NOTE *Internal Medicine*

Disseminated Histiocytic Sarcoma with Excessive Hemophagocytosis in a Cat

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ABSTRACT. A 10-year-old Japanese domestic cat was presented with anorexia and weight loss. Severe anemia and thrombocytopenia were detected. Abdominal radiography and ultrasonography revealed the presence of multiple masses in the spleen. Cytological analyses of the masses revealed several atypical histiocytic cells and considerable hemophagocytosis. A splenectomy was performed, and the mass was diagnosed as histiocytic sarcoma on the basis of histopathological, cytochemical and immunohistochemical analyses. Further, abnormal hemophagocytosis was observed in the bone marrow. The cat was administered prednisolone and lomustine, and it survived for 107 days after admission. An autopsy revealed the presence of neoplastic histiocytic cells in the bone marrow, liver, pancreatic lymph node and glomeruli. This is the first case of histiocytic sarcoma in a cat to be reported in Japan.
KEY WORDS: feline, hemophagocytosis, histiocytic sarcoma.

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Among histiocytic malignancies, histiocytic sarcoma (HS) is characterized by the presence of a solitary tumor, while disseminated HS is the term used to describe the condition with metastases to distant sites. Malignant histiocytosis (MH) is the condition wherein neoplasms simultaneously arise at multiple sites [8, 12]. Because HS progresses rapidly, the primary and metastatic sites become indistinguishable; therefore, it is difficult to clinically differentiate disseminated HS and MH. These conditions are uncommon in both dogs and cats [1, 4, 6, 7, 10, 14, 15, 17, 19, 21, 22]. Here, we report a case of HS in a cat characterized by excessive hemophagocytosis and the presence of splenic masses.

A 10-year-old neutered female domestic shorthaired cat presented with anorexia and weight loss over 2 months was referred to the Veterinary Medical Center at the University of Tokyo. No palpable lymphadenopathy was detected. A complete blood count performed on initial presentation revealed the presence of regenerative anemia (packed cell volume (PCV), 17%; reference range, 30–45%) and thrombocytopenia (10,000 cells/μl; reference range 200,000–800,000 cells/μl). A blood smear examination revealed severe anisocytosis and polychromatocytosis, and the presence of nucleated erythrocytes. No parasitic organisms were detected in the blood on microscopic examination. The blood biochemical profile was normal. The results of Direct Coombs' test were negative, and feline immunodeficiency virus (FIV) antibodies and feline leukemia virus (FeLV) antigens were not detected. Abdominal radiography revealed hepatosplenomegaly, and abdominal ultrasonography revealed the presence of 2 round masses arising from the spleen. Cytological analysis of the splenic masses, which was performed by fine-needle aspiration revealed extramedullary hematopoiesis and the presence of large abnormal histiocytoid cells with abundant hemophagocytic appearances. Not only mature erythrocytes but also erythroblasts were being phagocytosed as well. These histiocytoid cells were pleomorphic and had distinct multiple nucleoli (Fig. 1A). Cytochemical analyses revealed positive staining for alpha-naphthylbutyrate esterase (α-NBE) and inhibition of this enzyme by sodium fluoride; these results indicated that the observed cells originated from a monocyte or macrophage lineage (Fig. 1B).

Splenectomy followed by bone marrow evaluation was performed on day 19 after admission. Ecchymoses were observed on the surfaces of the 2 round masses (Fig. 2). There was no abdominal hemorrhage. No other abnormalities were observed within the abdominal cavity on macroscopic examination. On histopathological analysis, the masses were found to have scattered hemorrhagic and necrotic foci, extramedullary hematopoiesis, and a cobblestone-like appearance owing to the proliferation of large histiocytoid cells predominantly in the red pulp (Fig. 3A). These cells were round to polygonal in shape and had abundant vacuoles, erythrocytes and hemosiderin within the cytoplasm; the nuclei were round to oval in shape with fine chromatin and distinct nucleoli. Anisocytosis and anisokaryosis were also evident. Immunohistochemical analyses revealed that the cells did not express CD3 (as determined by using the rabbit anti-human CD3 polyclonal antibody; Dako Japan Inc., Tokyo, Japan) [2, 7, 9] and CD79a (as determined by using the mouse anti-human CD79a monoclonal antibody; Dako Japan Inc.) [2, 3, 7, 9] but strongly expressed lysozyme (as determined by using rabbit anti-human lysozyme polyclonal antibody; Dako

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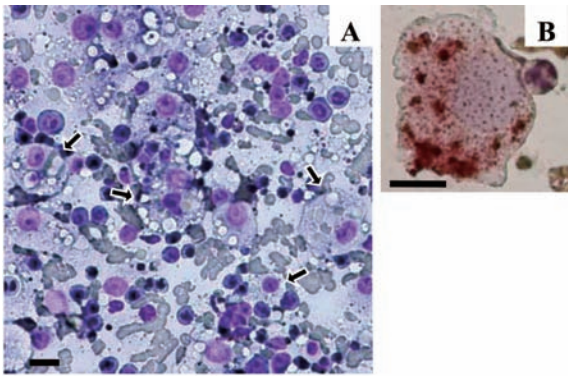

Fig. 1. Fine-needle aspirates of the splenic mass. (A) Large histiocytic cells engulfing erythrocytes (arrows) and extramedullary hematopoiesis are apparent (Wright-Giemsa staining; bar=10 μm). (B) Large atypical histiocytic cells showing erythrophagocytosis and positive staining for α-naphthylbutyrate esterase (bar=10 μm).

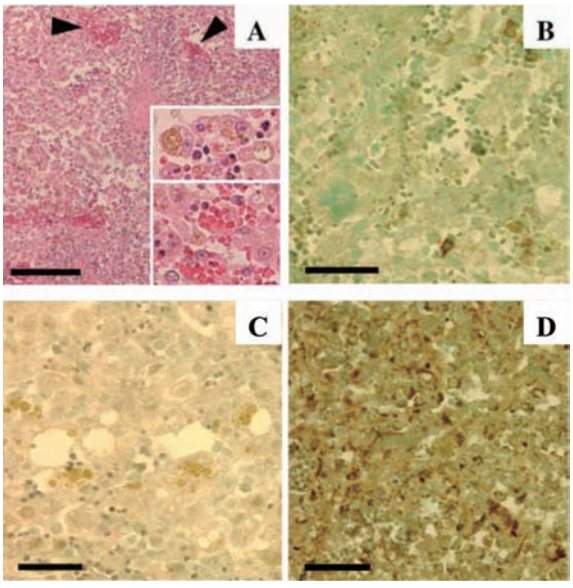

Fig. 3. Section of the splenic mass on histopathological examination. (A) Hemorrhagic spots are observed (arrowheads) (hematoxylin-eosin stain; bar=100 μm). Tumor cells containing hemosiderin and erythrocytes are shown in magnified images. Immunohistochemistry performed using antibodies against CD3 (B), CD79a (C) and lysozyme (D) (bar=25 μm). The tumor cells were stained negative for both CD3 and CD79a but positive for lysozyme.

Japan Inc.) [16] (Fig. 3B-D). Considering these results and the fact that the cells stained for α-NBE, it was concluded that these cells originated from histiocytes. Meanwhile, the bone marrow aspirate was cytologically evaluated. The cellularity was slightly increased, and erythroid hyperplasia was observed (myeloid/erythroid ratio, 0.36; reference range, 1.3–2.1). The abnormal histiocytic cells that were observed in the splenic masses were also occasionally

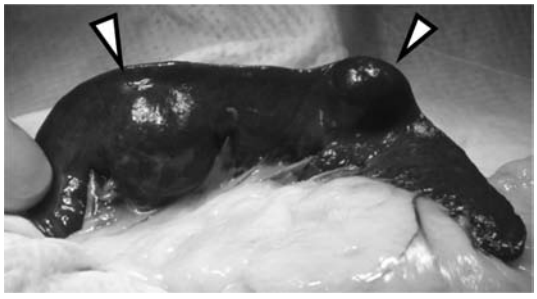

Fig. 2. Macroscopic view of the spleen during splenectomy. Two round splenic masses are observed (arrowheads).

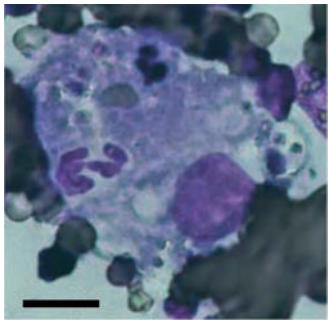

Fig. 4. A histiocytic cell which phagocytosed neutrophil found in the bone marrow specimen (bar=10 μm).

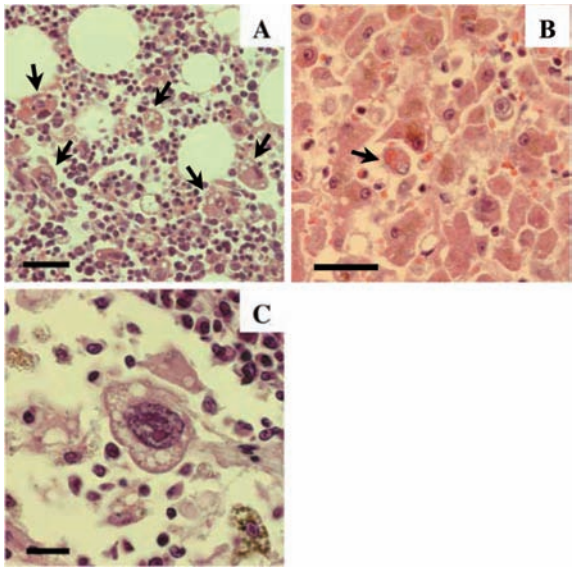

Fig. 5. Histopathological analyses of sections of the bone marrow (A), liver (B) and pancreatic lymph node (C) obtained during autopsy. Infiltrated malignant histiocytic cells are denoted by arrows (A and B; hematoxylin-eosin staining; bar =25 μm) and in magnified images (C; hematoxylin-eosin staining, bar=10 μm).

observed in the bone marrow. The cells were found to phagocytose not only erythrocytes but also erythroid progenitors and neutrophils (Fig. 4). On the basis of these findings, we diagnosed the condition as disseminated HS.

Although prednisolone (1.5 mg/kg BID) was administered daily from day 32 after admission, the anemia and thrombocytopenia were not ameliorated. On day 57, we initiated palliative chemotherapy with oral lomustine (CeeNU; Bristol-Myers Squibb, Princeton, NJ) at a dose of 50 mg/m^2. Two weeks later, leukopenia was observed with the leukocyte count being 4.1×10^3 cells/μl. Thereafter, leukopenia and thrombocytopenia gradually resolved but anemia persisted, and intermittent blood transfusions were required. The second dose of lomustine (60 mg/m^2) was administered 3 weeks after the first, and no consequent adverse effects such as gastrointestinal complications were observed. The cat died on day 107 after initial presentation.

An autopsy was conducted, and multiple organs were subjected to histopathological analyses. The bone marrow was reddish brown, and microscopic analyses revealed the presence of numerous neoplastic cells (Fig. 5A). Macroscopic examination of the liver revealed the presence of reddish puncta (1–2 mm in diameter) on its surface, and the hepatic lobular structures could not be distinguished. Histopathological analysis revealed extramedullary hematopoiesis as well as infiltration and proliferation of neoplastic cells within the hepatic sinusoid and parenchyma (Fig. 5B). Further, malignant cells were found in the pancreatic lymph nodes (Fig. 5C) and renal glomeruli. However, the brain, heart, lungs, gastrointestinal tract, uterus, thyroid gland and adrenal gland were not affected.

To the best of our knowledge, this is the first reported case of HS in a cat in Japan. In previously reported cases of HS or MH in cats, the affected animals had nonspecific signs, and the laboratory findings commonly included regenerative or nonregenerative anemia and thrombocytopenia [4, 6, 7, 10, 21, 22]. Additionally, hemophagocytosis was noted in the spleen, liver and bone marrow in some cases [4, 6, 7, 10]. The findings in the present case were consistent with those in previous reports. The case of a cat with HS showing poorly demarcated infiltrative lesions in the spleen was recently reported [7]; inconsistent with this report, the cat in the present case had splenic masses.

Differentiating the condition from lymphoma and determining the origin of the tumor cells are essential for the diagnosis of HS and MH [23]. Various markers such as lysozyme, alpha-1-antitrypsin, Mac 387 and MHC-II, and techniques such as the fluoride inhibition of nonspecific esterase have been used for diagnosis [1, 4, 6–8, 10, 11, 21, 22]. Antibodies against CD1c and MHC-II were not available for the present study. However, on the basis of the positive results obtained for lysozyme and α-NBE staining, the negative results for CD3 and CD79a staining, and the clinical and histopathological features of the condition, we diagnosed the tumor as malignant neoplasms affecting histiocytes. In a variant form of HS that affects dogs, wherein the tumor cells originate from macrophages, the findings include prominent hemophagocytosis and cell proliferation in the splenic red pulp and bone marrow with secondary liver involvement [11, 13]. The findings of present case resemble this characteristics.

In both dogs and cats, the prognosis of HS is extremely poor, and the condition progresses rapidly. Lomustine has been used as a chemotherapeutic agent for dogs with this condition [20]. The trial dose of lomustine administered in the present case was based on the doses previously administered to cats suffering from various malignancies [5, 18]. However, this dose was found to be ineffective. Therefore, future studies should focus on the development of an effective treatment strategy for this condition.

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