Plasmacytoid dendritic cells in angiolymphoid hyperplasia with eosinophilia

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Background: Angiolymphoid hyperplasia with eosinophilia (ALHE) is characterized by irregularly-shaped blood vessels with an inflammatory infiltrate. While absent from normal skin, plasmacytoid dendritic cells (pDCs) infiltrate the skin upon injury and during several infectious, inflammatory, and neoplastic entities. In addition to providing anti-viral resistance, pDCs link the innate and adaptive immune responses. In Kimura's disease (KD), pDCs have been reported to occur. Here, we investigate pDCs in ALHE.

Methods: Five ALHE and comparable 4 KD cases were immunohistochemically tested for pDC occurrence and type I IFN production using anti-BDCA-2 and anti- myxovirus protein A (MxA) antibodies, respectively. A semiquantitative scoring system was used.

Results: Plasmacytoid dendritic cells were present in all ALHE and KD cases with no statistically significant differences, while MxA expression was weak and patchy in most ALHE and KD cases.

Conclusions: pDCs are recruited into the lesions of ALHE. Despite the diminished ability to produce type I IFNs, the consistent presence of pDCs in all ALHE cases is in favor of some role of these cells in ALHE pathogenesis.

Keywords: angiolymphoid hyperplasia with eosinophilia, plasmacytoid dendritic cells, Kimura's disease, interferon

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INTRODUCTION

Angiolymphoid hyperplasia with eosinophilia (ALHE), or epithelioid hemangioma, is an uncommon skin disorder characterized by solitary or multiple papules or nodules commonly involving the head, especially auricular area, of white adults in their third decade of life [1-5]. Around 20% of patients may have peripheral blood eosinophilia and regional lymphadenopathy. Recurrences are observed in one third of ALHE patients, while metastasis has never been reported. Microscopically, ALHE exhibits irregularly-shaped blood vessels with an inflammatory infiltrate dominated by lymphocytes and eosinophils (Figure 1). The lymphocytes are mostly T-cells with an occasional admixture of B cells that may form lymphoid follicles [3-5]. The etiology of ALHE is not entirely elucidated, and it is still controversial as to whether ALHE is a benign neoplastic angioproliferative or reactive process associated with trauma [1-6]. Few studies have detected human herpesvirus-8 (HHV-8) in ALHE [6,7]. Others have demonstrated clonality in ALHE, suggesting the possibility of ALHE being a T-cell lymphoproliferative disorder [4]. Another uncertainty is the relationship of ALHE to Kimura's disease (KD), a disorder mainly affecting male Asians with certain clinical and histopathologic features in common with ALHE [1-3].

Plasmacytoid dendritic cells (pDC) belong to

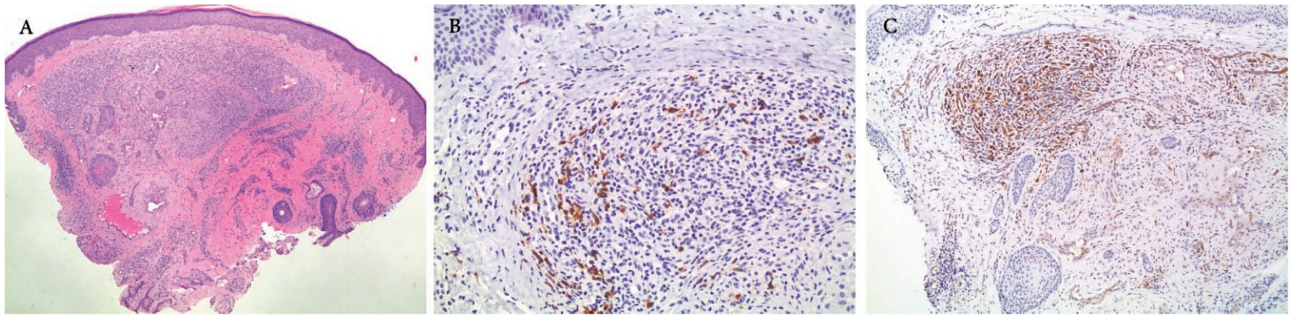

Figure 1. ALHE: A. Representative case (Hematoxylin-eosin stain; original magnification: ×40). B. BDCA-2 immunostaining highlighted numerous pDCs in a perivascular distribution (×100). C. Patchy MxA immunostaining of epithelium and inflammatory cells (×100).

a population of specialized dendritic cells that morphologically resemble plasma cells and express CD4, CD123, HLA-DR, blood-derived dendritic cell antigen-2 (BDCA-2), and Toll-like receptors (TLR)7 and TLR9 within endosomal compartments [8,9]. In addition to contributing to the host response against viral infections, pDCs link the innate and adaptive immune responses by controlling the function of myeloid DCs, lymphocytes, and natural killer cells [8,9]. This is mediated by different type I IFNs released upon pDCs activation and the production of other pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL6). While usually absent in normal skin, they appear to participate in wound healing as well as the pathogenesis of several cutaneous infectious (especially viral infections such as herpetic and poxvirus infections, etc), inflammatory/autoimmune (such as lupus erythematosus), and neoplastic (such as lymphomas) processes [8]. Rarely have pDCs been demonstrated in KD lesions [10,11]; however, there has been no previous attempt at investigating pDCs role in ALHE, hence the objective of the present study.

MATERIALS AND METHODS

The study was approved by the institutional review board of the American University of Beirut Medical Center. Archival materials with a diagnosis of ALHE and KD were retrieved from the dermatopathology database at the dermatology department at the American University of Beirut-Medical Center. A total of 5 ALHE and 4 KD cases met the inclusion criteria. The histologic sections of all cases were re-reviewed and the diagnoses were confirmed by the dermatopathologist. Only straightforward cases that fit the clinicopathological features of ALHE and KD were selected for the study. Cases with uncertain diagnosis were excluded. Clinical information was extracted and all patient data were deidentified.

Immunohistochemical staining

Immunohistochemical analysis was performed on 5-mm thick sections obtained from formalin-fixed, paraffin-embedded tissues. Following de-paraffinization and rehydration steps, antigen retrieval was performed using citrate buffer and steamer. Slides were treated with 3% hydrogen peroxide in methanol for 10 min to block the endogenous peroxidase. Samples were then incubated with appropriate blocking serum. Antibodies (Ab) to BDCA-2 (Mouse IgG1, Clone 124B3.13, Dilution 1:50, Dendritics, Lyon, France, EU) were used to localize pDCs and anti-human myxovirus protein A (MxA) monoclonal antibody (M143, University of Freiburg, Freiburg, Germany; dilution 1:100; Professor Otto Haller) to detect locally-induced type 1 IFN signature. Scoring of pDC content was done on formalin fixed paraffin-embedded tissue sections stained for BDCA2 and reported as percentage of the total mononuclear infiltrate: 0 (very rare positive cells), 1 (1–10% of positive cells), 2 (10–50% of positive cells), 3 (> 50% of positive cells). The MxA staining was scored as: 0 = negative, 1 = weak/patchy staining, and 2 = intense staining. Normal skin tissue served as negative control, while lupus erythematosus served as positive control [8].

Statistical analysis

Statistical analysis was performed through the use of Mann-Whitney test to analyze statistical

differences in pDC and MxA scores between ALHE and KD. A two-tailed P-value of < 0.05 was considered as statistically significant.

RESULTS

Patients (4 women and 1 man) with ALHE fell in the age range of 26 to 53 years (mean of 34 years), while those with KD ranged in age from 36 to 65 years (mean of 49 years). All 5 ALHE cases were located on the head in a periauricular distribution, while KD cases occurred on the trunk, neck and upper extremity in 2 (50%), 1 (25%), and 1 (25%) cases, respectively.

Plasmacytoid dendritic cells in ALHE and KD

This was assessed using antibodies against BDCA-2, which is a specific pDC marker expressed on pDC surface [8,9]. These cells were identified as medium-sized round cells and were present as scattered cells and as small clusters in all 5 ALHE (Figure 1) and 4 KD (Figure 2) cases admixed with the inflammatory infiltrate (Table 1). There was no statistically significant difference in pDC infiltration between cases of ALHE and KD with comparable pDC scores.

Expression of MxA

Myxovirus protein A (MxA), a protein induced by type 1 IFNs, is a surrogate marker of local tissue type 1 IFN production [8]. Thus, MxA expression represents an indirect assessment of pDC activity given that pDCs are the major sources and most potent producers of type I IFNs. Comparing MxA expression in ALHE and KD (Table 1), it turned out to be comparable with patchy and weak staining

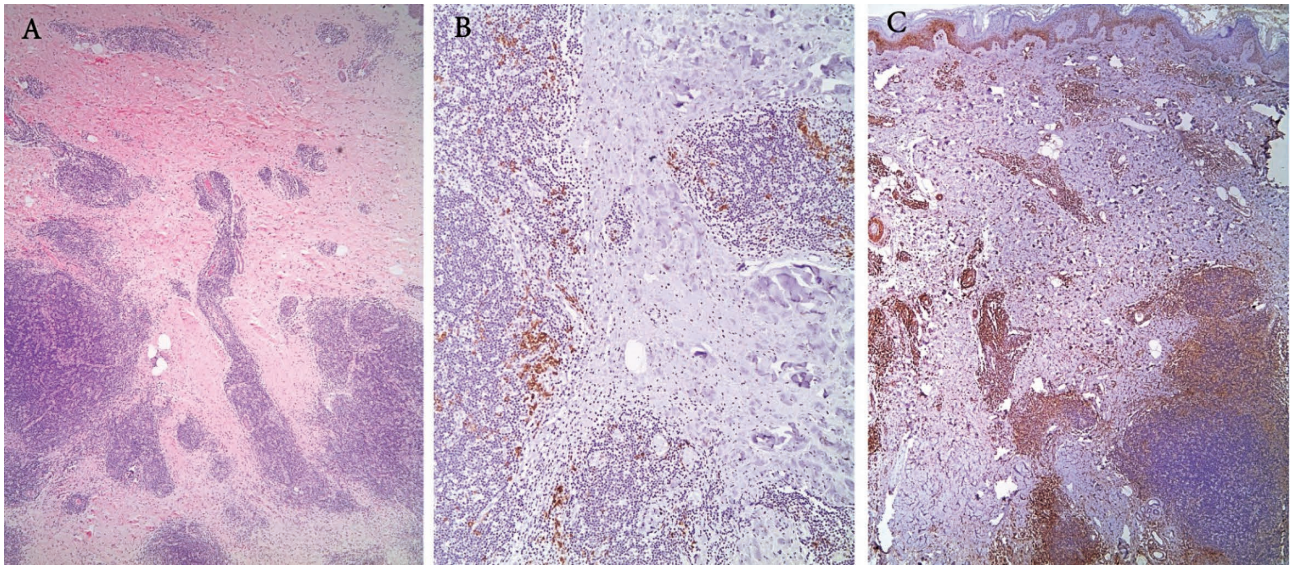

Figure 2. Kimura's disease: A. Representative case (Hematoxylin-eosin stain; original magnification: ×40). B. BDCA-2 immunostaining highlighted numerous pDCs within the inflammatory infiltrate (×100). C. Patchy MxA immunostaining of epithelium and inflammatory cells (×100).

Table1. pDC presence and MxA expression in ALHE and KD (%)

Entity (cases)	Age (yrs)	Gender	pDC infiltration	pDC score*				MxA score#		
				0	1	2	3	0	1	2
ALHE (5)	26 to 53	4F, 1M	5	0	0	5	0	0	4	1
KD (4)	36 to 65	4F	4	0	0	4	0	0	4	0
P value^			1	>0.05				>0.05		

Angiolymphoid hyperplasia with eosinophilia (ALHE), Kimura's disease (KD), myxovirus protein A (MxA); plasmacytoid dendritic cell (pDC)
* $BDCA2^+$ pDC content was scored as percentage of the 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 = weak/patchy, and 2 = intense.
^ Statistical analysis was performed via Mann-Whitney test to analyze the statistical differences in pDC and MxA scores between the two entities. A two-tailed P-value of < 0.05 is considered as statistically significant.

in most cases of ALHE (80%) and all cases of KD (Figures 1, 2).

DISCUSSION

In addition to the histopathological hallmark of blood vessels with plump epithelioid endothelial cells, ALHE is characterized by an associated mixture of inflammatory cells including lymphocytes (mostly T-cells with CD4 more than CD8 cells and small B-cell clusters), eosinophils, plasma cells, and histiocytes [3-5]. To the best of our knowledge, the presence of pDCs in ALHE has not been reported yet. Our hypothesis concerning the role of PDCs in ALHE was based on several observations. First, ALHE has been reported to occur at sites of trauma or injury, and pDCs are known to be recruited in the areas of skin injury [4,8,12]. This is comparable to other settings where skin injury leads to pDC recruitment, such as in wound healing or in Koebner phenomenon in psoriasis [12,13]. In the latter 2 settings, the release of self-nucleic acids may trigger pDC recruitment, which in turn serves as a critical step for the induction of early inflammatory responses and re-epithelization of injured skin. This immune recognition of released nucleic acids is facilitated by cathelicidin peptides, which are rapidly induced in skin wounds entailing the delivery of these nucleic acids to intracellular TLR compartments within pDCs [12,13]. Second, pDCs are involved in anti-viral resistance and ALHE has occasionally been reported to harbor HHV-8 virus or occur in association with systemic viral infections such as hepatitis C and HIV [6,8,14,15]. Actually, both RNA and DNA viruses are able to recruit and activate pDCs through their interaction with TLR-7 and TLR-9, respectively [9]. Third, imiquimod, an immunomodulator known to be a potent PDC activator through its effect on TLR-7 [16], has previously proved effective in several ALHE cases [17-19]. Finally, pDCs have rarely been demonstrated in KD, which some believe may be related to ALHE, especially that they can co-exist [20,21]. Based on morphological features alone, Chan et al. reported pDCs in 8 of 40 KD cases [10]. Recently, Dargent et al. demonstrated numerous pDCs in a KD case, which along with the presence of an inflammatory infiltrate rich in eosinophils and numerous CD1a-positive DCs¸ led them to suggest skin-based antigenic challenge as a conducive factor to KD pathogenesis [11].

Our study confirmed our hypothesis. Plasmacytoid DCs were present consistently in all ALHE and KD cases as scattered cells and small clusters admixed with other inflammatory cells. As indirectly assessed by MxA staining which was weak and patchy in most cases, type I IFN production was diminished in both ALHE and KD cases. Interestingly, evidence suggests that pDCs may signal through two different mechanisms based on various types of stimulants they may be exposed to (such as different types of CpG-containing oligodeoxynucleotides) [17]. One of the signaling pathways predominantly leads to type I IFN production, while the other mainly results in the production of pro-inflammatory cytokines IL-6 and TNF with small amounts of type I IFN, upregulation of CD80 and CD86, and maturation of pDCs with expression of MHC class II [9]. This then favors more antigen presentation, leading to the induction of B-cell proliferation and antibody production. Accordingly, it is hypothesized that Plasmacytoid DCs probably contribute to ALHE or KD through the second pathway, especially that the observed inflammatory pattern (composition and lymphoid follicle formation) is reminiscent of pDC role already documented in primary cutaneous marginal zone B-cell lymphoma (PCMZL) and cutaneous B-cell pseudolymphomas (B-PSL) [22]. Kutzner et al. reported clusters of pDCs in close proximity to T-cells and plasma cells in 23 of 23 (100%) PCMZL cases and 14 of 22 (64%) B-PSL cases, based on which they proposed that both entities belong to two ends of the same spectrum that is potentially antigen-driven [22]. Could similar mechanisms underlie ALHE and KD? This remains to be elucidated in future studies.

In summary, we have shown that pDCs are recruited into the skin lesions of ALHE and KD. Despite the diminished ability to produce type I IFNs demonstrated in our study, the consistent presence of pDCs in all ALHE and KD cases corroborate the significant role of these cells in their pathogenesis. Future studies are to focus on uncovering the exact mechanisms of pDC involvement in ALHE, which may have important therapeutic implications.

Conflict of Interest: None declared.

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