A Case of Malignant Histiocytosis

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Malignant histiocytosis is a rare, usually fatal malignant neoplasm of reticuloendothelial systems. The disease is associated with fever, malaise, weight loss, hepatosplenomegaly, lymphadenopathy, pancytopenia, jaundice, and purpura.

A 44-year-old female patient is described who had multiple, purple crusted nodules and plaques in the skin. In the laboratory study, pancytopenia was noted on the peripheral blood. In addition many atypical histiocytes were seen on the bone marrow aspiration. A lesional biopsy showed nodular infiltrations of atypical histiocytes in the dermis and some erythrophagocytosis was seen. Immunohistochemically, the histiocytes were weakly stained for lysozyme and α-1-antichymotrypsin, but were unstained for S-100 protein, cytokeratin, CEA(carcinoembryonic antigen), pan T/B marker CD30(ki-1), UCHL-1 LCA(leukocyte common antigen), and α-1-antitrypsin. (Ann Dermatol 8:(3)201~205, 1996).

Key Words : Atypical histiocytes, Malignant histiocytosis.

In 1939, Scott and Robb-Smith first recognized and described the term "histiocytic medullary reticulosis". Since that time, many cases have been reported in the literature under a variety of terms including aleukemic reticulosis, histiocytic reticulosis, malignant leukemic reticulosidhistiocytosis, malignant reticulosis, and histiocytic leukemia. At present the term malignant histiocytosis (MH), introduced by Rappaport in 1966, is widely used.

The specific cutaneous lesions of MH have been estimated to occur in about 10-15% of cases. In our country, Hahn reported that cutaneous lesions were noted in 21% of 14 cases. The cutaneous lesions may consist of macules, papules, nodules, or plaques that often undergo necrosis or ulceration. The eruption favors the lower extremities.

We report one patient with the clinical and histopathological features of MH.

REPORT OF A CASE

A 44-year-old woman was referred to our department with asymptomatic, multiple, purple crusted nodules and plaques on the right shoulder, trunk, and right thigh (Fig. 1). About 3 months ago, she was treated for fever, headache, and malaise at a local clinic but failed to respond. Thereafter, about 3 weeks prior to admission, a solitary, erythematous plaque developed on the right upper arm. Then the lesions spread to the right shoulder, trunk, and right thigh with crusted nodules and plaques. At the same time, facial lesions of purple, scaly patches developed, and she was admitted to our hospital. The past and family history were non-contributory.

Her temperature was 39.3°C. She looked pale and had hepatosplenomegaly, but lymphadenopathy was not seen. In the laboratory study, pancytopenia was noted on the peripheral blood (Hb, 7.2 gm/dl; Hct, 21.8%; WBC, 560 /mm³; platelet, 57,000 /mm³), and elevated serum AST (240

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Table 1. The list and specificity of primary antibodies

<table>
<thead>
<tr>
<th>Source</th>
<th>Dilution</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-100 Protein</td>
<td>DAKO</td>
<td>1:100 Melanocytes, Langerhans cell</td>
</tr>
<tr>
<td>Cytokeratin</td>
<td>DAKO</td>
<td>1:50 Epidermis and its appendages</td>
</tr>
<tr>
<td>CEA</td>
<td>DAKO</td>
<td>1:300 Eccrine and apocrine glands</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>DAKO</td>
<td>1:200 Macrophages</td>
</tr>
<tr>
<td>α-1 antitrypsin</td>
<td>DAKO</td>
<td>1:50 Macrophages</td>
</tr>
<tr>
<td>α-1 antichymotrypsin</td>
<td>DAKO</td>
<td>1:50 Macrophages, fibrohistiocytic tumors</td>
</tr>
<tr>
<td>CD3</td>
<td>DAKO</td>
<td>1:50 Pan T cells</td>
</tr>
<tr>
<td>CD19</td>
<td>DAKO</td>
<td>1:50 Pan B cells</td>
</tr>
<tr>
<td>CD20</td>
<td>DAKO</td>
<td>1:50 Pan B cells</td>
</tr>
<tr>
<td>CD30(Ki-1)</td>
<td>DAKO</td>
<td>1:20 Hodgkin and Reed-Sternberg cells</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>HLA-DR</td>
<td>*B-D</td>
<td>1:20 Class II antigen</td>
</tr>
<tr>
<td>LCA(CD45)</td>
<td>DAKO</td>
<td>1:100 Leukocytes</td>
</tr>
<tr>
<td>UCHL-1(CD45RO)</td>
<td>DAKO</td>
<td>1:50 Mature activated T cells</td>
</tr>
<tr>
<td>CD68</td>
<td>DAKO</td>
<td>1:50 Monocytes, macrophages</td>
</tr>
</tbody>
</table>

*B-D:Becton-Dickinson

Fig. 1. Asymptomatic, multiple, purple crusted nodules and plaques on the right shoulder.

Fig. 2. Biopsy specimen taken from a cutaneous lesion of the right shoulder showing nodular infiltration of atypical histiocytes in the dermis (H&E, × 100).

Fig. 3. Dense infiltrates composed of atypical histiocytes with hyperchromatic, pleomorphic nuclei and vacuolated cytoplasm (H&E, × 200).

Fig. 4. Atypical cells, mitosis and erythrophagocytosis (arrow) (H&E, × 1,000).
IU/L) and ferritin (1,000 µg/dl, normal: <120 µg/dl) levels. Other laboratory findings were negative or within normal limits.

A biopsy specimen taken from a cutaneous lesion of the right shoulder revealed nodular infiltrations of tumor cells in the middle to lower portion of the dermis (Fig. 2). The subcutaneous fat layer was not involved in the biopsy specimen. The infiltrates were composed of atypical histiocytes with hyperchromatic, pleomorphic nuclei and pale or vacuolated cytoplasm (Fig. 3). Some mitosis and erythrophagocytosis were observed (Fig. 4). Another biopsy specimen from a facial lesion showed perivascular and periappendageal infiltration with inflammatory cells. Immunohistochemically (Table), tumor cells of cutaneous lesion were weakly stained for lysozyme and α-1 antichymotrypsin (ACT) (Fig. 5), but were unstained for S-100 protein, cytokeratin, CEA, CD3, CD20, LCA (CD45), UCHL-1 (CD45RO), CD30 (Ki-1), and α-1 antitrypsin (AT). Atypical histiocytes and erythrophagocytosis were shown on the bone marrow aspiration (Fig. 6). In immunohistochemical stains of the bone marrow, atypical cells were positive for CD68 of monocyte marker (Fig. 7), whereas they were negative for CD19, UCHL-1, and HLA-DR.

The patient was treated with combination chemotherapy regimens (CHOP: cyclophosphamide, 750mg/m²/day; doxorubicin, 50mg/m²/day; vincristine, 1.4mg/m²/day, and prednisolone, 40mg/m²/day). Due to the occurrence of erythrocytopenia and thrombocytopenia, a transfusion was done. 8 days after treatment she died, most likely due to sepsis.

**DISCUSSION**

The etiology of MH remains unknown, but some authors consider it to be an infection of parasite and oncogenic virus. The disease may be associated with a genetic predisposition and chromosomal aberration. In our case, the etiology is unknown. It has been reported in all age groups with a median age of 35 years. The disease appears to involve males with a greater frequency than females, in a ratio of 2:3:1.

In the laboratory findings, intramedullary phagocytosis of histiocyte is responsible for the progressive pancytopenia. It has been reported that a high concentration of serum ferritin in malignancy might be due to a number of causes: anemia,
tissue necrosis, and injury of liver function. Tumor cells are important for the high concentration of serum ferritin in patients with MH. This indicates that ferritin perhaps plays an important role in tumor cell differentiation. In our patient, the level of serum ferritin was 1,000 μg/dl. Lysozyme and angiotensin 1-converting enzyme may be elevated.

In the skin, there is perivascular and peripendageal infiltration of atypical histiocytes in the middle to lower dermis and in the subcutaneous fat. In advanced lesions, fat necrosis may occur. Some of the histiocytes contain phagocytized erythrocytes, leukocytes, and nuclear debris in their cytoplasm. In the organ of the liver, spleen, and lymph node, neoplastic atypical histiocytic proliferation occurs with erythropagocytosis.

Cytochemical and immunohistochemical studies have shown that the cells in MH are negative for chloroacetate esterase, Sudan black B, alkaline phosphatase and β-glucuronidase, whereas acid phosphatase and nonspecific esterase reaction revealed diffusely positivity. The diagnostic significance of classical markers of histiocytes (AT, ACT, and lysozyme) is dependent on its specificity and efficiency. AT and ACT are not specific for MH since they may occur in T-cell lymphomas. Lysozyme is considered to be a specific marker of histiocytes within the lymphoreticular system. In the course of the disease, the loss of detectable enzyme has been observed in the poorly differentiated atypical histiocyte. Therefore, the immunocytochemical detection of lysozyme activity may be a helpful confirmatory test in MH. Isaacscon and co-workers believed that AT is the single most reliable marker of malignant histiocytes because it does not vary with the degree of cellular atypia. Some authors have reported ACT antigens were found more consistently than lysozyme or AT antigens within malignant histiocytes. In the Nemes study, lysozyme proved to be a reliable marker in all cases of MH. In our case, the tumor cells were weakly stained for lysozyme and ACT.

Without treatment, the disease is usually progressive and fatal. The patient usually dies within 6 months of onset. The present understanding of therapeutic effectiveness is limited, because of the rarity of the disease, its rapid fatality, and frequent diagnosis at necropsy. However, the beneficial effect of cytotoxic treatment has been reported with combination chemotherapy regimens (usually cyclophosphamide, doxorubicin, vincristine, and prednisolone).

In the histologic differential diagnosis, the following disorders should be included: large cell anaplastic T cell lymphoma (Ki-1 lymphoma), hemophagocytic syndrome (HPS), histiocytosis X, and acute monocytic leukemia. The majority of previously diagnosed MH (more than 90 percent of the cases) are now regarded as Ki-1 lymphoma. Due to the large tumor cells, the fatal course, and frequent loss of lymphoid lineage antigens, most cases of large cell anaplastic T cell lymphoma were formerly regarded as MH. A characteristic for Ki-1 lymphoma is the expression of cell-surface-associated CD 30 antigen (Ki-1 antigen). The diagnosis of true MH is based on the demonstration of at least two histiocytic markers with a negative reaction to pan B/T antigens. HPS is characterized by fever, wasting, lymphadenopathy, hepatosplenomegaly, pancytopenia, and coagulopathy. Cytophagic histiocytic panniculitis fits within the spectrum of HPS, and the most consistent histopathologic feature in HPS is a proliferation of mature histiocytes that exhibit prominent erythropagocytosis and cytophagocytosis. In cytophagic histiocytic panniculitis, the histiocytes are reactive and are stimulated by T-cell lymphocytes. The clinical course of cytophagic histiocytic panniculitis and MH are inseparable, but histopathologic evaluation reveals predominantly atypical bizarre histiocytes in most cases of MH. Phagocytosis by obviously malignant histiocytes is relatively uncommon. Ducatman documented that cytophagic histiocytic panniculitis represents a low-grade form of MH, with involvement confined to the skin for a protracted period. The infiltrate in histiocytosis X is seen in the upper dermis with frequent invasion of the epidermis, and the tumor cells have a slightly foamy eosinophilic cytoplasm and few atypia. MH has been called a subleukemic form of monocytic leukemia.

REFERENCES

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A Case of Malignant Histiocytosis


