LyP (a CD30-positive lymphoproliferative disorder often considered a low-grade variant of cutaneous T-cell lymphoma) is not entirely surprising. Evidence is now clear that although pDCs are active (with type I interferon production) in cutaneous inflammatory conditions (especially those characterized by interface dermatitis[27,28]), these cells are either immature or inactive (even if recruited) in cutaneous malignancies including cutaneous lymphomas.[29,30] The difference in MxA expression (and thus in the activated state of pDCs) also explains how imiquimod (an activator of pDCs[31,32]) and interferon alpha treatment (a counterpart of endogenous type I interferon produced by active pDCs[33,34]) can be effective in treating LyP and other cutaneous lymphomas. Although our sample size is small, it is the largest study to the best of our knowledge on the topic and may prove to be a scaffold for future studies.

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