We describe a 56-year-old woman with histiocytic sarcoma involving the bone marrow. The neoplastic cells proliferated diffusely and showed occasional erythrophagocytosis. Immunohistochemically, the neoplastic cells were positive for CD68, lysozyme, CD4 and CD163, but negative for B- and T-cell markers, S100 protein and epithelial markers. The patient received multi-agent chemotherapy and is living at 22 months after diagnosis without recurrence. Histiocytic sarcoma is an exceedingly rare hematopoietic neoplasm and the prognosis is poor due to its rapid progression, widespread disease and poor response to therapy. It is important to recognize this rare neoplasm and to confirm the diagnosis using specific immunohistochemical markers.

Key words: histiocytic sarcoma, true malignant histiocytosis, immunohistochemical findings, histiocyte/macrophage-specific antigen

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Histiocytic Sarcoma: Identification of Its Histiocytic Origin Using Immunohistochemistry

Chikamasa Yoshida and Makoto Takeuchi

Abstract

We describe a 56-year-old woman with histiocytic sarcoma involving the bone marrow. The neoplastic cells proliferated diffusely and showed occasional erythrophagocytosis. Immunohistochemically, the neoplastic cells were positive for CD68, lysozyme, CD4 and CD163, but negative for B- and T-cell markers, S100 protein and epithelial markers. The patient received multi-agent chemotherapy and is living at 22 months after diagnosis without recurrence. Histiocytic sarcoma is an exceedingly rare hematopoietic neoplasm and the prognosis is poor due to its rapid progression, widespread disease and poor response to therapy. It is important to recognize this rare neoplasm and to confirm the diagnosis using specific immunohistochemical markers.

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Introduction

Histiocytic sarcoma, which is also called true malignant histiocytosis, is an exceedingly rare hematopoietic neoplasm. Neoplasms originally classified as “histiocytic lymphomas” by Rappoport have encompassed a biologically heterogeneous group of disorders (1). Owing to advances in immunohistochemistry and molecular biology, the majority of so called “histiocytic lymphomas”, which were considered to be neoplasms of histiocyte/macrophage origin based on their morphological features, were actually T- or B-cell non-Hodgkin’s lymphomas or a reactive proliferation of histiocytes associated with lymphomas (2-4). The recent World Health Organization (WHO) classification strictly specifies the origin of the neoplastic cells to exclude diseases originating from cells other than histiocytes/macrophages, such as lymphomas and other neoplasms.

We recently encountered a case of histiocytic sarcoma whose diagnosis was confirmed by immunohistochemistry of a bone marrow biopsy specimen. The patient’s tumor responded to multi-agent chemotherapy including etoposide followed by recombinant human granulocyte-colony stimulating factor (rhG-CSF). The patient is living at 22 months after diagnosis without recurrence. Here, the morphologic and immunohistochemical features of the neoplasm are described in detail, and its differential diagnoses are discussed.

Case Report

A 56-year-old woman presented to us with fatigue and a spiking fever in November 2005. Physical examination showed that she was febrile, pale and had mild hepatomegaly, but no skin lesions, neurological abnormalities or lymphadenopathy. Her general condition was poor with an Eastern Cooperative Oncology Group performance status of 4. A complete blood count showed a leukocyte count of 1.8×10^9/L with 2% granulocytes, 74% lymphocytes and 24% monocytes, a hemoglobin of 6.4 g/dL and a platelet count of 11×10^9/L. Serum biochemistry studies revealed a markedly elevated lactic dehydrogenase (LDH) of 9,990 U/L (normal range: 120-240 U/L) and ferritin of 191,800 ng/mL (normal range: 10-160 ng/mL), as well as liver and renal dysfunction with a total bilirubin of 2.1 mg/dL (normal range: 0.2-1.0 mg/dL), aspartate aminotransferase of 1,543 U/L (normal range: 10-160 ng/mL), as well as liver and renal dysfunction with a total bilirubin of 2.1 mg/dL (normal range: 0.2-1.0 mg/dL), aspartate aminotransferase of 1,543 U/L (normal range: 10-35 U/L), alanine aminotransferase of 445 U/L (normal range: 7-42 U/L), blood urea nitrogen of 44 mg/dL (normal range: 8-22 mg/dL) and creatinine of 2.47 mg/dL.
Figure 1. Histopathologic features of the bone marrow biopsy specimen. (A) Neoplastic cells had proliferated diffusely and the normal hematopoietic architecture was destroyed (Hematoxylin and Eosin staining, original magnification ×100). (B) Neoplastic cells had abundant eosinophilic cytoplasm and round to oval nuclei (Hematoxylin and Eosin staining, original magnification ×400). (C) CD68 (KP-1) immunohistochemical staining (original magnification ×400): the cytoplasms of tumor cells were diffusely positive for CD68 antibody. (D) Lysozyme immunohistochemical staining (original magnification ×400): the cytoplasms of tumor cells were diffusely positive for lysozyme antibody. (E) CD163 immunohistochemical staining (original magnification ×400): tumor cells were focally positive for CD163 antibody. (F) S100 protein immunohistochemical staining (original magnification ×400): tumor cells were negative for S100 protein antibody.

(normal range: 0.45-0.80 mg/dL). Coagulation tests showed that the prothrombin time was 13.7 seconds, an international normalized ratio of 1.44, fibrinogen of 116 mg/dL and fibrinogen degradation product of 48.0 mg/L. Blood and urine cultures were negative. The chest X-ray was normal and a computed tomography of the abdomen demonstrated mild hepatomegaly, but no splenomegaly or lymphadenopathy. A bone marrow aspiration was performed, but only a small sample was obtained which showed proliferation of large atypical cells. The morphological and immunohistochemical characteristics of these cells were investigated in detail using the bone marrow biopsy specimen. Morphologically, the large atypical cells had abundant eosinophilic cytoplasm and round to oval nuclei, and there was diffuse proliferation of these cells with occasional erythrophagocytosis (Fig. 1A and 1B). Normal hematopoietic cells were absent. These atypical cells were negative for CD20/CD79a (B-cell markers), CD3 (T-cell marker), CD56 (NK cell marker), CD138 (plasma cell marker), cytokeratin (melanocyte and epithelial marker) and epithelial membrane antigen (epithelial marker), but positive for CD68 (KP-1/PG-M1: macrophage/histiocytic marker) (Fig. 1C), lysozyme (macrophage/histiocytic marker) (Fig. 1D) and CD4 (T-cell and macrophage/histiocytic marker) by immunohistochemistry. Moreover, these cells were also positive for the highly specific macrophage/histiocytic marker, CD163 (Fig. 1E). These
cells were negative for S100 protein (melanocyte, Langerhans cell and interdigitating dendritic cell marker) (Fig. 1F) (Table 1). Based upon these results, a diagnosis of histiocytic sarcoma (true malignant histiocytosis) with disseminated intravascular coagulation (DIC) was made. The results of a polymerase chain reaction analysis for the rearrangements of the immunoglobulin heavy chain and T-cell receptor genes in paraffin-embedded tissues, which revealed no rearrangements of these genes (data not shown), supported our diagnosis.

Modified CHOEP-14 chemotherapy (cyclophosphamide 750 mg/m² day 1, doxorubicin 50 mg/m² day 1, vincristine 1.4 mg/m² day 1, etoposide 100 mg/m² day 1 and prednisolone 50 mg/m² days 1-5 followed by rhG-CSF (filgrastim) at a dose of 300 μg/day) was administered immediately, and intravenous heparin was also administered because of the DIC. Due to the liver and renal dysfunction, the dose of cyclophosphamide was reduced to 75% of the standard dose above and doxorubicin was reduced to 25% of the standard dose above during the first 2 courses of chemotherapy. After the administration of the first course of CHOEP-14, her serum biochemistry values including the LDH and coagulation tests normalized and her hepatomegaly also improved; however, the pancytopenia persisted and residual neoplastic cells were observed in the bone marrow at day 12. Therefore, a second course of dose-reduced CHOEP-14 was administered. The pancytopenia resolved at day 10 of the second course, and the bone marrow aspiration revealed no neoplastic cells, as well as no erythrophagocytosis. Her general condition and laboratory data also improved (Fig. 2). Six additional cycles of modified CHOEP-14 (full-dose as cited above) were administered, and the patient is living at 22 months after diagnosis without recurrence.

**Table 1. Immunohistochemical Results of the Bone Marrow Biopsy Specimen**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD68 (KP-1)</td>
<td>+</td>
</tr>
<tr>
<td>CD68 (PG-M1)</td>
<td>+/-</td>
</tr>
<tr>
<td>CD68 (Ki-M1P)</td>
<td>+</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>+</td>
</tr>
<tr>
<td>CD163</td>
<td>+/-</td>
</tr>
<tr>
<td>CD79a</td>
<td>-</td>
</tr>
<tr>
<td>CD20</td>
<td>-</td>
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<tr>
<td>CD3</td>
<td>-</td>
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<tr>
<td>CD4</td>
<td>+</td>
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<tr>
<td>CD56</td>
<td>-</td>
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<tr>
<td>CD138</td>
<td>-</td>
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<td>S100 protein</td>
<td>-</td>
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<td>Cytokeratin</td>
<td>-</td>
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<td>EMA</td>
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Results: +, > 50%; +/-, 25 – 50%; -, < 25%.

**Figure 2.** Clinical course during the first 2 courses of chemotherapy. After 2 cycles of modified CHOEP-14, the pancytopenia resolved with the normalization of her laboratory data, and the bone marrow aspiration revealed no neoplastic cells.
Discussion

The WHO classification defined histiocytic sarcoma as a malignant proliferation of cells showing morphologic and immunophenotypic features similar to those of mature tissue histiocytes (5). The diagnosis of histiocytic sarcoma relies predominantly on the morphological features of the histiocytic lineage, and the exclusion of lymphoma and other poorly differentiated large cell malignancies (i.e. carcinoma and melanoma) by immunohistochemical studies. In this case, the bone marrow was infiltrated with proliferating large tumor cells, which had abundant eosinophilic cytoplasm and round to oval nuclei, and showed occasional erythrophagocytosis. These cells were positive for histiocytic markers, CD68 (KP-1 and PG-M1), lysozyme and CD163, but negative for B-cell, T/NK-cell, epithelial cell markers and S100 protein. Therefore, we excluded lymphoma, carcinoma and melanoma from the diagnosis of this case. Because of the resemblance of its clinical features, hemophagocytic syndrome, which is a reactive proliferation of histiocytes and is generally associated with lymphoma in adults, should also be differentiated. In this case, while occasional erythrophagocytosis was seen, the abnormal cells in the bone marrow had proliferated diffusely and destroyed the normal hematopoietic system. These pathological findings were different from that of hemophagocytic syndrome. From these results, we believe that this case is neoplasm of the histiocytic lineage.

The WHO classification divided histiocytic and dendritic cell neoplasms into 6 categories, such as histiocytic sarcoma, Langerhans cell histiocytosis, Langerhans cell sarcoma, follicular dendritic cell sarcoma/tumor, interdigitating dendritic cell sarcoma/tumor and dendritic cell sarcoma not otherwise specified (6). Pileri et al recommended immunostaining for CD68, lysozyme, CD1a, S100 protein, CD21 and CD35 for the differential diagnosis of this entity (7). In their article, histiocytic sarcoma expressed CD68 (in 100% of the cases) and lysozyme (in 96% of the cases); however, the Langerhans cell marker (CD1a) and follicular dendritic cell marker (CD21/35) were negative, and focal reactivity for the S100 protein (typically expressed in Langerhans cell tumors) was observed (in 33% of the cases). However, the high incidence of cross-reactivity of the immunohistochemical antibodies originally believed to be specific for histiocytes presents a difficult problem. For example, KP-1 stains myeloid cells and some types of malignant lymphomas (8), while PG-M1 stains megakaryocytes, some types of carcinomas and melanoma cells (9). Recently, CD163, a hemoglobin scavenger receptor (10), also was shown to identify histiocytic cells with a high degree of specificity, and has became a promising marker for the diagnosis of histiocytic malignancies (11, 12). In this case, the neoplastic cells in the bone marrow were positive for multiple CD68 antibodies such as KP-1 and PG-M1, as well as lysozyme and CD163. Finally, we concluded that the diagnosis of this case was a histiocytic sarcoma.

Histiocytic sarcoma commonly presents at extranodal sites such as the bone marrow, liver, spleen and intestines; moreover, some cases show a systemic presentation, fulfilling the historical criteria for the diagnosis of ‘malignant histiocytosis’ (1). Although most cases have been treated with a regimen similar to that used for lymphomas, their prognoses were poor due to rapid progression, the presence of widespread disease and their poor response to therapy. Pileri et al reported that among the 12 cases treated with chemotherapy with or without radiotherapy, only 2 cases maintained complete remission while 7 cases died of disease (7). Recent data have shown promising results with the addition of etoposide to conventional CHOP chemotherapy on complete remission rate and event-free survival, and the interval reduction from 3 to 2 weeks using rhG-CSF (CHOEP-14) had a significant effect on overall survival in patients suffering from aggressive lymphoma under 60 years old (13). Therefore, we administered a modified CHOEP-14 to the present patient in consideration of her general condition. As a result, she has lived for 22 months after the diagnosis without recurrence. It is important to recognize this exceedingly rare neoplasm and to confirm its diagnosis using specific immunohistochemical markers, as quickly as possible.

References


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