Lichen Sclerosus Exhibiting Histologic Signs of Lymphedema: An Essential Factor in the Pathogenesis of Verruciform Xanthoma

Recently, Fite et al1 reported a series of vulvar verruciform xanthomas (VX) and attributed VX pathogenesis to disorders that injure the dermo-epidermal junction (DEJ), namely lichen sclerosus (LS). While we agree that damage to the DEJ is the source of debris found in the xanthomatous macrophages of VX, the LS theory does not explain the accumulation of lipophages in the papillary dermis or the superimposition of verrucous epidermal hyperplasia—the 2 pathognomonic features of VX.

Our research group2 has recently reported evidence that VX is a complication of localized lymphedema, which has many causes, including trauma, surgery, radiation therapy, neoplasia, infection, and inflammatory dermatoses.3 Specifically, scarring due to trauma, repeated irritation, and/or chronic inflammation can obstruct lymphatics and lead to lymphostasis, histologically denoted by lymphangiectases. Regional lymphostasis, because of disrupted immune cell trafficking, creates a localized area of immunosuppression permitting latent human papillomavirus (HPV) infection to manifest as warts.4 Macrophages ingest lipid-rich debris derived from overlying damaged and/or proliferating keratinocytes and accumulate in the papillary dermis because of poor lymphatic drainage. In corollary, increased lymphatic flow leads to regression of VX.2 Based on this mechanistic framework, we sought to determine if histologic evidence of lymphedema existed in LS that would explain the relative frequent occurrence of VX in vulvar LS, 60% in the series reported by Fite et al.1

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 (Dako; 1:200) and CD68, a macrophage marker (Ventana Medical Systems; prediluted), using an automated method (Ventana Medical Systems). Normal skin from elliptical excisions of benign and malignant skin tumors was used for controls (cases previously reported4). 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 described5). 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. STATA software, version 11.2 (StataCorp LP), was used for statistical analysis, with significance set at P < .05. The institutional review board of Albany Medical College approved this study.

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 underlying 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.3 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.3 While only a few reports of VX have documented HPV infection,1 the low frequency of detection has been attributed to the sensitivity and specificity of the methods used...
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 al1 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 sclerosus</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>

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Author Affiliations: Divisions of Dermatopathology and Dermatology, Department of Pathology, Albany Medical College, Albany, New York (Dr Carlson and Mr Dias Carlson); and Department of Dermatology, University of Connecticut Medical Center, Farmington (Dr Murphy). Dr Rohwedder is the owner of Bio-Med-Molec Service, a private company in Kalkar, Germany.

Correspondence: Dr Carlson, Albany Medical College, 47 New Scotland Ave, MC-81, Albany, NY 12208 (CarlsoA@mail.amc.edu).

Author Contributions: Study concept and design: J. A. Carlson and Rohwedder. Acquisition of data: G. D. Dias Carlson.

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We appreciate the interest of Carlson et al in our article on verrucous xanthoma. As well as their comment about the possible etiologic roles of lymphostasis and HPV. Our 10 verrucous xanthoma cases were all associated with another verrucous condition, mainly lichen planus or HPV, with lupus radiodermatitis (1 case), and Paget disease (1 case). Our findings sustain the hypothesis of Zegarelli et al.2 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 (e.g., Paget disease, lichen planus, graft-versus-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 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 acanthotic 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 holocytes 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

Charlotte Fite, MD
Françoise Plantier, MD
Micheline Moyal-Barracco, MD

Author Affiliations: Departments of Dermatology (Drs Fite and Moyal-Barracco) and Pathology (Dr Plantier), Assistance Publique des Hôpitaux de Paris (APHP), Hôpital Cochin, Paris Descartes University, Paris, France.

Correspondence: Dr Fite, APHP, Department of Dermatology, 27 rue du Faubourg Saint-Jacques, Paris, 75014 France (Charlotte.fite@noos.fr).

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.

Efficacy and Safety of Apremilast in Chronic Cutaneous Sarcoidosis

Pentoxifylline, a phosphodiesterase type 4 inhibitor, is reported to be effective for the treatment of sarcoidosis.1 However, the adverse events associated with this drug have limited its general use. Apremilast is a new phosphodiesterase type 4 inhibitor that blocks the synthesis of proinflammatory cytokines and chemokines, such as tumor necrosis factor, interferon γ, and the interleukins...