Involvement of Plasmacytoid Dendritic Cells in the Immunological Response Against Orf Infection

Plasmacytoid dendritic cells (PDCs) are specialized dendritic cells with a significant role in antiviral resistance.1,2 Plasmacytoid dendritic cells have never been studied in orf infection.

Methods | Our institutional review board approved the study. Archival materials with a diagnosis of orf infection and inflamed molluscum contagiosum (I-MC) were retrieved from our dermatopathology database. A total of 5 orf and 5 comparable I-MC cases fit the inclusion criteria. As described before,2 immunohistochemical analysis was performed on sections obtained from formalin-fixed, paraffin-embedded tissue using antibodies to BDCA-2 (mouse IgG1, clone 124B3.13, dilution 1:50; Dendritics) and myxovirus protein A (MxA) (M143, University of Freiburg, Germany; dilution 1:100).1,2 Although anti-BDCA-2 antibody is a specific PDC marker, anti-MxA antibody indirectly assesses PDC activity because MxA is an interferon (IFN)-α/β-inducible intracellular protein well established as a surrogate marker for local type I IFN production.1,2 We used a semiquantitative scoring system to assess PDC recruitment and MxA staining (Table).

Results | Demographic data and results are summarized in the Table. Although PDCs were present in all orf (Figure) and I-MC cases, they were significantly less abundant in orf cases. Although the difference was not significant, orf cases tended to have less type I IFN production than I-MC cases.

Discussion | Plasmacytoid dendritic cells exhibit plasma cell morphologic characteristics and express CD4, CD123, BDCA-2, and toll-like receptors 7 (TLR-7) and TLR-9 in endosomal compartments.1 They are capable of producing large quantities of type I IFNs against pathogenic agents.1 They not only provide antiviral resistance but also link innate and adaptive immunity by controlling function of myeloid dendritic cells, lymphocytes, and natural killer cells. In the skin, PDCs are involved in several infections (mainly viral), inflammatory processes (such as lupus and psoriasis), and malignant neoplasms.1,2 A parapox virus that infects sheep, orf can be transmitted to humans by direct inoculation and typically presents as a solitary lesion that progresses through several stages, including macular/popular, vesicular, nodular with weeping, papillomatous or verrucous, and finally dry crust. Healing occurs in 4 to 8 weeks.3,4 Characteristic histological features include parakeratotic crust, acanthosis, intraepidermal vesiculation, increased dermal vascularity, cytoplasmic and nuclear vacuolation, and dense mixed infiltrate composed of lymphocytes, histiocytes, neutrophils, and eosinophils.3,4 Despite its recently highlighted role against many cutaneous viral infections, such as I-MC and herpes,1,2 PDCs have never been studied in orf cases.

Albeit small, this study is the first to demonstrate the presence of PDCs in orf infection. This finding is probably mediated by the interaction of the parapox DNA virus with TLR-9, which usually recognizes DNA viruses. We confirmed previous findings that I-MC lesions are highly immunogenic with an ongoing PDC-mediated regression process.2 Similarly, PDCs were shown in our study to be part of the host response against orf infection, although significantly less abundant and tending to be less active (activity indirectly assessed by MxA expression because PDCs are the most potent producers of local type I IFN, secreting up to 1000 times more IFN-α/β than other cells) than in I-MC lesions.1,2 One explanation of this finding could be related to the early age of orf lesions studied (1-2 weeks in 4 cases), which is a limitation of our study, because PDC concentration and activity may differ at different stages of the infection. Early on, the orf virus releases immunomodulatory proteins, such as ovine IFN resistance protein and vascular endothelial growth factor E (inhibits development and functional dendritic cell maturation), that suppress the host’s immune reaction. This suppression allows the virus to replicate

Table. PDC and MxA Scores in Orf and I-MC

<table>
<thead>
<tr>
<th>Entity</th>
<th>Sex, No. M/F</th>
<th>Age, y</th>
<th>Duration, wk</th>
<th>Frequency of PDC Infiltration, %</th>
<th>BDCA-2* PDCa</th>
<th>MxAa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orf</td>
<td>5/0</td>
<td>40-50</td>
<td>1-5</td>
<td>5</td>
<td>0 3 2 0 0</td>
<td>0 1 2</td>
</tr>
<tr>
<td>I-MC</td>
<td>4/1</td>
<td>9-57</td>
<td>4-28</td>
<td>5</td>
<td>0 0 0 5 0</td>
<td>0 5</td>
</tr>
</tbody>
</table>

Abbreviations: I-MC, inflamed molluscum contagiosum; MxA, myxovirus protein A; NA, not available; PDC, plasmacytoid dendritic cells.

Statistical analysis was performed to compare PDC and MxA scores between orf and I-MC using the Mann-Whitney test with a 2-tailed P < .05 considered statistically significant.
for some period before the host can mount an effective immune response. This finding is further supported by the reported effectiveness of imiquimod, an immunomodulator known to be a potent PDC activator through its effect on TLR-7, in clearing orf.5-6

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Author Contributions: Dr Abbas had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Data acquisition, analysis, or interpretation of data: All authors.

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Study supervision: Abbas.

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OBSERVATIONS

Granuloma Inframammary Adultorum

Granuloma inframammary adultorum represents a variant of erosive papulonodular dermatosis (EPND) with predominant clinical components of papules and nodules. We describe herein a patient who presented with worsening skin lesions.

Report of a Case | A woman in her 60s with a history of inverse psoriasis presented with 2 months of “draining sores” under her breasts. Prior to the development of the sores, she had experienced a progressive burning sensation and tenderness in the affected areas and had been self-treating the inframammary skin with betamethasone valerate, 0.1%, ointment. Physical examination revealed foul-smelling, well-demarcated, erythematous, macerated plaques with multiple eroded reddish-purple papules and nodules beneath her pendulous breasts extend-