Syndrome of the Sea-Blue Histiocyte


A 39-year-old male was admitted with fever, systemic lymph node swelling, liver dysfunction and mild splenomegaly. Liver biopsy specimen showed histiocytic aggregation in portal areas. These histiocytes were closely packed with granules, dyed sea-blue with May-Giemsa staining. Further microscopical examination of lymph nodes, gastro-intestinal tract and bone marrow also revealed the accumulation of sea-blue histiocytes. Activities of lipid metabolic enzymes were normal and hematopoietic diseases which are sometimes accompanied by secondary sea-blue histiocytosis were ruled out. We diagnosed this case as syndrome of the sea-blue histiocyte. (Internal Medicine 35: 419-421, 1996)

Key words: lymph node, cirrhosis, May-Giemsa

Introduction

The syndrome of the sea-blue histiocyte is a rare disorder first described by Silverstein et al in 1970 (1). It was given the name due to the histiocyte color upon May-Giemsa staining. The etiology is unknown. The clinical course is usually benign but some cases develop fatal liver cirrhosis (2-4). Here, we are report a case of this syndrome with a review of the literature.

Case Report

A 39-year-old male was referred to our hospital for further examination of fever and systemic lymph node swelling in December 1993. He was not the product of consanguinous marriage. He has no brothers or sisters. He had a history of miliary tuberculosis-like pulmonary shadow in July 1992. At that time, cultures for tuberculosis from sputa and bone marrow were negative. The shadow disappeared spontaneously after one month. On physical examination, both the liver and spleen were slightly palpable. Lymph node swelling was detected in both the bilateral cervical and inguinal area which were elastic firm, measuring 1 to 2 cm in diameter.

Peripheral blood count was within the normal limits. Liver function tests showed a slight elevation of glutamic-oxalacetate transaminase (GOT) 53 IU/l, glutamic-pyruvic transaminase (GPT) 102 IU/l and alkaliphsphatase (ALP) 357 IU/l. Although immunological tests showed C-reactive protein of 16.6 mg/dl, anti-nucleus antibody of 80x (speckled type) and elevation of polyclonal IgG, the diagnostic criteria of systemic lupus erythematosis was not fulfilled. Hepatitis B surface antigen and antibody to HCV and HCV RNA were negative. There was no evidence of viral infection from the serological tests.

We conducted a liver biopsy because of the liver dysfunction. The specimen showed focal aggregation of foamy histiocytes in several portal areas (Fig. 1). There was neither fibrosis nor infiltration of lymphocytes. As the histiocytes were closely packed with granules dyed sea-blue with May-Giemsa staining, we made a preliminary diagnosis of syndrome of the sea-blue histiocyte and carried out biopsies of the gastrointestinal tract, bone marrow and lymph nodes.

Although there were no abnormal findings from total colonoscopy, biopsy specimens of the rectum revealed histiocytic aggregation in the submucosal area, and these histiocytes were also dyed blue with Giemsa staining (Fig. 2). Biopsy specimens of gastric mucosa and the left cervical lymph node also demonstrated the same histiocytic aggregation (data not shown). Bone marrow aspiration showed a nuclear cell count of $30.4 \times 10^4/\mu l$ and a myeloid erythroid ratio of 2.2, with many histiocytes dyed sea-blue with Giemsa staining (Fig. 3). There was no morphological abnormality of hematopoietic cells in bone marrow. Ophthalmological examination showed no abnormality. High fever and bilateral pleural effusion appeared in January 13, 1994 and we performed pleurocentesis. The pleural effusion showed a character of exdate, but bacterial cultures were cell negative. Cytology of effusion showed many histiocytes phagocytosing granulocytes (Fig. 4). The computer tomogra-
Figure 1. Histiocytes containing fine granules aggregate in the portal area of the liver (May-Giemsa stain, ×200).

Figure 2. Histiocytic aggregation in rectal mucosa (HE stain, ×200).

Figure 3. Sea-blue histiocyte in bone marrow (May-Giemsa stain, ×1,000).

Figure 4. Histiocytes phagocytose granulocytes in pleural effusion (May-Giemsa stain, ×600).

Table 1. Activities of Lipid Metabolic Enzymes in Leukocytes

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Patient</th>
<th>Mean±2SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sphingomyelinase</td>
<td>1.1</td>
<td>4.0±3.0</td>
</tr>
<tr>
<td>β-galactosidase</td>
<td>107</td>
<td>132±60</td>
</tr>
<tr>
<td>β-glucosidase</td>
<td>10.6</td>
<td>22±24</td>
</tr>
<tr>
<td>β-hexosaminidase</td>
<td>1,466</td>
<td>1,088±492</td>
</tr>
<tr>
<td>Arylsulfatase</td>
<td>62.4</td>
<td>77±32</td>
</tr>
</tbody>
</table>

*n mol/mg protein of leukocyte/h.

We tried biopsies again in June 1994, when he had no symptoms, in order to rule out secondary sea-blue histiocytosis including hematopoietic diseases and some infectious diseases. Sea blue histiocytes still existed in the liver, lymph node, gastrointestinal tract and bone marrow; thus, secondary histiocytosis was ruled out.

Activities of lipid metabolic enzymes in leukocytes (Table 1)

Activities of lipid metabolic enzymes in leukocytes were examined for differential diagnosis from lipid storage diseases including Nieman-Pick disease which also shows sea-blue histiocytosis. Sphingomyelinase was slightly decreased, but other enzyme activities were within the normal range. In conclusion, this patient was diagnosed as syndrome of the sea-blue histiocyte. The patient is presently followed up as an outpatient and there is no progression of liver dysfunction.

Discussion

Syndrome of the sea-blue histiocyte, firstly reported by
Syndrome of the Sea-Blue Histiocyte

Silverstein in 1970 is a congenital disease which is thought to be autosomal recessive. The clinical symptoms are abnormal liver function, abnormal lung shadow due to histiocyte invasion, splenomegaly with thrombocytopenia and lymph node swelling (1).

As for the cases of this syndrome reported previously, sex incidence is almost equal and age incidence of the patients ranges from one to 83 years, with an average of about 40 years at the time of diagnosis. About 15% of patients suffer death because of liver cirrosis. The size of the affected histiocytes is variable from 15–60 μm in diameter. They are dyed blue by May-Giemsa and brownish yellow on H-E staining.

Other diseases which show sea-blue histiocytosis are lipidosis including Nieman-Pick disease, some hematopoietic diseases and secondary states of some kinds of infection (5–8). In the present case, lipidosis and hematopoietic disease were ruled out by lipid enzyme activity and the clinical course (9), and syndrome of sea-blue histiocyte was conclusively diagnosed by the lack of histological change on the biopsies 4 months after discharge.

Although the exact mechanism of pleural effusion in this patient is unknown, the numerous histiocytes phagocytosing granulocytes seen in the effusion might be abnormally activated histiocytes in this disease. The mechanism of blue granule storage is also unknown. Sea-blue granules are thought to be formed from bilirubin or RBC in histiocytes in some cases, because erythrocytes or bilirubin are observed in phagocytic histiocytes (10).

Sixty-eight cases of syndrome of the sea-blue histiocyte have been reported in the world, but in Japan only one other case has been reported (10). The reason for the low number of reports in Japan is thought to be either a low frequency of this gene abnormality or it has been overlooked, as this disease is not generally known in Japan.

Silverstein et al reported the prognosis of this disease including a review of previous cases. In his report (1), seven of the nine patients had somewhat prolonged, but benign courses whereas two had progressive hepatic failure resulting in death. Purpura or bleeding was observed in seven of the nine patients, and thrombocytopenia was documented in four. Cirrhosis was observed in two.

Because liver function abnormality was relatively mild, the prognosis of the present case might be benign, but careful observation is needed.

If lymph node swelling, liver dysfunction and splenomegaly are noted, the syndrome of sea-blue histiocyte should be taken into consideration as a differential diagnosis and May-Giemsa staining is needed as the histiocytes of this disease may not to be recognized only by H-E staining.

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References