HIV-negative Primary Bone Marrow Hodgkin Lymphoma Manifesting with a High Fever Associated with Hemophagocytosis as the Initial Symptom: A Case Report and Review of the Previous Literature

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Abstract

A 68-year-old man was referred to our hospital due to a high fever and pancytopenia. Neither tumors nor infectious lesions were detected. Hemophagocytosis was observed on the bone marrow (BM) smear, although without abnormal cells. Prednisolone therapy was ineffective for the patient’s high fever. Later on, we obtained the results of a BM biopsy indicating the presence of infiltration of atypical Reed-Sternberg cells, leading to a diagnosis of HIV-negative primary bone marrow Hodgkin lymphoma (PBMHL). However, the patient died of multiple organ failure before receiving chemotherapy. As the clinical course of PBMHL is rapid, physicians must keep in mind its possibility in similar cases.

Key words: primary bone marrow lymphoma, Hodgkin lymphoma, hemophagocytosis


Introduction

The majority of cases of Hodgkin lymphoma (HL) are chemotherapy-sensitive and curable, with a 5-year survival rate of 65-90% (1). Nevertheless, primary bone marrow Hodgkin lymphoma (PBMHL) is rapidly progressive, and its prognosis is unfavorable. To date, only 12 cases of PBMHL have been reported. Among them, nine patients were human immunodeficiency virus (HIV)-positive (2-5), while three patients were HIV-negative (6-8). We herein report a rare case of HIV-negative PBMHL that manifested with a high fever associated with hemophagocytosis as the initial symptom.

Case Report

A 68-year-old man was admitted to another hospital complaining of a high fever during the first week of August 2013. He had previously been healthy and did not have a past history of disorders causing immunodeficiency (i.e., autoimmune disease, cancer and the like). Because pancytopenia gradually progressed, he was referred to our hospital at the beginning of September. Pancytopenia was observed in the peripheral blood: white blood cell count = 3.2×10⁹/L with a normal differential, hemoglobin level= 7.8 g/dL and platelet count= 16×10⁹/L. Other laboratory data were as follows: aspartate aminotransferase (AST)=141 IU/L (normal range: 7-40), alanine aminotransferase (ALT)=151 IU/L (normal range: <35), lactase dehydrogenase= 243 IU/L (normal range: 100-225), C-reactive protein= 13.4 mg/dL (normal range: <0.03), soluble interleukin-2 receptor = 26,667 U/mL (normal range: <505) and ferritin= 7,767 ng/mL (normal range: 25-250). No autoantibodies were detected, and the complement levels were within the normal ranges. Serological tests for Epstein-Barr Virus (EBV) showed a past infec-

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tion pattern, while tests for HIV were negative. Lumbar puncture and magnetic resonance imaging revealed no abnormalities, and no tumors or infectious lesions were detected on enhanced computed tomography scanning of the neck to the pelvis. The patient exhibited hepatosplenomegaly, although it was not prominent. However, an abnormal uptake was observed in the bone marrow (BM) on gallium-67 scintigraphy. We initially suspected Asian-variant intravascular large B-cell lymphoma (IVLBCL) (9). Therefore, we performed BM aspiration and a biopsy. The BM smear was hypocellular, and no abnormal cells were detected; however, severe hemophagocytosis induced by activated macrophages was observed, indicating the presence of hemophagocytic syndrome (HPS) (Fig. 1A). Antibiotic therapy started on admission was ineffective, and treatment with neither prednisolone (PSL) (1 mg/kg/day) nor consecutive plasma exchange for three days was effective in reducing the high fever. Ten days after admission, we obtained the results of the BM biopsy, which revealed infiltration of atypical Reed-Sternberg cells (RSCs) (Fig. 1B, C). The RSCs were positive for CD30 and paired box gene (PAX)-5 (Fig. 2A, B) as well as EBV-encoded RNA (EBER)-1 (Fig. 2C). In addition, the RSCs were positive for B cell Oct binding protein (BOB)-1 (Fig. 2D) but negative for CD3, CD5, CD20, CD79a, anaplastic lymphoma kinase (ALK) and octamer-binding transcription factor (Oct)-2 (Fig. 2E). Due to the limited number of paraffin sections, we were unable to confirm the expression of EBV nuclear antigen (EBNA)-2. Finally, the differential diagnosis of EBV-positive diffuse large B-cell lymphoma (DLBCL) of the elderly was made based on CD20 negativity. The CD30-positive cells were positive for EBER-1 on in-situ hybridization (Fig. 2C). Based on the expression pattern of these molecules and the morphological characteristics, a diagnosis of PBMHL was made. At that point, we were unable to administer combination chemotherapy [doxorubicin, bleomycin, vinblastine and dacarbazine, adriamycin, bleomycin, vinblastine and dacarbazine (ABVD)] due to multiple organ failure, and the patient consequently died soon thereafter.

**Discussion**

It is very difficult to diagnose PBMHL, even for pathologists specializing in lymphoma, as typical RSCs are absent (10) and only a few of these cells are found in the histological specimens (2, 6). In order to diagnose PBMHL, it is necessary to exclude the possibility of EBV-positive DLBCL of the elderly. For this differential diagnosis, the level of CD15, a classical marker for the diagnosis of classical Hodgkin lymphoma, is not useful, as atypical RSCs

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**Figure 1.** (A) Bone marrow aspiration showed hemophagocytosis by activated histiocytes (May & Giemsa staining, ×400). (B) (C) Bone marrow biopsy (Hematoxylin and Eosin staining, ×400): the white arrowheads show atypical Reed-Sternberg cells (RSCs) in a background of small lymphocytes.
Figure 2. Immunohistochemical staining shows Reed-Sternberg cells (RSCs) positive for CD30 (A), PAX-5 (B) and in-situ hybridization with EBER-1 (C). The cells slightly expressed BOB-1 (D) and were negative for Oct-2 (E).

Table. Clinical Features of HIV-negative PBMHL Patients in Previous Reports.

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Hemophagocytosis</th>
<th>Treatment</th>
<th>Response</th>
<th>Time from the onset of symptoms to diagnosis</th>
<th>Survival time from diagnosis</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>M</td>
<td>Fever, cytopenia</td>
<td>-</td>
<td>ABVD</td>
<td>No remission</td>
<td>6 months</td>
<td>Diagnosed by autopsy</td>
<td>Ponzoni et al. (6)</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>M</td>
<td>Fever, cytopenia</td>
<td>-</td>
<td>ABVD</td>
<td>No remission</td>
<td>More than a month</td>
<td>21 days</td>
<td>Cacoub et al. (7)</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>F</td>
<td>Fever, cytopenia</td>
<td>-</td>
<td>ABVD 1 AVD 5</td>
<td>Complete remission</td>
<td>4 months</td>
<td>PFS : 15 months</td>
<td>Dholaria et al. (8)</td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>M</td>
<td>Fever, cytopenia</td>
<td>+</td>
<td>not done</td>
<td>-</td>
<td>2 months</td>
<td>2 months</td>
<td>Our case</td>
</tr>
</tbody>
</table>

M: male, F: female, ABVD: adriamycin, bleomycin, vinblastine and dacarbazine, AVD: ABVD without bleomycin, PFS: progression free survival

often lack an expression of this molecule in cases of PBMHL. However, in a previous paper, the authors showed that, although EBV-positive DLBCL cells were positive for both B-cell transcription factors, BOB-1 and Oct-2, the RSCs expressed neither factor or only expressed one factor (11). PBMHL is very rare, with only 13 cases, including
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