

8개월 동안 발열을 보인 환자에서 골수검사로 진단된 조직구육종 1예

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A Case of Histiocytic Sarcoma Diagnosed by Bone Marrow Biopsy in a Patient Suffering from Fever for 8 Months

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Histiocytic sarcoma is a malignant proliferation of cells showing morphologic and immunophenotypic features similar to those of mature tissue histiocytes and is known for its rapid progression and poor prognosis. We describe a case of histiocytic sarcoma diagnosed by bone marrow biopsy. A 64-yr-old male was admitted for fever and weight loss that persisted for 8 months. The patient died undiagnosed on the 7th hospitalization day. A bone marrow biopsy performed just before the patient's death revealed diffuse proliferation of large pleomorphic neoplastic cells with large, round to oval nuclei, vesicular chromatin, and abundant foamy cytoplasm. These cells were positive for histiocytic markers, CD68, lysozyme, CD21, and S-100 protein, but negative for B-cell, T/NK-cell, and epithelial cell markers, thus confirming the presence of histiocytic sarcoma. (*Korean J Lab Med* 2009;29:282-5)

Key Words : *Histiocytic sarcoma, Bone marrow biopsy, Immunohistochemistry*

INTRODUCTION

Histiocytic sarcoma is a rare neoplasm characterized by the malignant proliferation of cells that have the morphologic and immunophenotypic features of mature tissue histiocytes [1]. It is an aggressive neoplasm with poor prognosis, and the mechanism underlying its pathogenesis is still unknown [1]. Characteristic features of this sarcoma include the appearance of a solitary mass with systemic manifestations such as fever and weight loss.

Histiocytic sarcoma can be diagnosed on the basis of the morphological features of the histiocytic lineage and by excluding the possibility of lymphoma and other poorly differentiated large-cell malignancies [2]. The diagnosis is confirmed if the biopsy results are positive for more than one immunophenotypic marker for mature histiocytic cells (e.g., CD68, lysozyme, CD11c, and CD14) and negative for myeloid markers (e.g., myeloperoxidase, CD33, and CD34), accessory/dendritic cell markers (CD1a, CD21, and CD35), CD30, HMB-45, epithelial membrane antigen, or keratin [1]. Histiocytic sarcomas usually occur in the intestinal tract, skin, and soft tissues [1]; therefore, diagnosis of these sarcomas by bone marrow biopsy has rarely been reported. We report a case of histiocytic sarcoma diagnosed by bone marrow biopsy just before the patient's death.

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CASE REPORT

A 64-yr-old man presented with fever of unknown origin (FUO), which persisted for 8 months. The diagnostic tests for FUO performed in the previous hospital did not help determine the cause of the fever; therefore, he received only symptomatic therapy with drugs such as antipyretics and empirical antibiotics for 8 months. Since whole-body positron emission tomography (PET) revealed several high-intensity lesions in the bone, intestine, skin, and soft tissues, multiple bone metastases were suspected. However, no specific findings were obtained on performing 3 bone biopsies and several lymph-node and soft-tissue biopsies. Bone marrow biopsy revealed marked reactive plasmacytosis, mild reactive eosinophilia, mild reactive histiocytosis, and characteristics of anemia of chronic disease. Despite all these efforts, the cause of fever could not be found. The patient was discharged after being prescribed empirical anti-tuberculosis medication.

However, he was rehospitalized for dyspnea about 2

months later. Physical examination only revealed that he had pitting edema of the leg. A complete blood count showed a leukocyte count of 14,300/mL with 1% myelocytes, 1% metamyelocytes, 74% neutrophils, 11% lymphocytes, 9% monocytes, 3% eosinophils, and 1% atypical lymphocytes. Normoblasts were also seen at a frequency of 1 per 100 WBCs. The hemoglobin was 8.3 g/dL, and the platelet count was 60,000/ μ L. Serum biochemistry revealed an elevated total bilirubin level of 10.7 mg/dL (reference interval: 0.2–1.2 mg/dL), alkaline phosphatase level of 388 IU/L (reference interval: 40–120 IU/L), and gamma glutamyl transferase level of 201 IU/L (reference interval: 11–63 IU/L). The aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LD) levels were normal. The total protein level was 6.6 g/dL (reference interval: 6–8 g/dL) and the albumin level, 1.3 g/dL (reference interval: 3.3–5.2 g/dL); serum electrophoresis revealed polyclonal gammopathy. The ferritin concentration was 4,252 ng/mL (reference interval: 20–320 ng/mL). Coagulation tests revealed that the prothrom-

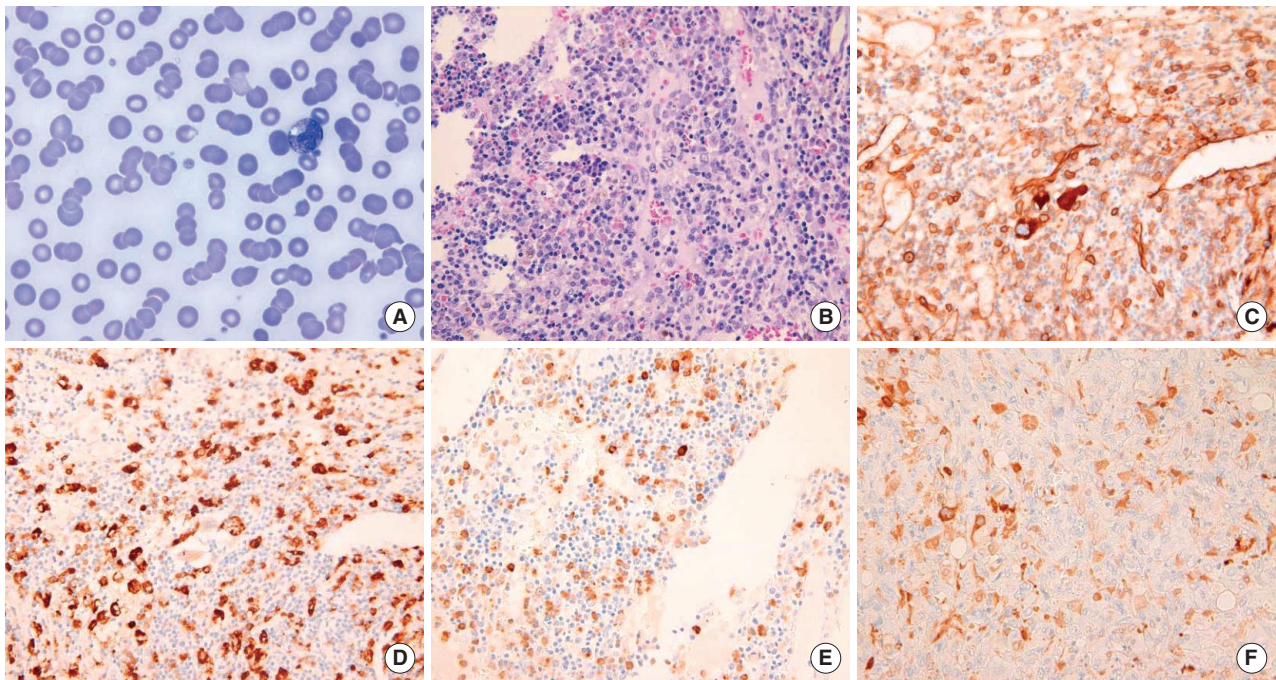


Fig. 1. Morphologic and immunohistochemical features of the peripheral blood and bone marrow specimen. (A) Rouleaux formation in the peripheral blood smear (Wright stain, $\times 1,000$). (B) Biopsy specimen showing high cellularity, diffuse fibrosis, and large pleomorphic neoplastic cells (H&E stain, $\times 400$). (C) Biopsy specimen showing CD31+ (immunohistochemistry, $\times 400$). (D) Biopsy specimen showing CD68+ cells (immunohistochemistry, $\times 400$). (E) Biopsy specimen showing lysozyme-positive cells (immunohistochemistry, $\times 400$). (F) Biopsy specimen showing S100 protein-positive cells (immunohistochemistry, $\times 400$).

bin time was 19.0 sec (reference interval: 10–13 sec), activated PTT was 50.5 sec (reference interval: 25.0–35.0 sec). The concentration of fibrinogen was 552 mg/dL (reference interval: 200–400 mg/dL); that of fibrinogen degradation product, 40.0 μ g/dL (normal: negative); that of D-dimer, 2.00 μ g/mL (reference interval: <0.4 μ g/mL); and that of antithrombin III, 28% (reference interval: 80–120%). Direct Coombs test was positive, and blood and urine cultures were negative. A chest radiograph revealed increased heart size, diffuse peribronchial infiltration in the middle zone of both the lungs, and prominent interstitial markings in both lungs. Computed tomography of the abdomen and upper pelvis showed the presence of hepatosplenomegaly and multiple osteolytic lesions in the lumbar spine and left acetabulum. Bone marrow biopsy was refused by the patient. He did not respond to a 4-day dexametha-

sone therapy and died because of respiratory failure.

Bone marrow biopsy and liver biopsy were obtained just before his death. Bone marrow aspiration failed because the aspirate contained little or no marrow. The bone marrow biopsy showed a cellularity of over 95%, diffuse fibrosis, increased number of sinusoids, and diffuse non-cohesive proliferation of large pleomorphic neoplastic cells with large, round to oval nuclei, vesicular chromatin, and abundant foamy cytoplasm (Fig. 1). Immunohistochemistry revealed cells that were CD99⁺, vimentin⁺, S100⁺, CD31⁺, CD68⁺, lysozyme⁺, CD21⁺, CD4⁺, CD56⁺, cytokeratin⁻, SMA⁻, SMMHC⁻, and HMB45⁻ (Table 1). Reactive lymphocytes were positive for CD3, CD20, and CD79 α . Masson trichrome staining revealed fine collagen fibers, and iron staining revealed increased hemosiderin. Liver biopsy showed non-specific hepatitis, and there was no evidence of malignancy. The diagnosis of histiocytic sarcoma was confirmed by the presence of the morphologic and immunohistochemical features described above.

Table 1. Comparison of the immunohistochemical features of histiocytic sarcoma in this case and several other reported cases

Antibody	This case	Yoshida et al. (2007) [2]	Park et al. (2006) [7]	Paik et al. (2005) [8]	Kim et al. (1999) [9]
CD68	+	+	+	+	+
Lysozyme	±	+	+	+	+
CD163	NT	±	NT	NT	NT
CD79 α	-	-	NT	NT	NT
CD20	-	-	NT	NT	-
CD21	±	NT	NT	-	NT
CD3	-	-	NT	-	-
CD4	±	+	NT	NT	NT
CD13	NT	NT	NT	NT	-
CD30	NT	NT	-	-	NT
CD31	+	NT	+	NT	NT
CD34	NT	NT	-	NT	-
LCA	NT	NT	+	+	NT
CD45RO	NT	NT	+	NT	-
CD56	-	-	NT	NT	NT
CD99	+	NT	NT	NT	NT
CD117	NT	NT	-	NT	NT
CD138	NT	-	NT	NT	NT
S100 protein	+	-	-	-	+
Desmin	NT	NT	-	NT	NT
Vimentin	+	NT	NT	NT	NT
Cytokeratin	-	-	NT	NT	NT
HMB45	-	NT	NT	-	NT
SMMHC	-	NT	NT	NT	NT
SMA	-	NT	-	NT	NT
EMA	NT	-	NT	-	NT

Abbreviations: NT, not tested; LCA, leukocyte common antigen; HMB, human melanoma black; SMMHC, smooth muscle myosin heavy chain; SMA, smooth muscle actin; EMA, epithelial membrane antigen.

DISCUSSION

The recent WHO classification defined histiocytic sarcoma as a malignant proliferation of cells showing morphologic and immunophenotypic features similar to those of mature tissue histiocytes [1]. Histological sections of sarcomas usually show large, round to oval neoplastic cells with abundant cytoplasm. Hemophagocytosis occurs occasionally in the neoplastic cells [1]. The immunohistochemical profile shows the expression of lysosomal (macrophage/histiocytic) markers such as CD68 (in 100% cases), lysozyme (in 98% cases), CD11c, CD14 with the absence of myeloid markers (CD33, CD34, and myeloperoxidase), and accessory/dendritic cell markers [1, 3]. Pileri et al. [3] recommended immunostaining for CD68, lysozyme, CD1a, S100 protein, CD21, and CD35 for the differential diagnosis of histiocytic and accessory dendritic cell neoplasms. CD163, a hemoglobin scavenger receptor, has been suggested as a novel diagnostic marker for histiocytic malignancies [4]. In our case, the bone marrow of the patient was infiltrated with proliferating large pleomorphic neoplastic cells

that had large, round to oval nuclei, vesicular chromatin, and abundant foamy cytoplasm. These cells were positive for histiocytic markers, CD68, lysozyme, CD21, and S-100 protein, but negative for B-cell, T/NK-cell, and epithelial cell markers. Therefore, we could confirm the diagnosis of histiocytic sarcoma by excluding the possibility of lymphoma, carcinoma, and melanoma.

Histiocytic sarcoma occurs in individuals across a wide age range; it is mostly found in adults (median age, 46 yr) with a predilection for males [5]. In the majority of the cases, it occurs in extranodal sites, most commonly the intestinal tract, skin, and soft tissues [1]. The cause or pathophysiology is still unknown, except, possibly, when mediastinal germ cell tumors are the precursor lesions [3, 6].

In Korea, several cases of histiocytic sarcoma were reported. Two cases were diagnosed on the basis of a solitary mass in the rectum [7] and spleen [8]. In one case, the diagnosis was based on the results of bone marrow biopsy [9]. Their immunohistochemical profiles showed the presence of macrophage/histiocyte markers and the absence of myeloid and lymphoid markers (Table 1).

The prognosis of histiocytic sarcoma is poor [5]. Most patients (60–80%) expire due to progressive disease, because they are diagnosed too late [3, 4]. However, some patients with small, localized primary tumors have a more favorable long-term outcome [3]. Some patients have shown more than 10 yr of disease-free survival [10]. With regard to cases in Korea, a patient with histiocytic sarcoma presented with a 2-cm rectal mass and survived for 32 months without relapse [7]. A patient with a multinodular splenic mass showed 15 months of disease-free survival [8]. In contrast, a patient with disseminated histiocytic sarcoma diagnosed by bone marrow biopsy, died only 5 months after diagnosis [9].

In our case, a PET scan of the 64-yr-old male patient showed multiple high-density lesions in the bone, intestine, skin, and soft tissue. However, there was no evidence of malignant histiocytic proliferation in the bone, soft-tissue, lymph-node, and liver biopsies. The patient suffered from FUO and weight loss for 8 months. Performing diagnostic tests for FUO 3 times did not help determine the cause of the fever. He showed no response to

empirical anti-tuberculosis medication and dexamethasone therapy and died from respiratory failure. The diagnosis was made posthumously on the basis of a bone marrow biopsy taken just before his death.

Understanding this exceedingly rare malignancy is highly important in order to diagnose and treat the patient in time.

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