Histiocytic Sarcoma of the Spleen
- A Case Report and Review of the Literature -

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Received: July 27, 2005
Accepted: August 30, 2005

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Histiocytic neoplasm is one of the rarest tumors in hematopoietic and lymphoid system. Although several cases have already been reported, the scarcity of cases still restricts the understanding of its biologic behavior. Furthermore, historical confusion of the diagnostic terminology, so-called 'histiocytic' lymphoma used in the Rappaport classification for describing large T- or B-cell lymphoma, has also made it difficult to isolate 'true histiocytic' neoplasm among previously reported cases. True histiocytic sarcoma is characterized by CD68 (+), S-100 protein (-), CD1a (-), CD21 (-) in immunohistochemistry, and the presence of lysosomes but absence of Birbeck granules, junctions, desmosomes, or cytoplasmic projections in electron microscopy. In Korea, a few localized histiocytic neoplasms with immunohistochemical or ultrastructural studies have been described. However, primary splenic histiocytic sarcoma has not been reported yet. Here we report the first Korean case of primary splenic histiocytic sarcoma. In addition, based on the present case and review of literature, we demonstrate that splenic histiocytic sarcoma is characteristically accompanied by prominent hemophagocytosis and thrombocytopenia.

CASE REPORT

A 64-year-old woman was admitted to Seoul National University Hospital (SNUH) because of exertional dyspnea and intermittent dizziness for one month. She also complained of easy bruisability which had appeared one year ago. Laboratory test showed thrombocytopenia (platelet 17,000/µL), macrocytic normochromic anemia (hemoglobin 7.2 g/dL, MCV 118 fL, MCH 34 pg) with negative direct/indirect Coombs’ test, and a raised reticulocyte count (15.8%). WBC count was 5.6 × 10^3/µL (segmented neutrophil 80%, lymphocyte 8.7%, monocyte 2.9%, eosinophil 1.5%). LDH was increased up to 777 IU/L. Total protein and albumin concentration in serum was decreased to 5.2 and 2.9 g/dL. Antinuclear antibody, Mycoplasma antibody,
cold agglutinin, anti-HCV antibody, HBs antigen and Ham’s test were all negative. Bone marrow examination disclosed hypercellular marrow with erythroid and megakaryocytic hyperplasia. Abdominal CT scan revealed splenomagaly with multiple low attenuating masses (Fig. 1A). Neither high dose dexamethasone nor intravenous immunoglobulin showed any effect on thrombocytopenia of the patient. It was also refractory to platelet transfusion. Therefore, splenectomy was performed for both diagnostic and therapeutic purposes.

Grossly, spleen was enlarged up to 18 × 13 × 8 cm. On the cut surface, brown to tan-colored multinodular mass lesion replaced the entire spleen (Fig. 1B). Microscopically, the mass-forming area was filled with large cells with histiocytic morphology and hemophagocytic activity. They had abundant eosinophilic cytoplasm and round to oval and vesicular nuclei (Fig. 1C). They showed variable degrees of nuclear atypia and occasional mitotic figures including atypical mitosis (Fig. 1D). Atypical multinucleated cells were also frequently observed. RBCs, degenerated RBCs, and leukocytes were observed in the cytoplasm of the tumor cells (Fig. 1E). Outside of mass-forming area was compressed and had relatively well-preserved red pulp and white pulp structures. However, scattered tumor cells were also noted in the sinuses. In immunohistochemistry, large hemophagocytic cells were diffusely strong positive for leukocyte common antigen (LCA), CD68 (PG-M1), and lysozyme, and alpha1-antitrypsin, and negative for S-100 protein, myeloperoxidase, CD21, CD1a, CD3, L26, CD30, ALK, epithelial membrane antigen (EMA), and HMB-45 (Fig. 1F). EBV in situ hybridization for EBV-encoded RNA (EBER) 1 and 2 was negative. Monoclonal proliferation of B- or T-cells was not observed in the result of gene rearrangement study for immunoglobulin heavy chain and T-cell receptor gamma chain.

The patient dramatically recovered from thrombocytopenia and anemia after splenectomy. However, platelet count abruptly decreased within two months after splenectomy, and did not recover over 50,000/\(\mu L\). Under the suspicion of tumor recurrence, chemotherapy was with started bleomycin, vincristine and prednisolone eighth month after splenectomy. Nevertheless, the patient deteriorated with persistent refractory thrombocytopenia, and died 15 months after splenectomy due to pneumonia, probably complicated by long-term use of prednisolone.

**DISCUSSION**

Histiocytic sarcoma is defined as a malignant proliferation of cells showing morphologic and immunophenotypic features similar to those of mature tissue histiocytes. It shows expression of
Primary splenic histiocytic sarcoma shows some unique features, shared by the previously reported splenic cases\textsuperscript{8-10} and the present case, different from the cases of other primary sites\textsuperscript{2,3} (Table 1). All cases were characterized by prominent hemophagocytosis by neoplastic cells, which resulted in severe thrombocytopenia and anemia.\textsuperscript{8-10} In fact, hemophagocytosis is supposed to be the feature more commonly seen in reactive cells than in tumor cells,\textsuperscript{1,4} which frequently makes it difficult to distinguish the neoplastic hemophagocytic cells from reactive hemophagocytic cells. However, the mass formation in the spleen and the distinct atypism of infiltrating histiocytes are thought to be important features discriminating primary splenic histiocytic sarcoma from secondary splenic involvement of so-called ‘systemic malignant histiocytosis’ or hemophagocytic syndrome.\textsuperscript{8-10} In addition, hypoproteinemia is another remarkable feature of splenic histiocytic sarcoma, which was also reported in previous splenic cases.\textsuperscript{8} The present case is the first Korean case of primary splenic histiocytic sarcoma showing typical clinical

### Table 1. Clinicopathologic features of primary splenic histiocytic sarcoma

<table>
<thead>
<tr>
<th>Case 1\textsuperscript{a}</th>
<th>Case 2\textsuperscript{a}</th>
<th>Case 3\textsuperscript{a}</th>
<th>Case 4\textsuperscript{a}</th>
<th>Case 5\textsuperscript{a}</th>
<th>The present case</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age/Sex</strong></td>
<td>29/M</td>
<td>60/M</td>
<td>66/F</td>
<td>38/M</td>
<td>71/F</td>
</tr>
<tr>
<td><strong>Initial symptom</strong></td>
<td>Tibial edema</td>
<td>Tibial edema</td>
<td>Tibial edema</td>
<td>General weakness</td>
<td>General weakness</td>
</tr>
<tr>
<td><strong>Hypoproteinemia</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Anemia/Thrombocytopenia</strong></td>
<td>+/-/+</td>
<td>+/-/+</td>
<td>+/-/+</td>
<td>NA/NA</td>
<td>+/-/NA</td>
</tr>
<tr>
<td><strong>Hematomegaly</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Lymphadenopathy</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Tumor size (cm)</strong></td>
<td>17 × 13 × 8</td>
<td>8 × 8 × 8</td>
<td>1 × 1–3 × 3</td>
<td>1.5</td>
<td>14 × 12 × 10</td>
</tr>
<tr>
<td><strong>Splenectomy to recurrence</strong></td>
<td>3 yr</td>
<td>4 mo</td>
<td>6 mo</td>
<td>NA</td>
<td>6 mo</td>
</tr>
<tr>
<td><strong>Cause of death</strong></td>
<td>Pneumonia</td>
<td>GI bleeding</td>
<td>Brain hemorrhage</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Involved organ at autopsy</strong></td>
<td>Liver</td>
<td>Liver, BM</td>
<td>Liver, BM</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

\textsuperscript{a} indicates the case that autopsy was not done, but involvement was identified on biopsy; BM, bone marrow; +, present; -, absent; +, borderline; NA, not applicable; yr, year; mo, month.

1. Historical misuse of the term, ‘histiocytic’, is now almost corrected by the advances of immunohistochemical technique. The so-called ‘diffuse histiocytic lymphoma’ is now mainly categorized as diffuse large B-cell lymphoma. The previously called ‘histiocytic medullary reticulosis’ and ‘malignant histiocytosis’ were defined as systemic malignant disease of histiocytes affecting the entire reticuloendothelial system at initial presentation, often with severe clinical symptoms. Most cases of them are now thought to be systemic anaplastic large cell lymphoma or malignant lymphoma of T-cell or B-cell lineage with abundant reactive histiocytes.\textsuperscript{1,4,5} Other cases of them are regarded as hemophagocytic syndrome,\textsuperscript{8-10} which is non-clonal or non-neoplastic proliferation of histiocytes, frequently associated with viral infection. Taken together, the ‘true histiocytic’ neoplasm is thought to be extremely rare\textsuperscript{1,4,5} and the distinction of it from non-histiocytic or non-neoplastic disorder always requires immunophenotyping and consideration of clinical settings.

2. Taken together, the ‘true histiocytic’ neoplasm is thought to be extremely rare and the distinction of it from non-histiocytic or non-neoplastic disorder always requires immunophenotyping and consideration of clinical settings. One or more histiocytic markers but no accessory/dendritic cell markers, and is not associated with acute monocytic leukemia.\textsuperscript{1}

3. It is a rare tumor reported in lymph nodes and multiple extranodal sites including gastrointestinal tract, bone marrow, skin and central nervous system.\textsuperscript{1,4,6} Clinically, solitary mass formation is the main presentation, although systemic symptoms such as fever, weight loss are also common.\textsuperscript{1,4}

When neoplastic proliferation of cells with so-called histiocytic morphology is encountered, several neoplasms derived from phagocytes and accessory cells are often considered in differential diagnosis. World Health Organization Classification divides histiocytic and dendritic neoplasms as follows; histiocytic sarcoma, Langerhan cell histiocytosis, Langerhans cell sarcoma, interdigitating dendritic cell sarcoma/tumor, follicular dendritic cell sarcoma/tumor, dendritic cell sarcoma, not otherwise specified.\textsuperscript{1} This classification is based on their normal counterpart cells of origin, which can be readily identified nowadays by immunohistochemistry and electron microscopy. Histiocytic markers include CD68, lysozyme, alpha1-antitrypsin, CD21, CD23, and CD35.\textsuperscript{1,4} All of which were positive in the present case. Interdigitating dendritic cells and Langerhans cells show strong immunoreactivity for S-100 protein and CD21, supporting its ‘true’ histiocytic origin. The present case was negative for S-100 protein and CD21, supporting its ‘true’ histiocytic origin.

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presentation such as thrombocytopenia and anemia with splenic mass formation, as was described similarly in other countries. The present case also showed poor clinical outcome as other splenic cases did.\textsuperscript{8-10}

In conclusion, the primary splenic histiocytic sarcoma is a neoplastic proliferation of histiocytes with prominent hemophagocytosis. And it often causes poor clinical outcome mainly associated with profound thrombocytopenia and anemia. The present case displayed some clinicopathologic features same as several previous reports in other countries.\textsuperscript{8-10} The precise recognition of this rare but clinically aggressive entities would be important to increase the diagnostic accessibility for pathologists and to make an appropriate therapeutic choice for clinicians.

REFERENCES