Three Cases of Intravascular Large B-Cell Lymphoma Detected in a Biopsy of Skin Lesions

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Abstract
Intravascular large B-cell lymphoma (IVL) is a rare subtype of extranodal malignant lymphoma. The proliferation of neoplastic B cells within small blood vessels causes eruptions and other symptoms in a variety of organs. The random skin biopsy is useful for diagnosing this condition in its early stages. In order to assess the diagnostic utility of this method, we examined 3 cases with the aim of comparing the occurrence of tumor cells in lesional skin and healthy-looking skin by performing a random skin biopsy of 32 separate sites. Our findings from the total of 32 biopsy specimens collected from the 3 cases indicated that 16 of the 17 sites on the lesional skin and 1 of the 15 sites on the healthy-looking skin were positive for neoplastic cells. This finding suggested that IVL cells occurred more frequently in the lesional skin than in the healthy-looking skin.

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Case Report
Case 1
An 85-year-old man had reportedly suffered from a fever 1 month prior to consultation. He was referred to the dermatology clinic for suspected IVL based on elevated lactate dehydrogenase (LDH) at 557 µg/dl (normal range: 115–221), soluble interleukin-2 receptor (sIL-2R) at 2,140 U/ml (normal range: 145–519) and the presence of atypical cells in a peripheral blood smear. A physical examination showed asymptomatic pigmented macules on his thighs (fig. 1a). Analysis of a skin biopsy taken from the pigmented macules revealed large hyperchromatic cells filling the lumina of small vessels within the subcutis. The CD20 and CD79a immunostains were positive, and those for CD3, CD34, CD68 and CD45RO were negative, for neoplastic cells. Five other samples yielded the same observations, but 6 samples of healthy-looking skin yielded no neoplastic cells (fig. 2a). Chemotherapy was discussed as an option but finally withheld due to the patient’s age and...
deteriorating functional status. The patient was transferred to another hospital and received palliative care and died almost 2 years after discharge.

Case 2
A 78-year-old man was referred to our hospital for a fever of unknown origin. IVL was suspected from elevated LDH (964 μg/dl) and sIL-2R (1,070 U/ml), a previous partial response to corticosteroids and progressive neurological abnormality. A physical examination showed a red, papule-like senile angioma in his anterior cervical region (fig. 1b), erythema on the right brachium and purpura on the right antebraclium (fig. 1c). A skin biopsy taken from the erythema on his arm revealed large hyperchromatic cells filling the lumina of small vessels within the dermis and subcutis. CD20 and MUM-1 immunostains were positive (fig. 2b), and those for CD79a, CD3, CD45RO and bcl-6 were negative, for neoplastic cells. A biopsy specimen of the other erythematous lesion and purpura yielded the same findings, while 1 of the 9 samples of healthy-looking skin also yielded neoplastic cells. Following steroid pulse therapy, the patient's condition became complicated with tumor lysis syndrome. The patient later expired.

Case 3
A 73-year-old woman had reportedly suffered from fever and somnolence 2 months prior to her first consultation at our hospital. The MRI showed pachymeningeal hypertrophy. The patient was referred to the dermatology clinic after she had noticed eruptions on her abdomen. Laboratory findings indicated elevated LDH of 2,940 μg/dl and sIL-2R of 3,360 U/ml. Ferritin levels in patients 1, 2 and 3 were 222.5, 1,639 and 3,360 ng/ml (normal range: up to 125), respectively.

A skin biopsy taken from the erythema on the abdomen demonstrated large hyperchromatic cells filling the lumina of small vessels within the subcutis. The CD20, CD5, CD10, CD19, bcl-2 and MUM-1 immunostains were positive (fig. 3b, d), and the CD3, CD45RO and bcl-6 stains were negative, for neoplastic cells. A biopsy specimen from 8 other erythematous lesions yielded the same observations (table 1).

The differential diagnoses of intravascular histiocytosis, CD30 lymphoproliferation and benign lymphocyte accumulation were ruled out on the basis of the negative immunophenotype of CD68, the lack of cutaneous involvement such as nodules with ulceration and the monoclonality of the immunophenotype, respectively.

Our findings from the total of 32 biopsy specimens collected from these 3 cases indicated that 16 of the 17 sites on the lesional skin were positive for neoplastic cells, while only 1 of the 15 sites on the healthy-looking skin was positive for neoplastic cells (table 2). IVL cells were found predominantly in lesional skin. Statistical analysis by the χ² test showed a significant difference between these two groups as indicated. The patient responded to chemotherapy including cyclophosphamide, pirarubicin, prednisolone and rituximab. He was subsequently transferred to another hospital for further management.
**Table 1. Patient data**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age, years</th>
<th>Sex</th>
<th>Symptom</th>
<th>Eruption</th>
<th>WBC/Hb/Plt, mm$^3$</th>
<th>LDH, U/l</th>
<th>sIL-2R, U/ml</th>
<th>Variant of IVL</th>
<th>HPS</th>
<th>IVL positive in skin biopsy specimen (positive/total skin lesion)</th>
<th>CD20</th>
<th>MUM-1</th>
<th>CD3</th>
<th>CD45RO</th>
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<tbody>
<tr>
<td>1</td>
<td>85</td>
<td>M</td>
<td>fever</td>
<td>pigmented macules</td>
<td>6,600/11.7/19.1</td>
<td>653</td>
<td>1,420</td>
<td>European n.d.</td>
<td>6/12</td>
<td>+ n.d.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>M</td>
<td>fever, general fatigue</td>
<td>erythema, purpura</td>
<td>5,900/10.7/23.2</td>
<td>964</td>
<td>1,070</td>
<td>Asian +</td>
<td>3/12</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>F</td>
<td>fever, confusion</td>
<td>erythema</td>
<td>5,900/9.0/4.9</td>
<td>3,050</td>
<td>3,360</td>
<td>Asian +</td>
<td>8/8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

WBC = White blood cells; Hb = hemoglobin; Plt = platelets; HPS = hemophagocytic syndrome; n.d. = not detected; + = positive; – = negative.

**Table 2. Neoplastic cells in skin biopsies**

<table>
<thead>
<tr>
<th></th>
<th>IVL cells</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>positive</td>
<td>negative</td>
</tr>
<tr>
<td>Skin lesion</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Healthy-looking skin</td>
<td>1</td>
<td>14</td>
</tr>
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</table>

**Discussion**

IVL, first reported by Pfleger and Tappeiner [2] in 1959, is an extranodal malignant lymphoma with a poor prognosis occurring principally among the elderly population at a rate of 1 in a million. IVL is classified as a subtype of diffuse large B-cell lymphoma by the WHO, and is known to exist in the variants T-cell and NK-cell types as well, although these are very rare [3].

It has been suggested that the absence of adhesion molecules CD29 (β1-integrin) and CD54 (ICAM-1) [2], matrix metalloproteinase-2 and -9 expression in addition to the lack of CD20 and CD54 [4] of IVL cells comprise some of the features peculiar to IVL.

As the prognosis for this disease is poor, the biopsy is essential for early diagnosis and treatment. The diagnosis of IVL can be made solely on the basis of immunohistochemical confirmation of the presence of neoplastic cells in samples of the skin, liver, spleen or bone marrow. Among the methods which may be used for diagnosis, the skin biopsy is preferred because it is relatively simple to perform and minimally invasive, and because a random skin biopsy from normal-appearing skin is more sensitive than a bone marrow biopsy for the diagnosis of IVL [5–8]. In case 3 in the present study, however, the patient had submitted to a random biopsy of healthy-looking skin at another hospital. IVL was not diagnosed because the results of the biopsy were negative although the patient was considered susceptible to the condition. IVL was eventually diagnosed in the patient subsequent to a lesional skin biopsy performed by a dermatologist at our hosp
tal 2 months later. All IVL cells were observed in the lesional skin in case 3. Thus, while the random skin biopsy is indeed a valuable method for diagnosing IVL, its use is recommended with the caveat that the lesional skin of the patient be tested by a dermatologist, if possible, to ensure the accuracy of the diagnosis, because faint skin lesions are at times difficult to detect.

We examined 3 cases in order to compare the presence or absence of tumor cells in lesional and healthy-looking skin by performing a random skin biopsy in 32 separate sites. As a result, IVL cells were found in 16 out of 17 samples of lesional skin, and only 1 out of 15 samples of healthy-looking skin, pointing to a significant difference between these two groups as indicated by the $\chi^2$ test. Zuckerman et al. [9] have reported that the incidence of skin lesions in IVL is 39% and that these skin lesions exhibit a variety of findings including erythematous eruptions such as red papule-like senile angiomas, telangiectasia-like vascular spinders, nodules and subcutaneous tumors.

To the list of these reported observations, we may also add the additional findings of IVL cells in the dermis and/or adipose tissue under all of the 6 pigmented macules from which samples were taken. The skin eruptions observed have sometimes been explained as the result of the embolization of blood vessels caused by the proliferation of neoplastic cells, with this in turn leading to the formation of compensatory collateral circulation. The mechanism generating pigmented macules is not clear, although it is assumed to be postinflammatory pigmentation caused by a tumor-associated immune reaction.

The so-called Asian IVL (AIVL) is characterized by the rapid proliferation of tumor cells in the bone marrow and the blood vessels of the liver and spleen, hemophagocytic syndrome and the absence of neurological abnormalities and skin lesions [10, 11]. On the other hand, the European variant of IVL is characterized by a more indolent progression and microvascular occlusions in the CNS, skin, kidney and lung. One type of AIVL, which is accompanied by hemophagocytic syndrome, has an especially poor prognosis. Of the 3 cases examined here, case 1, a patient with the European variant, declined to give consent to chemotherapy but has survived and continues to be treated at another hospital. In case 2, AIVL was diagnosed and the patient expired shortly after diagnosis. In case 3, following the diagnosis of AIVL, the patient received chemotherapy and continues to be under observation at another hospital.

In this study, we demonstrated the diagnostic utility of analyzing skin eruptions for the early detection of IVL, as skin eruptions, which may resemble a senile angiomma or even a pigmented macule or purpura at first glance, may be accompanied by the presence of neoplastic cells more frequently than healthy-looking skin.

**Statement of Ethics**

The local ethics committee acknowledged and found sufficient the signed agreement to report the cases.

**Disclosure Statement**

No conflict of interest, financial or otherwise, exists.

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**References**