Verruciform Xanthoma and Lichen Sclerosus—A Common Presentation of Lymphedema

Verruciform xanthomas (VX) are a common cutaneous lesion characterized by yellow, waxy papules, often located on the extremities. The pathogenesis of VX has been largely attributed to the role of human papillomavirus (HPV) infection and the immune response to latent HPV within the skin. However, the role of lymphatic abnormalities in the development of VX has not been as extensively studied.

Lymphatic Drainage and Skin Pathology

Lymphatic vessels play a crucial role in the normal functioning of the skin. They help in the removal of macromolecules, waste products, and immune cells. In the context of VX, lymphatic abnormalities such as lymphangiectases have been observed in association with VX lesions. These findings suggest that lymphatic abnormalities may be involved in the pathogenesis of VX.

The Role of Inflammation

Inflammation plays a significant role in the development of VX and other skin lesions. The inflammatory response can lead to fibrosis and scarring, which are common features of VX. The presence of immune cells, such as macrophages, is also a significant feature of VX, as they are involved in the clearance of lipid-rich debris derived from overlying damaged and/or proliferating keratinocytes and accumulate in the papillary dermis because of poor lymphatic drainage.

Methods

Over a 3-month period in 2011, all diagnosed cases of LS in the Department of Pathology at Albany Medical College were retrieved. Formalin-fixed paraffin-embedded sections were immunostained with antibodies to D2-40, a lymphatic specific marker, and CD68, a macrophage marker. The lymphatic density was measured by counting the number of D2-40 expressing vessels per millimeter squared. Lymphatic vessels were categorized as dilated or collapsed; the maximal dilation of the former was measured (methods previously described). In addition, the presence or absence of D2-40 expression by the basal layer of the epidermis and aggregates of CD68-positive cells at the DEJ were recorded.

Results

The Table lists the overall results of this study, revealing that LS specimens exhibited significantly more dilated lymphatics and greater dilation of lymphatic vessels than did controls. In addition, dilated lymphatics significantly outnumbered collapsed vessels in LS samples, whereas collapsed lymphatics significantly outnumbered dilated vessels in controls (P ≤ .03). Notably, collapsed lymphatic vessels were seen within the sclerotic zone, often in areas of inflammation, but lymphangiectases were found throughout the zone of sclerosis, mostly in its deep aspect, which also contained dilated blood vessels. The D2-40 expression of basal keratinocytes was frequent in LS, a phenomenon that has been described in localized lymphedema. Conspicuously, CD68+ macrophages could be found forming small aggregates at the DEJ in more than half of LS cases (Figure).

Comment

Lichen sclerosus has been likened to an “inflammatory scar.” Therefore, it is not surprising to find that the hallmark feature of LS, its sclerosis, which progressively replaces the upper dermis over time, disrupts lymphatic drainage by effacing the normal dermal architecture, leading to signs of lymphostasis—numerous dilated lymphatic vessels. Scarring and lymphangiectases are ubiquitous features underlying warts and are suspected pathogenic factors.

While only a few reports of VX have documented HPV infection, the low frequency of detection has been attributed to the sensitivity and specificity of the methods used to detect and identify HPV. The presence of HPV in the skin may play a role in the development of VX, possibly through the stimulation of an immune response leading to the formation of warts. Additionally, macrophages may ingest lipid-rich debris derived from overlying damaged and/or proliferating keratinocytes and accumulate in the papillary dermis because of poor lymphatic drainage. This phenomenon is consistent with the histological features of VX, which include the presence of CD68+ macrophages and the accumulation of lipid-rich debris derived from overlying damaged and/or proliferating keratinocytes.

The presence of CD68+ macrophages in VX lesions is consistent with the role of macrophages in the immune response to latent HPV infection. Macrophages are known to play a role in the clearance of debris and the resolution of inflammation, and their presence in VX lesions suggests a possible role in the resolution of HPV infection.

In conclusion, VX and LS share many features, including lymphatic abnormalities, inflammation, and the presence of macrophages, which suggests a common pathogenic mechanism. Further studies are needed to elucidate the role of HPV in the development of VX and to better understand the mechanisms underlying the development of lymphedema in LS.
where low copy number of β-HPV and genital-mucosal HPV have been presumptively missed. Indeed, LS has been reported to harbor a high frequency of HPV genotypes. Thus, LS displays all the etiologic elements necessary for the formation of VX—lymphostasis and latent HPV infection. We agree with Fite et al that the identification of VX requires a search for a primary disorder that produces a milieu of latent or clinically evident lymphedema—an essential factor in the pathogenesis of VX.

### Table. Increased Numbers of and Greater Dilation of Lymphatic Vessels Evidence of Lymphedema in Lichen Sclerosus

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Patient Age, y</th>
<th>Sex, F/M, No.</th>
<th>Site</th>
<th>Total LVs, No./mm²</th>
<th>Collapsed LVs/mm²</th>
<th>Dilated LVs/mm²</th>
<th>Maximum Dilation, mm²</th>
<th>CD68⁺ at DEJ, %</th>
<th>D2-40⁺, BK, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichen sclerosis</td>
<td>61 (16) (24-84)</td>
<td>16/2</td>
<td>Genital, 4 trunk</td>
<td>8.2 (4.4) (2.0-19.0)</td>
<td>2.7 (1.4) (0-6.0)</td>
<td>5.5 (3.3) (0.7-13)</td>
<td>0.05 (0.02) (0.03-0.12)</td>
<td>56</td>
<td>61</td>
</tr>
<tr>
<td>Normal skin</td>
<td>56 (22) (17-86)</td>
<td>5/4</td>
<td>Genital, 5 trunk</td>
<td>6.6 (5.6) (2.2-18.5)</td>
<td>3.8 (2.4) (1.0-8.5)</td>
<td>2.7 (3.3) (0-10.0)</td>
<td>0.03 (0.01) (0-0.05)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: BK, basal keratinocytes; DEJ, dermoepidermal junction; LVs, lymphatic vessels.

a Unless otherwise noted, data are reported as mean (SD) (range) values.
b D2-40⁺-expressing vessels counted.
c Clusters of CD68⁺ macrophages at the DEJ.
d Boldface type indicates significant difference, P < .05.

**Figure.** Immunohistopathologic specimens. A and B, An advanced lesion of stereotypical lichen sclerosus exhibits a vertically oriented, dilated lymphatic vessel with irregular valves in the deepest region of the sclerosis (hematoxylin-eosin, original magnifications ×40 [A] and ×100 [B]). C, Staining with D2-40 antibodies shows expression by epidermal basal keratinocytes (single yellow arrow), and dilated lymphatics with the deep aspect of the sclerosis are evident (double-headed yellow arrow); a non-D2-40⁺-dilated vessel (vein) is found in the mid dermis (black arrow), signifying concomitant disruption of blood flow in addition to lymphatic drainage (note that a small dilated lymphatic is found adjacent to the dilated vein) (original magnification ×40). D, Staining with CD68 antibodies labels a cluster of macrophages at the dermoepidermal junction overlying the sclerosis—the putative site of lipophage accumulation in verruciform xanthoma (original magnification ×400). E, Staining with D2-40 antibodies reveals collapsed lymphatic vessels in a region of inflammation underlying the dermal sclerosis (yellow asterisk) (original magnification ×100).

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In reply

We appreciate the interest of Carlson et al in our article on verrucal VX1 as well as their comment about the possible etiologic roles of lymphostasis and HPV. Our 10 verrucal VX cases were all associated with another vulvar condition, mainly LS but also lichen planus (2 cases), vulvar radiodermatitis (1 case), and Paget disease (1 case). Our findings sustain the hypothesis of Zegarelli et al2 that damage to the epithelium—particularly of the DEJ, in our opinion, could trigger the following cascade: (1) entrapment of epithelial cells in the papillary dermis; (2) subsequent degeneration of these cells and lipid formation; (3) engulfment of released lipids by macrophages; and (4) accumulation of foam cells between the rete ridges.

Carlson et al object that this hypothesis does not explain why macrophages accumulate in the papillary dermis. We think that the superficial location of the xanthomatous cells can be explained by the fact that the papillary dermis is the part of the dermis, which is the closest of the damaged epidermis. The poor lymphatic drainage reported by Carlson et al in 14 genital and 4 trunk LS cases could account for the accumulation of macrophages in the papillary dermis. However, to confirm this hypothesis one should demonstrate the following: (1) that all the other conditions associated with mucosal or cutaneous VX are associated with lymphostasis (eg, Paget disease, lichen planus, graft-vs-host disease, discoid lupus erythematosus, pemphigus vulgaris, recessive dystrophic epidermolysis bullosa, lichen planus, epidermal nevus); (2) that lymphostasis is not just an incidental finding related to inflammation, whatever its cause. In addition, if an increased number and dilation of lymphatic vessels is present in most LS cases, these abnormalities cannot alone explain alone the occurrence of VX with LS. Indeed, VX only exceptionally occurs concomitantly with LS.

The second hypothesis advanced by Carlson et al is that the verrucous epidermal hyperplasia that is a hallmark of VX could be related to an HPV infection. This HPV infection may have been facilitated by the lymphostasis, the source of the disrupted immune-cell trafficking and consequently of localized immunosuppression. This interesting assumption is not corroborated either by the pathologic features of VX or by the available virologic data. Indeed, we found that the verrucous hyperplasia of VX had specific, almost pathognomonic, histologic features that differ from those of HPV infections: wedge-shaped parakeratosis forming deep invaginations into the anacanthotic epithelium and exhibiting a characteristic orange hue under hematoxylin-eosin stain; and neutrophilic infiltrate at the junction between the superficial parakeratotic layers and the underlying stratum spinulosum. In addition, neither họceres nor atypia were observed.

In our retrospective study, no HPV search was performed. However, the data collected from the literature are mainly negative, even though very sensitive methods were used.1 A few cases with a positive HPV search have been reported,4 but these findings could have been incidental: HPV may be present on normal vulvar or oral mucosa in as many as 23.3% of the cases.5

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1. Fite C, Plantier F, Dupin N, Avril MF, Moyal-Barracco M. Vulvar verruciform xanthoma: ten cases associated with lichen sclerosus, lichen planus, or other conditions. Arch Dermatol. 2011;147(9):1087-1092.

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