A patient with lichen sclerosus, Langerhans cell histiocytosis, and invasive squamous cell carcinoma of the vulva

Michiel Simons, MD; Hedwig P. Van De Nieuwenhof, MD; Irene A.M. Van Der Avoort, MD; Johan Bulten, MD, PhD; Joanne A. De Hullu, MD, PhD

Langerhans cell histiocytosis (LCH), previously named histiocytosis X, is a disorder hallmarked by a clonal proliferation of Langerhans cells (LCs). These cells are bone marrow-derived, antigen-presenting cells, which differ from other histiocytes in being CD1a- and S-100-positive on immunohistochemical staining.1,2 This uncontrolled proliferation may affect many sites of the human body and may cause destruction of the involved tissues. Sites commonly involved include bone, skin, lung, and brain tissue. Disease presentation may vary from mild activity in 1 organ, to extensive systemic involvement with life-threatening consequences.3 The disorder was first described more than a century ago, but the cause still remains largely obscure.

LCH restricted to the vulvar area is a rare phenomenon. To our knowledge, only 12 cases are described in the current literature.4-14 We describe a new and unique case of vulvar LCH, preceded by lichen sclerosus (LS) and followed by the development of an invasive squamous cell carcinoma (SCC) of the vulva in a 33-year-old patient. Even though development of vulvar SCC is connected with LS, this case gives rise to the question of whether LCH possibly has contributed...
to the tumor development or progression in this young patient.

**Case Report**

A 33-year-old woman was referred to our tertiary vulvar clinic with painful, pruritic, and irritating lesions of the vulvar area existing more than 2 years, causing mild dyspareunia. Prior treatment with ultrapotent corticosteroids was ineffective. On physical examination, the right labium showed a 4-cm papillomatous tumor and the left labium showed multiple sharply limited hypertrophic spots, in the absence of regional lymphadenopathy.

The lesions were biopsied, and histology showed LS without dysplasia. Because ultrapotent corticosteroid treatment was ineffective, a skinning local excision was carried out, and histology showed a differentiated vulvar intraepithelial neoplasia (dVIN) lesion without invasive growth in addition to LS.

At follow-up, initially, there were no signs of vulvar recurrences, but 1 year later, the patient noticed a new verrucous lesion (1.5 cm large and 3 mm thick), which was situated on the right labium minus with a verrucous aspect (Figure 1). The tumor grew slowly despite local immunosuppressive treatment with tacrolimus and hence it was decided to excise the lesion within one month. At the time of the procedure, the tumor had outgrown excisable size and extended from the right labium minus to the clitoris. Again, biopsies were taken and histology showed a tumorous monotonous proliferation of atypical cells, with cerebriform or grooved nuclei and abundant mitotic activity (Figure 2, A). Eosinophils were scattered throughout the proliferating cells. Immunohistochemistry was performed and showed that the monotonous cells were positive for CD1a (Figure 2, B), vimentin, and S-100 (Figure 2, C), all pointing to a diagnosis of LCH.

The patient was subjected to extensive metastatic workup to exclude systemic localizations of LCH, including computed tomography of the brain, the thorax, and abdomen, chest x-rays, bone marrow aspirate, and bone scintigraphy. This revealed no evidence of disease. Regarding the solitary vulvar lesion and patient’s age, the patient was treated locally with CO2 laser vaporization, after which the lesion completely disappeared. The appearance of the vulva remained with signs of LS, showing white and papillomatous tissue.

During the follow-up period, 23 months after the diagnosis LCH was made, the patient had a suspicious lesion develop on the left labium minus (Figure 3, A), which was biopsied. Histology showed a poorly differentiated SCC with a depth of invasion of 1.6 mm. A dVIN lesion was found adjacent to the tumor. Additional imaging revealed no signs of metastatic disease. A wide local excision with sentinel node procedure was performed. Definitive pathology showed a 9-mm diameter SCC with a depth of invasion of 4 mm without the presence of LCH (International Federation of Gyne-

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**Figure 2**

**LC staining**

A. Hematoxylin-eosin staining (×200) showing a monotonous proliferation of LCs with sharp cell margins and slightly atypical cerebriform or grooved nuclei. B, LCs, staining positive for CD1a on immunohistochemical staining (×200). C, LCs, staining positive for S-100 on immunohistochemical staining (×200).

LC, Langerhans cell.

**Figure 3**

**Lesions on labium**

A. Vulvar SCC on the left labium minus, 9 mm diameter and with a depth of invasion of 4 mm. B, Lesion on the right labium minus, which turned out to be dVIN on histologic examination.

dVIN, differentiated vulvar intraepithelial neoplasia; SCC, squamous cell carcinoma.

cology and Obstetrics stage IB). There were no signs of metastatic disease or LCH in the sentinel nodes.

The patient was regularly seen in our clinic for follow-up of her vulvar SCC. Verrucous lesions that histologically turned out to be a dVIN frequently developed (Figure 3, B). The patient refused additional surgery to prevent future recurrence of a vulvar SCC and preferred occasional CO₂ laser vaporization treatments. In the following 11 months, the patient had a local recurrence develop on the clitoris and 2 metastatic groin nodes (bilateral). She was treated with surgery and radiotherapy.

**Comment**

In our case, the patient presented with LS of the vulva, followed by LCH. Eventually, she developed a vulvar SCC. LCH of the genital tract is rare, and lesions isolated to the vulva are seldom described in the current literature (Table). Apart from this being a new rare case of isolated vulvar LCH, the question emerges whether LCH could have played a role in tumor development of our young patient. The possible association between LCH and malignant neoplasms had been recognized many years ago. Cases in which LCH preceded both solid and hematologic malignancies have been described, although it remains unclear whether there was a causal relation or it was the consequence of LCH treatment. LCH is a clinical entity mainly occurring in children and the cause of this disease is still a matter of debate. It has been recognized as a clonal proliferation of bone marrow-derived LCs, but it still remains unclear what is the initiator of this process. The diagnosis of LCH is dependent on immunohistopathologic characteristics. The presence of Birbeck granules on electron microscopy or positive staining for CD1a and S-100 antigens

### TABLE
Other cases of LCH solely restricted to the vulvar area

<table>
<thead>
<tr>
<th>Case reference</th>
<th>Age of onset, y</th>
<th>Primary morphological presentation</th>
<th>Treatment</th>
<th>Response</th>
<th>Outcome, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axiotis et al⁴</td>
<td>85</td>
<td>Vulvar ulcer</td>
<td>Topical corticosteroids</td>
<td>PR</td>
<td>LR (48)</td>
</tr>
<tr>
<td>Dietrich et al⁶</td>
<td>29</td>
<td>ns</td>
<td>Vulvar radiation and oral prednisone; topical corticosteroids; local excision; radiation and radical vulvar excision</td>
<td>PR; CR; CR; CR; LR (24); LR (12); LR (24); LR (4)</td>
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<tr>
<td>Ishigaki et al⁶</td>
<td>65</td>
<td>Vulvar and perineal ulcers</td>
<td>Local excision</td>
<td>CR</td>
<td>NED (12)</td>
</tr>
<tr>
<td>Meehan and Smoller⁷</td>
<td>76</td>
<td>Grouped papules and erosions</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>Umbilicated papules</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Mottl et al⁸</td>
<td>16.5</td>
<td>Erythematous plaques with induration</td>
<td>Chemotherapy; chemotherapy</td>
<td>CR; CR</td>
<td>LR (9); NED (18)</td>
</tr>
<tr>
<td>Padula et al⁹</td>
<td>31</td>
<td>Nodular vulvar ulcer</td>
<td>Local radiation; local radiation; radical vulvectomy; thalidomide</td>
<td>CR; CR</td>
<td>LR (21); LR (1); LR (4); NED (ns)</td>
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<tr>
<td>Pan et al¹⁰</td>
<td>49</td>
<td>Vulvar ulcers</td>
<td>Local radiation</td>
<td>CR</td>
<td>NED (5)</td>
</tr>
<tr>
<td>Rose et al¹¹</td>
<td>50</td>
<td>Vulvar ulcers</td>
<td>Local radiation; local radiation</td>
<td>CR; CR</td>
<td>LR (5); NED (ns)</td>
</tr>
<tr>
<td>Santillan et al¹²</td>
<td>33</td>
<td>Nodular vulvar lesion</td>
<td>Local radiation; local excision; local radiation; radical vulvar excision; thalidomide</td>
<td>CR; PR; CR; CR; CR</td>
<td>LR (21); LR (5); LR (18); LR (3); NED (ns)</td>
</tr>
<tr>
<td>Solano et al¹³</td>
<td>40</td>
<td>Vulvar ulcers</td>
<td>Chemotherapy and excision</td>
<td>CR</td>
<td>NED (18)</td>
</tr>
<tr>
<td>Venizelos et al¹⁴</td>
<td>64</td>
<td>Vulvar ulcer</td>
<td>Local radiation and partial vulvectomy</td>
<td>CR</td>
<td>NED (22)</td>
</tr>
</tbody>
</table>

In case of recurrence, subsequent therapy is shown as well behind semicolons.

CR, complete response; LCH, Langerhans cell histiocytosis; LR, local recurrence; NED, no evidence of disease; ns, not specified; PR, partial response.

are key features necessary for definitive diagnosis, together with morphologic features on light microscopy.\textsuperscript{1}

In clinical presentation, the occurrence of osseous and pulmonary LCH predominates; skin, lymph nodes, or endocrine tissues are rarely primary sites of the disease. LCH is an underdiagnosed disease because the primary lesions are not always correctly assessed. Recognition of this disease is of paramount importance, because multisystem involvement can lead to a life-threatening course of disease.\textsuperscript{2,3} Although none of treatment options has proven superior, resection is the recommended treatment.\textsuperscript{16} Spontaneous remission may occur.\textsuperscript{3}

To briefly analyze the effect that LCH might have on tumor development, we will firstly describe normal LC function and its behavior in a carcinogenic microenvironment together with factors that influence development of vulvar SCCs.

LCs normally compromise an antigen-presenting cell (APC) population found in the epidermal skin layer and function as a sentry of the peripheral immune system. LCs internalize antigens and migrate to more distant lymph nodes where they become immunostimulatory to T-cells by antigen presentation.\textsuperscript{2,16}""