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Short Communication

Secondary Sea-blue Histiocytosis Derived from Niemann-Pick Disease

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Sea-blue histiocytosis is a rare disorder seen in patients with lipid metabolic or ceroid storage diseases. Sea-blue histiocytes are ceroid-laden macrophages detectable by May-Giemsa staining. We report a case of a 28-year-old woman diagnosed with Niemann-Pick disease at 2 or 3 years of age. To confirm this diagnosis, we examined her bone marrow, which revealed scattered foci containing aggregates of foamy macrophages. May-Giemsa staining identified blue-staining foamy macrophages, referred to as sea-blue histiocytes. In summary, we report the detection of sea-blue histiocytosis in an adult with Niemann-Pick disease. 〔*J Clin Exp Hematopathol 47(1) : 19-21, 2007*〕

Keywords : sea-blue histiocytosis, Niemann-Pick disease

INTRODUCTION

Sea-blue histiocytes, first described by Möschlin in 1947[1], are found in many lipid metabolic diseases. In 1970, Silverstein reported the syndrome of sea-blue histiocytosis[2]. This disorder is classified as either primary or secondary ; most cases are secondary to lipid metabolic diseases, such as Niemann-Pick disease, Fabry's disease, or ceroid storage diseases[3-5].

CLINICAL SUMMARY

A 28-year-old woman presented with acute abdominal pain, which continued into the next day. Emergent abdominal computed tomography revealed bleeding in the abdominal cavity and marked splenomegaly. Abdominal laparoscopy demonstrated bleeding from the corpus luteum of the right ovary. The patient was treated with coagulation therapy to stop the bleeding and a blood transfusion. Laboratory analysis of her peripheral blood exhibited anemia and thrombocytopenia (red blood cells : 255 x $10^4/\mu$l ; hemoglobin : 7.3 g/dl ; white blood cells : 4100/μl ; platelets : 7.7 x $10^4/\mu$l). The patient had been diagnosed with Niemann-Pick disease at two or three years of age at another hospital. To confirm the diagnosis of Niemann-Pick disease, we performed a bone marrow aspiration and biopsy. The patient did not complain of any central nervous system symptoms. Chest X-ray radiological examination did not reveal any abnormal findings.

IMMUNOHISTOCHEMICAL STAINING

Bone marrow specimens aspirated from the sternum were immediately immersed in 10% formalin. Paraffin-embedded sections of the bone marrow biopsy were prepared, deparaffinized in xylene, and rehydrated with a graded ethanol series. After washing three times in 0.01 M phosphate-buffered saline (PBS), pH 7.4, for 5 min each, sections were incubated at room temperature (RT) with 0.3% hydrogen dioxide in methanol for 20 min to eliminate endogenous peroxidase activity. After washing four times in PBS for 5 min each, sections were incubated for 2 hr with a mouse anti-human CD68 monoclonal antibody (KP-1, DAKO, Glostrup, Denmark) (dilution titer ; 1 : 300) at RT. After washing four times in PBS for 5 min each, sections were incubated for 20 min at RT with a biotinylated anti-rabbit immunoglobulin antibody (DAKO) (dilution titer ; 1 : 1,000), followed by incubation with Avidin-Biotin-Peroxidase complex (DAKO) for 20 min. Sections were then incubated for 5 min with diaminobenzidine-H_2O_2 solution (30 μg diaminobenzidine in 0.05 M Tris buffer). Positive immunohistochemical staining was confirmed by the production of brown dye.

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PATHOLOGICAL FINDINGS

Examination of a bone marrow core biopsy obtained from the sternum demonstrated a hypercellular marrow. Scattered foci containing aggregates of foamy histiocytes were observed (Fig. 1a, 1b). May-Giemsa staining revealed blue-staining foamy histiocytes, referred to as sea-blue histiocytes (Fig. 2). These histiocytes were stained blue by the Schmorl reaction (Fig. 3) ; a small number of these cells contained brown-colored pigments within the cytoplasm. The aggregated histiocytes stained with an anti-CD68 antibody, suggesting that these cells are derived from macrophages (Fig. 4).

ACIDIC SPHINGOMYELINASE ACTIVITY

Acidic sphingomyelinase enzymatic activity in peripheral blood leukocytes was low (0.73 nmol/mg/h) in comparison to normal (3.54 nmol/mg/h).

DISCUSSION

Examination of bone marrow specimens obtained from the sternum demonstrated scattered foci of aggregated foamy macrophages. May-Giemsa staining revealed sea-blue histiocytes, blue-staining foamy macrophages. These macrophages also stained blue with the Schmorl reaction. A small proportion of these cells contained collections of brown-colored

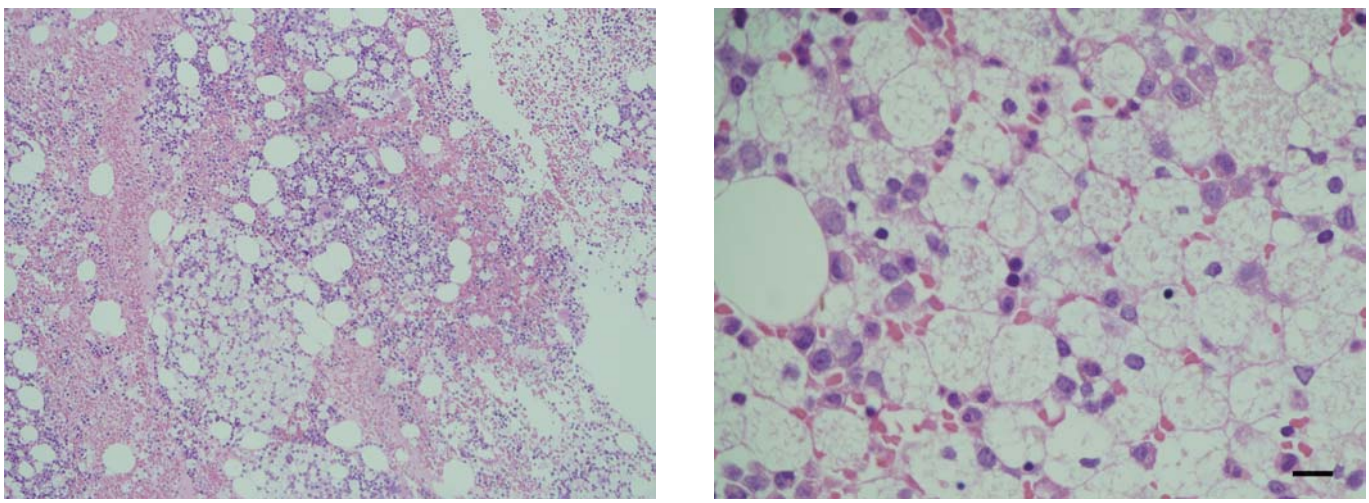

Fig. 1. Hematoxylin-eosin staining of bone marrow. (*1a*) Low-power view of the bone marrow specimen. (*1b*) High-power view of the specimen. Scattered foci of foamy histiocytes were present. *Bar* = 20 μm.

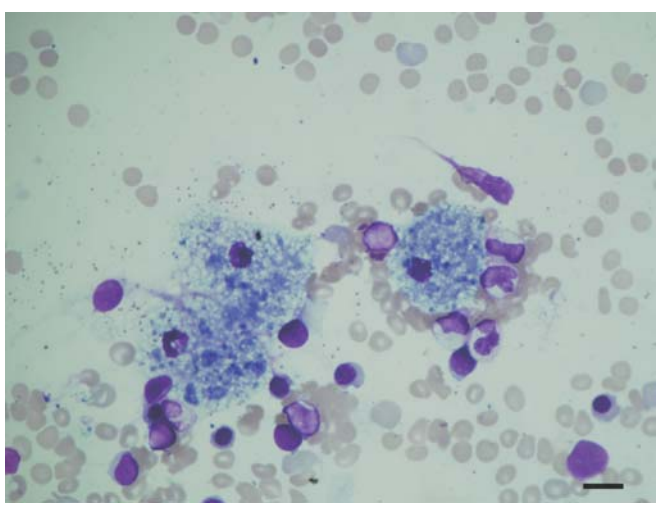

Fig. 2. May-Giemsa staining of the bone marrow smear. Multiple blue-colored granules were found in the cytoplasm of histiocytes. *Bar* = 20 μm.

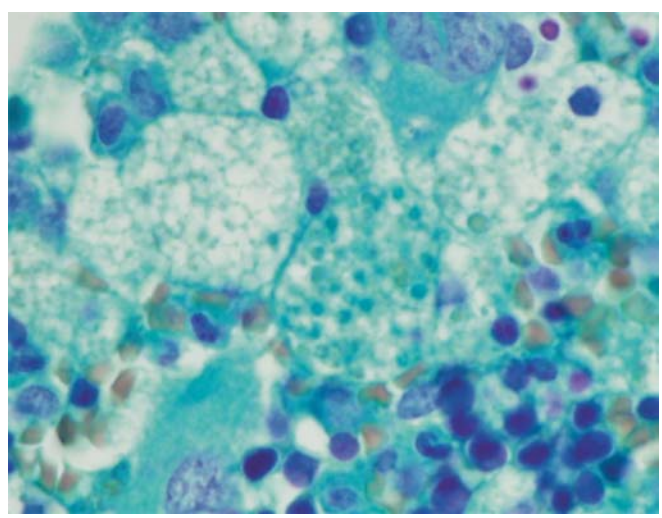

Fig. 3. Schmorl reaction of bone marrow specimens. Histiocytes were stained blue by the Schmorl reaction. Approx. × 400.

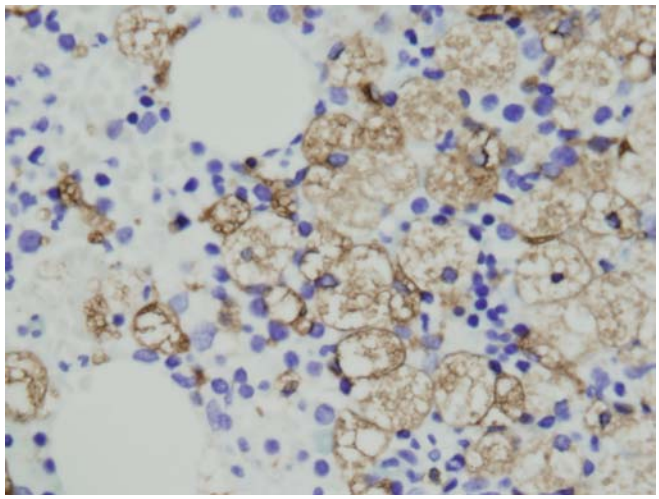

Fig. 4. CD68 immunostaining of bone marrow specimen. Aggregated histiocytes were positive for an anti-CD68 antibody by immunohistochemistry. Sample was counterstained with hematoxylin. × 200

pigments in the cytoplasm. These findings indicated that the observed sea-blue histiocytes were ceroid-laden macrophages secondary to Niemann-Pick disease.

To confirm that the appearance of the sea-blue histiocytes was secondary to Niemann-Pick disease, we measured acidic sphingomyelinase enzymatic activity in peripheral blood leukocytes. The acidic sphingomyelinase activity seen in peripheral blood leukocytes was lower (0.73 nmol/mg/h) than normal (3.54 nmol/mg/h), confirming a diagnosis of sea-blue histiocytosis secondary to Niemann-Pick disease. In general, the identification of aggregated foamy macrophages upon bone marrow examination should always prompt the performance of May-Giemsa staining, as the foamy macrophages may be sea-blue histiocytes.

The patient had no central neurological symptoms and has remained alive for a long period of time, suggesting that she has type B Niemann-Pick disease. Sea-blue histiocytes were first described by Möschlin in 1947[1]. In 1970, Silverstein initially reported the syndrome of sea-blue histiocytosis[2]. Sea-blue histiocytosis, which is observed in multiple lipid metabolic diseases, is typically classified as primary or secondary. Long *et al*.[6], however, questioned the existence of primary sea-blue histiocytosis, as most cases appear to be secondary to lipid metabolic diseases, such as Niemann-Pick disease[6-8]. If sea-blue histiocytosis is identified, a differential diagnosis including the various lipid metabolic disorders and ceroid storage diseases is helpful in determining the pathogenesis of the disease.

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