Langerhans Cell Histiocytosis on the Vulva: A Case Report and Review of the Literature

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Langerhans cell histiocytosis (LCH) of the female genital tract is rare. Only 20 cases of primary vulva LCH have been previously reported in the medical literature. In this report, we describe an additional case of LCH on the vulva. A 28-year-old Chinese woman presented with a two-year history of ulcerous lesions on the left vulva. No associated temperature, tiredness, or general malaise was observed. A diagnosis of LCH had been made by biopsy. Histological and immunohistochemical findings were characteristic of LCH. After two weeks of combined medical therapy, including interferon, prednisone, and methotrexate (MTX), the lesion started to cicatrize. Now, the patient was well throughout a 18-month follow up, showing no symptoms or signs of local recurrence or systemic spread. The occurrence of LCH on the vulva is very unusual. It is necessary to perform a biopsy on the lesion, rule out the possibility of multiorgan involvement. There are no standard treatment options for this rare disease. The most effective treatment options remain elusive. In our case, combined medical therapy was proved to be effective.

Key words: Langerhans cell histiocytosis (LCH); vulva; treatment

Langerhans cell histiocytosis (LCH), also known as Histiocytosis X, is characterized by an organ-specific infiltration of cells with many morphological features and immunohistochemical markers of Langerhans cells. Clinically, LCH ranges from self-healing lesions to a multisystem involvement with organ dysfunction resistant to current therapies. The lesions appear in multiple organs, for example in the bones, skin, and lungs. But genital LCH as the only manifestation of this disease is very unusual. Initially, Lane et al.¹ reported LCH in a 6-year-old child in 1939. We here report an additional case of LCH on the vulva.
Case report

A 28-year-old woman, gravida 2, para 1, discovered a ulcerous lesion on her left vulva in 2009. She felt pruritus in the area sometimes, but had no other cutaneous lesions, and she had no associated temperature, tiredness, or general malaise. She was given a course of oral antivirus medicine in local hospital, but the lesions had continued to spread. Physical examination revealed a ulcerous lesion of 1.0 cm $\times$ 1.5 cm on the left vulva (Figure 1). Regional lymph nodes were not enlarged.

A diagnosis of LCH had be made in March 2011 after biopsy. Biopsy and histological findings revealed that the lesions consisted of diffuse infiltrates of Langerhans cells with indented or grooved nuclei, some of Langerhans cells showed karyokinesis. Various numbers of eosinophils, lymphocytes, and neutrophils were also present (Figure 2). Immunohistochemical stains revealed that histiocytic cells were strongly positive for S-100 protein, CD1a, CD68 and vimentin, negative for HMB-45 (Figure 3). These results led to a diagnosis of LCH.

The tests for the extent of disease including bone marrow biopsy, and PET-CT of bone, thorax and abdomen, but no abnormalities were detected in any other area. According to these results, the patient was diagnosed with LCH involving the vulva only.

Because the patient refused surgical excision, we decided to treat her with combined therapy. The treatment was commenced from April 2011, including interferon, prednisone, and methotrexate (MTX). The lesion started to cicatrize after two weeks therapy. Now, the patient was well throughout a 18-month follow up, showing no symptoms or signs of local recurrence or systemic spread.
Langerhans cell, also called dendritic antigen presenting cell, is normal distribution in bone, lymph node, skin, mucous membrane, and internal organ, especially in skin. Histiocytosis X, which included Letterer-Siwe’s disease, Hand-Shuller-Christian’s disease, and eosinophilic granuloma, was renamed Langerhans cell histiocytosis in 1985 by the Histiocytic Society[2]. The diagnosis of LCH has been based on a histopathological pattern in biopsy specimens showing mono- or multinucleated Langerhans cells, histiocytes, and eosinophils. For a definitive diagnosis of LCH, Birbeck’s granules must be detected by electronic microscopy, or else the S-100 protein must be found, or the histiocytic cells in lesions consistent with LCH must be found to be positive for CD1 antibodies[3].

LCH is a very rare disease. The pathogenesis of most histiocytoses remains unclear. A possible cytokine-related pathway[4] and a potential role of granulocyte-macrophage-colony stimulating factor (GM-CSF)[5] have been suggested. LCH chiefly affects infants, but may also occur in adults. An epidemiological study in French showed that the annual incidence rate is 4.6/10^6 in children (0 to 14-year-old)[6] and only 1–2/10^6 in adults[7]. LCH lesions are common in the bone, lung, skin, liver, spleen, and lymph nodes. In 30.6% of patients, LCH involved more than one body system. Twenty-five percent of patients had skin and/or mucous membrane LCH. The most common mucous membranes involved are the genitalia and oral mucous[8].

Axiotis et al.[9] divided four distinct patterns of LCH involvement in the female genital

![Figure 3 Immunohistochemical results](image-url)

A: positive for CD1a (× 200); B: strongly positive for S-100 protein, arrow shows tumor embolus in blood vessel (× 400); C: positive for CD68 (× 200)
tract: 1) pure genital LCH, in which the disease is limited to the genital tract only; 2) genital tract LCH with subsequent multiorgan involvement; 3) oral or cutaneous LCH with subsequent genital and multiorgan involvement; 4) diabetes insipidus with organ involvement.

Pure genital LCH on the vulva is very rare. At present, there are only 20 cases reported in the English literature (Table 1). Because the clinical manifestation of genital LCH is not particular, making a definite diagnosis of this disease is not easy.

Genital LCH should be differentiated by a tissue biopsy from other dermatologic disorders such as diaper rash, seborrhoea dermatitis, eczema, genital tuberculosis and sexually transmitted diseases (syphilis, herpes and granuloma inguinale). As in our patient, HPV and syphilis antibody had been tested. Several neoplastic processes can also resemble LCH, including squamous cell carcinoma, malignant melanoma, sarcoma and Paget’s disease of the vulva[23].

The diagnosis of LCH is performed by tissue biopsy only. For ruling out multiorgan involvement, the routine evaluation should include bone marrow biopsy, chest X-ray, CT of

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**Table 1 Cases reported in literature of LCH on the vulva**

<table>
<thead>
<tr>
<th>Report</th>
<th>Age (year)</th>
<th>Excision</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>Others</th>
<th>Response</th>
<th>Outcome (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axiotis[9]</td>
<td>85</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Corticosteroid</td>
<td>NR</td>
<td>LTF</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>Corticosteroid</td>
<td>CR</td>
<td>NEOD(156)</td>
</tr>
<tr>
<td>Rose[12]</td>
<td>50</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>PR</td>
<td>LTF</td>
</tr>
<tr>
<td>Saurel[13]</td>
<td>91</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>PR</td>
<td>Die of other disease</td>
</tr>
<tr>
<td>Savell[14]</td>
<td>76</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>CR</td>
<td>NEOD(8)</td>
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<tr>
<td></td>
<td>54</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>CR</td>
<td>NEOD(21)</td>
</tr>
<tr>
<td>Solano[16]</td>
<td>40</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>CR</td>
<td>NEOD(24)</td>
</tr>
<tr>
<td>Pather[27]</td>
<td>45</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>CR</td>
<td>NEOD(24)</td>
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<tr>
<td>Santillan[18]</td>
<td>33</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>Thalidomide</td>
<td>CR</td>
<td>NEOD(12)</td>
</tr>
<tr>
<td>Padula[19]</td>
<td>31</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>Thalidomide</td>
<td>CR</td>
<td>NEOD(19)</td>
</tr>
<tr>
<td>Ishigaki[20]</td>
<td>52</td>
<td>—</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>CR</td>
<td>NEOD</td>
</tr>
<tr>
<td>Dietrich[21]</td>
<td>65</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>CR</td>
<td>NEOD(12)</td>
</tr>
<tr>
<td>Venizeles[22]</td>
<td>41</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>CR</td>
<td>LTF</td>
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<tr>
<td>Mottl[23]</td>
<td>29</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>Corticosteroid</td>
<td>PR</td>
<td>LTF</td>
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<tr>
<td>Beneder[24]</td>
<td>64</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<td></td>
<td>16</td>
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<td>—</td>
<td>+</td>
<td>—</td>
<td>CR</td>
<td>NEOD(6)</td>
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<tr>
<td></td>
<td>49</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>CR</td>
<td>NEOD(51)</td>
</tr>
</tbody>
</table>

CR: complete response  PR: partial response  NR: no response
LTF: lost to follow-up  NEOD: no evidence of disease
the abdomen and pelvis, and a bone scan. We used PET-CT to scan total body, also could confirm the range of lesion.

Because of the small number of cases reported, there is no standard recommendation for the management of genital LCH. Methods of treatment primarily included surgery, radiotherapy and chemotherapy. Other forms of treatment have also been used including topical corticosteroids, topical nitrogenated mustard, thalidomide, or combined therapy. Axiotis et al.\(^9\) suggested treating genital lesions initially by complete excision, but 50% of the patients with genital LCH relapsed after surgery\(^{[25]}\). Radiotherapy and chemotherapy were demonstrated to be beneficial in several cases. Thalidomide was also used in two cases of genital LCH with good results; this may have been due to its action on TNF-\(\alpha\)\(^{[26]}\).

Chemotherapy for multisystem disease is beneficial\(^{[14]}\), but there are few data referring to the use of chemotherapy for very localized disease. Systemic treatment with vincristine did not clear up the lesions of the patient described by Solano et al.\(^{[16]}\), and after the surgical excision, the patient remained cured. The patient that was treated according to the LCH II protocol with vinblastine and prednisone by Mottl et al.\(^{[27]}\) relapsed as well after 8 months and received a second-line treatment with 2-chlorodeoxyadenosine. Eighteen months later she still has no sign of recurrence. In our patient, we suggested complete excision initially, but the patient refused. Then we decided to treat her with combined therapy. The medical scheme was commenced from April, including interferon \(3 \times 10^6\) IU ih. 3 times a week, prednisone 15 mg po. bid, and MTX 5 mg po. 2 times a week. The lesion started to cicatrize after two weeks therapy. Now, the patient was well throughout a 18-month follow up, showing no symptoms or signs of local recurrence or systemic spread. Because the prognosis is unknown, we will continue to follow the patient closely.

References

8. Howarth DM, Gilchrist GS, Mullan BP, et al. Langerhans cell histiocytosis; diagnosis, natural history,

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