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Histiocytic Sarcoma of the Spleen
- A Case Report and Review of the Literature -

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True histiocytic sarcoma is an extremely rare tumor. Its clinicopathological features are not clearly understood. Here, we report the first Korean case of primary splenic histiocytic sarcoma. A 64-year-old female having refractory thrombocytopenia, anemia and splenic mass was admitted to the hospital, and received splenectomy. Grossly, spleen was enlarged up to 18×13×8 cm and occupied with multinodular masses. Microscopically, the masses were composed of atyical large cells with abudant cytoplasm and vesicular nuclei with prominent hemophagocytosis. The tumor cells were CD68 (+), S-100 protein (-), CD21 (-), CD1a (-). After splenectomy, thrombocytopenia and anemia were corrected. However two months later the symptoms recurred, and the patient died 15 months after splenectomy. This case shared the common clinicopathologic features with the several previously reported cases in other countries, represented by splenic mass formation and prominent hemophagocytosis associated with thrombocytopenia and anemia, often leading to poor outcome.

Key Words : Histiocytic sarcoma; Spleen; Thrombocytopenia

Histiocytic neoplasm is one of the rarest tumors in hematopoietic and lymphoid system. Although several cases have already been reported, the scarcity of cases still restricts the understanding of its biologic behavior.[1] Furthermore, historical confusion of the diagnostic terminology, so-called 'histiocytic' lymphoma used in the Rapparport classification for describing large T- or B-cell lymphoma, has also made it difficult to isolate 'true histiocytic' neoplasm among previously reported cases. True histiocytic sarcoma is characterized by CD68 (+), S-100 protein (-), CD1a (-), CD21 (-) in immunohistochemistry, and the presence of lysosomes but absence of Birbeck granules, junctions, desmosomes, or cytoplasmic projections in electron microscopy. In Korea, a few localized histiocytic neoplasms with immunohistochemical or ultrastructural studies have been described.[2,3] However, primary splenic histiocytic sarcoma has not been reported yet. Here we report the first Korean case of primary splenic histiocytic sarcoma. In addition, based on the present case and review of literature, we demonstrate that splenic histiocytic sarcoma is characteristically accompanied by prominent hemophagocytosis and thrombocytopenia.

CASE REPORT

A 64-year-old woman was admitted to Seoul National University Hospital (SNUH) because of exertional dyspnea and intermittent dizziness for one month. She also complained of easy bruisablility which had appeared one year ago. Laboratory test showed thrombocytopenia (platelet 17,000/μL), macrocytic normochromic anemia (hemoglobin 7.2 g/dL, MCV 118 fL, MCH 34 pg) with negative direct/indirect Coombs' test, and a raised reticulocyte count (15.8%). WBC count was $5.6\times10^3/\mu$L (segmented neutrophil 80%, lymphocyte 8.7%, monocyte 2.9%, eosinophil 1.5%). LDH was increased up to 777 IU/L. Total protein and albumin concentration in serum was decreased to 5.2 and 2.9 g/dL. Antinuclear antibody, Mycoplasma antibody,

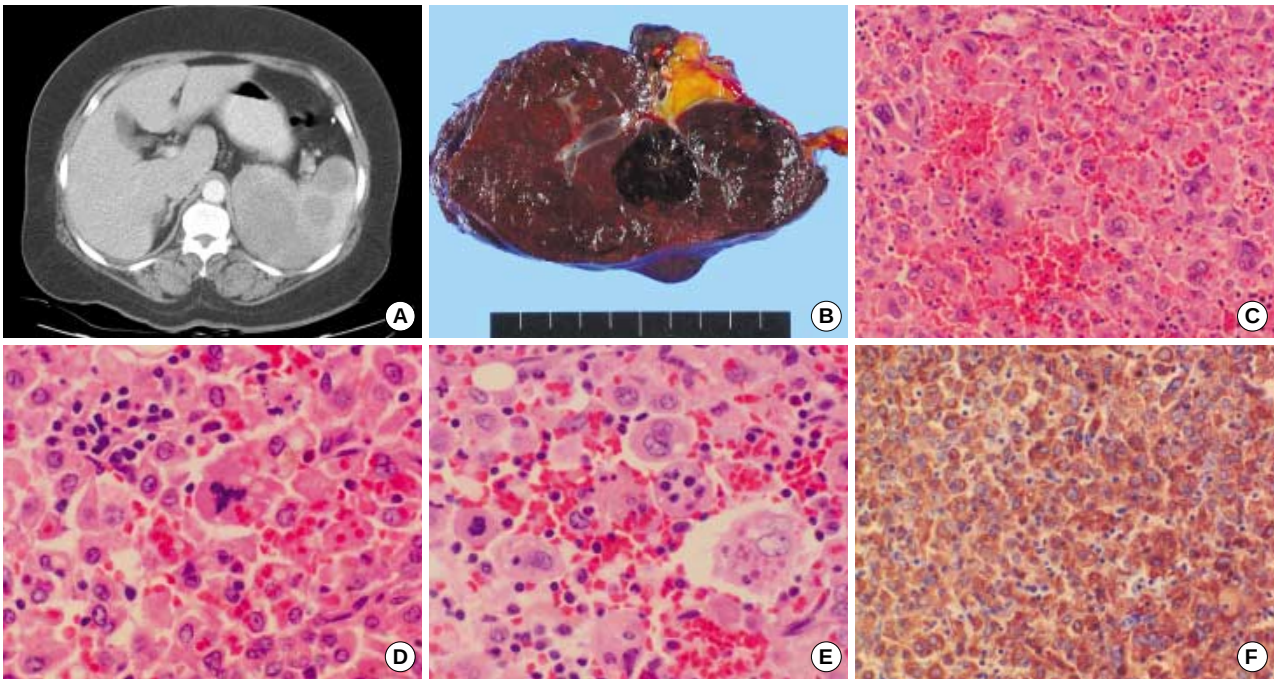

Fig. 1. On CT scan (A) and cut surface of gross specimen (B), multinodular masses replacing entire spleen are shown. (C) The masses are composed of atypical large cells with abundant eosinophilic cytoplasm and vesicular nuclei, with occasional mitotic figures including atypical mitosis (D) and hemophagocytic activity (E). (F) The tumor cells are diffuse strong positive for CD68 immunostaining.

cold agglutinin, anti-HCV antibody, HBs antigen and Ham's test were all negative. Bone marrow examination disclosed hypercellular marrow with erythroid and megakaryocytic hyperplasia. Abdominal CT scan revealed splenomagaly with multiple low attenuating masses (Fig. 1A). Neither high dose dexamethasone nor intravenous immunoglobulin showed any effect on thrombocytopenia of the patient. It was also refractory to platelet transfusion. Therefore, splenectomy was performed for both diagnostic and therapeutic purposes.

Grossly, spleen was enlarged up to $18 \times 13 \times 8$ cm. On the cut surface, brown to tan-colored multinodular mass lesion replaced the entire spleen (Fig. 1B). Microscopically, the mass-forming area was filled with large cells with histiocytic morphology and hemophagocytic activity. They had abundant eosinophilic cytoplasm and round to oval and vesicular nuclei (Fig. 1C). They showed variable degrees of nuclear atypia and occasional mitotic figures including atypical mitosis (Fig. 1D). Atypical multinucleated cells were also frequently observed. RBCs, degenerated RBCs, and leukocytes were observed in the cytoplasm of the tumor cells (Fig. 1E). Outside of mass-forming area was compressed and had relatively well-preserved red pulp and white pulp structures. However, scattered tumor cells were also noted in the sinuses. In immunohistochemistry, large hemophagocytic cells were diffusely strong positive for leukocyte common antigen (LCA), CD68 (PG-M1), and lysozyme, and alpha1-antitrypsin, and negative for S-100 protein, myeloperoxidase, CD21, CD1a, CD3, L26, CD30, ALK, epithelial membrane antigen (EMA), and HMB-45 (Fig. 1F). EBV in situ hybridization for EBV-encoded RNA (EBER) 1 and 2 was negative. Monoclonal proliferation of B- or T-cells was not observed in the result of gene rearrangement study for immunoglobulin heavy chain and T-cell receptor gamma chain.

The patient dramatically recovered from thrombocytopenia and anemia after splenectomy. However, platelet count abruptly decreased within two months after splenectomy, and did not recover over 50,000/μL. Under the suspicion of tumor recurrence, chemotherapy was with started bleomycin, vincristine and prednisolone eighth month after splenectomy. Nevertheless, the patient deteriorated with persistent refractory thrombocytopenia, and died 15 months after splenectomy due to pneumonia, probably complicated by long-term use of prednisolone.

DISCUSSION

Histiocytic sarcoma is defined as a malignant proliferation of cells showing morphologic and immunophenotypic features similar to those of mature tissue histiocytes. It shows expression of

Table 1. Clinicopathologic features of primary splenic histiocytic sarcoma

	Case 1[8]	Case 2[8]	Case 3[8]	Case 4[9]	Case 5[10]	The present case
Age/Sex	29/M	60/M	66/F	38/M	71/F	64/F
Initial symptom	Tibial edema	Tibial edema	Tibial edema	General weakness	General weakness	Exertional dyspnea
Hypoproteinemia	+	+	+	NA	NA	+
Anemia/Thrombocytopenia	+–/+	+–/+	+/+	NA/+	+/+	+/+
Hepatomegaly	–	–	–	–	–	–
Lymphadenopathy	–	–	–	–	–	–
Tumor size (cm)	17×13×8	8×8×8	1×1~3×3	~1.5	14×12×10	18×13×8
Splenectomy to recurrence	3 yr	4 mo	6mo	NA	6 mo	2 mo
Splenectomy to death	5 yr 1 mo	1 yr 6 mo	2 yr 6 mo	NA	7 mo	1 yr 3 mo
Cause of death	Pneumonia	GI bleeding	Brain hemorrhage	NA	NA	Pneumonia
Involved organ at autopsy	Liver	Liver, BM	Liver, BM	NA	(Liver[a])	NA

[a] indicates the case that autopsy was not done, but involvement was identified on biopsy; BM, bone marrow; +, present: –, absent; +–, borderline; NA, not applicable; yr, year; mo, month.

one or more histiocytic markers but no accessory/dendritic cell markers, and is not associated with acute monocytic leukemia.[1] It is a rare tumor reported in lymph nodes and multiple extranodal sites including gastrointestinal tract, bone marrow, skin and central nervous system.[1,4-6] Clinically, solitary mass formation is the main presentation, although systemic symptoms such as fever, weight loss are also common.[1,4]

When neoplastic proliferation of cells with so-called histiocytic morphology is encountered, several neoplasms derived from phagocytes and accessory cells are often considered in differential diagnosis. World Health Organization Classification divides histiocytic and dendritic neoplasms as follows; histiocytic sarcoma, Langerhans cell histiocytosis, Langerhans cell sarcoma, interdigitating dendritic cell sarcoma/tumor, follicular dendritic cell sarcoma/tumor, dendritic cell sarcoma, not otherwise specified.[1] This classification is based on their normal counterpart cells of origin, which can be readily identified nowadays by immunohistochemistry and electron microscopy. Histiocytic markers include CD68, lysozyme, alpha1-antitrypsin,[1,4] all of which were positive in the present case. Interdigitating dendritic cells and Langerhans cells show strong immunoreactivity for S-100 protein and MHC Class II antigens, and follicular dendritic cells express CD21, CD23, and CD35.[1,4] The present case was negative for S-100 protein and CD21, supporting its 'true' histiocytic origin.

Historical misuse of the term, 'histiocytic', is now almost corrected by the advances of immunohistochemical technique. The so-called 'diffuse histiocytic lymphoma' is now mainly categorized as diffuse large B-cell lymphoma. The previously called 'histiocytic medullary reticulosis' and 'malignant histiocytosis' were defined as systemic malignant disease of histiocytes affecting the entire reticuloendothelial system at initial presentation, often with severe clinical symptoms. Most cases of them are now thought to be systemic anaplastic large cell lymphoma or malignant lymphoma of T-cell or B-cell linage with abundant reactive histiocytes.[1,4,6,7] Other cases of them are regarded as hemophagocytic syndrome,[1] which is non-clonal or non-neoplastic proliferation of histiocytes, frequently associated with viral infection. Taken together, the 'true histiocytic' neoplasm is thought to be extremely rare[4,7] and the distinction of it from non-histiocytic or non-neoplastic disorder always requires immunophenotyping and consideration of clinical settings.

Primary splenic histiocytic sarcoma shows some unique features, shared by the previously reported splenic cases[8-10] and the present case, different from the cases of other primary sites[2,5] (Table 1). All cases were characterized by prominent hemophagocytosis by neoplastic cells, which resulted in severe thrombocytopenia and anemia.[8-10] In fact, hemophagocytosis is supposed to be the feature more commonly seen in reactive cells than in tumor cells,[1,4] which frequently makes it difficult to distinguish the neoplastic hemophagocytic cells from reactive hemophagocytic cells. However, the mass formation in the spleen and the distinct atypism of infiltrating histiocytes are thought to be important features discriminating primary splenic histiocytic sarcoma from secondary splenic involvement of so-called 'systemic malignant histiocytosis' or hemophagocytic syndrome.[8-10] In addition, hypoproteinemia is another remarkable feature of splenic histiocytic sarcoma, which was also reported in previous splenic cases[8] (Table 1).

In Korea, three localized tumors with 'true histiocytic' differentiation by immunohistochemistry or electron microscopy have been reported.[2,3] They included one case localized in liver with hemophagocytosis but no anemia or thrombocytopenia,[2] and two cases in skin and tonsil with no mention about hematologic complication.[3] Therefore, the present case is the first Korean case of primary splenic histiocytic sarcoma showing typical clinical

presentation such as thrombocytopenia and anemia with splenic mass formation, as was described similarly in other countries. The present case also showed poor clinical outcome as other splenic cases did.[8-10]

In conclusion, the primary splenic histiocytic sarcoma is a neoplastic proliferation of histiocytes with prominent hemophagocytosis. And it often causes poor clinical outcome mainly associated with profound thrombocytopenia and anemia. The present case displayed some clinicopathologic features same as several previous reports in other countries.[8-10] The precise recognition of this rare but clinically aggressive entities would be important to increase the diagnostic accessibility for pathologists and to make an appropriate therapeutic choice for clinicians.

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