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CASE REPORT

Primary histiocytic sarcoma of the spleen associated with hemophagocytosis

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Abstract We report a patient with primary histiocytic sarcoma of the spleen associated with prominent hemophagocytosis. Although thrombocytopenia, probably due to hemophagocytosis, was refractory to corticosteroid therapy, the transfusion of platelets, and splenic irradiation, partial splenic embolization was effective and facilitated splenectomy for a diagnosis. The majority of the spleen showed necrosis, but viable neoplastic cells with pleomorphic nuclei and abundant cytoplasm, showing occasional erythrocytes or leukocytes, were still discernible. The neoplastic cells expressed CD68, lysozyme, and S-100 protein, and were negative for lymphoid, myeloid, and epithelial cell markers. CD163, a monocyte/macrophage-specific molecule, was positive in only some of them. Despite multiagent chemotherapy, the patient died of the disease, showing a rapidly progressive clinical course. Although the preoperative diagnosis of primary splenic histiocytic sarcoma is difficult, it has been confirmed in patients with splenomegaly of unknown etiology that clinicolaboratory features suggestive of hemophagocytosis may be important clues suggestive to the disease. CD163 expression by neoplastic cells could be confirmed only after careful observation, because the molecule may only be seen in some of the neoplastic cells.

Keywords Histiocytic sarcoma · Spleen · Hemophagocytosis

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1 Introduction

Histiocytic sarcoma can be defined as "a malignant neoplastic process whose normal counterpart is a mature tissue histiocyte" [1]. In the past, the term "histiocytic" was used for cells in various states of reactive and neoplastic proliferation, such as histiocytic lymphoma, malignant histiocytosis, histiocytic medullary reticulosis, etc. However, the majority of cases that have been included in these categories were later found to be of nonhistiocytic origin, and the remaining true histiocytic neoplasms constitute a category of histiocytic sarcoma. Thus, "true" histiocytic sarcoma is a rare neoplasm primarily involving lymph nodes, the skin, and intestine, and that involving multiple sites may be referred to as "true" malignant histiocytosis. Because primary histiocytic sarcoma of the spleen is extremely rare, accounting for only 17% (3/18) according to a recent large series [2], its clinicopathologic features have not been well characterized.

In this study, we report the difficulty in obtaining a sample for pathologic examination as well as in the hematopathologic interpretation by describing such a patient showing prominent hemophagocytosis.

Table 1 Laboratory findings on admission

Peripheral blood		**Chemistry**	
WBC	7,400/μl	TP	5.0 g/dl
Stab.	8%	ALB	3.0 g/dl
Seg.	83%	T.Bil	1.7 mg/dl
Lymph.	5%	AST	30 IU/L
Eosino.	0%	ALT	18 IU/L
Baso.	1%	LDH	311 IU/L (110–225)
Mono.	3%	ALP	291 IU/L
RBC	171 × 10^4/μl	BUN	16.7 mg/dl
MCV	116.3 fl	Cre	0.5 mg/dl
Hb	6.2 g/dl	**Serology**	
PLT	0.5 × 10^4/μl	CRP	0.3 mg/dl
Coagulation		Soluble IL-2R	2,980 U/ml
PT-INR	1.11	Ferritin	175 ng/ml
APTT	30.0 S		
Fibrinogen	524 mg/dl		

2 Case report

A 58-year-old woman was admitted to our hospital because of dyspnea on exertion. She had no other symptoms such as fever, weight loss, nor night sweat. On physical examination, the spleen was found to have enlarged and was palpable 4 cm below the left costal margin. No hepatomegaly nor peripheral lymphadenopathy was evident. A complete blood count showed anemia and thrombocytopenia, but the leukocyte count was within the normal range, with normal differential counts (Table 1). The serum lactate dehydrogenase and soluble IL-2R levels were slightly elevated. Bone marrow aspiration showed no atypical cells and no hemophagocytosis, with a normal karyotype. An abdominal computed tomography scan identified splenomegaly, and a tumor showing a heterogeneous nodular appearance (Fig. 1). Based on these findings, malignant lymphoma was first considered in the differential diagnosis. Although splenectomy was attempted to confirm the diagnosis, thrombocytopenia persisted despite high-dose corticosteroid therapy, the transfusion of platelets, and splenic irradiation (15 Gy). However, partial splenic embolization resulted in a gradual increase in the platelet count, allowing us to perform splenectomy (Fig. 2).

At surgery, the liver was of normal consistency and appearance, and exploration of the abdomen showed no evidence of metastatic lesions. The resected spleen weighed 800 g and measured 14.5 × 8.5 × 9.5 cm. When sectioned, most areas of the spleen showed necrosis due to embolization of the splenic artery, but a small portion around the splenic hilus appeared to be still viable and was occupied by multiple, ill-defined nodules (Fig. 3a, b). Histologically, these nodules were composed of numerous

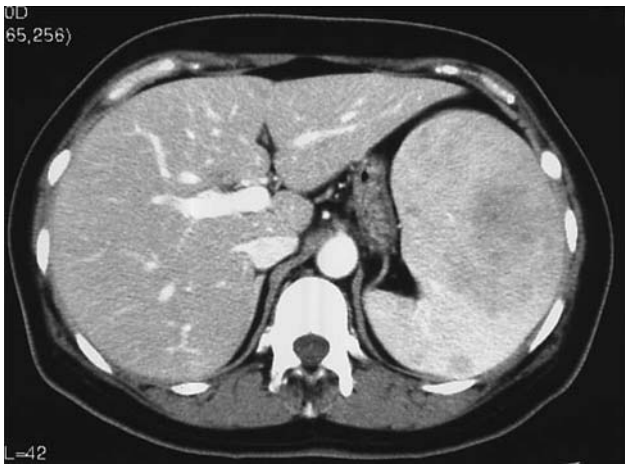

Fig. 1 Abdominal computed tomography scan reveals splenomegaly and a tumor showing a heterogeneous nodular appearance

medium-sized and large cells containing abundant, pale to eosinophilic cytoplasm and polymorphic nuclei with moderately condensed chromatin and medium-sized to large nucleoli (Fig. 3c). Numerous giant cells, with bizarre-shaped and lobulated nuclei, were dispersed among the earlier mentioned neoplastic cells. Some of the tumor cells displayed phagocytic activity for erythrocytes or leukocytes (Fig. 3d). Immunohistochemically, the majority of tumor cells expressed CD15, CD68 (both KP-1 and PG-M1) (Fig. 3e), CD74, S-100 protein, LN-5, lysozyme, and fascin. Furthermore, some of the tumor cells, other than the giant cells with bizarre-shaped and lobulated nuclei, were positive for CD163 (Fig. 3f). Tumor cells revealed no staining for CD1a, CD3ε, CD4, CD21, CD30, CD31, CD34, CD45, CD45RO, epithelial membrane antigen, keratin, von Willebrand factor, HMB-45, nor myeloperoxidase. Southern blot analysis of splenic tissue for the antigen receptor genes (immunoglobulin heavy chain and the T-cell receptor δ, γ, or β chain genes) showed no clonally rearranged bands. These clinical and laboratory findings led us to a diagnosis of histiocytic sarcoma, stage I_E disease.

After splenectomy, thrombocytopenia was improved, but the platelet count still remained around 20,000/μL. The patient was treated via multiagent chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) and DeVIC (etoposide, carboplatin, ifosfamide, and dexamethasone), but the tumor progressed to the liver. The patient died of the disease, showing a rapidly progressive clinical course, 3 months after the diagnosis. Permission for autopsy was not granted.

3 Discussion

The common primary sites of histiocytic sarcoma have been shown to be the lymph nodes, skin, and gastrointestinal tract

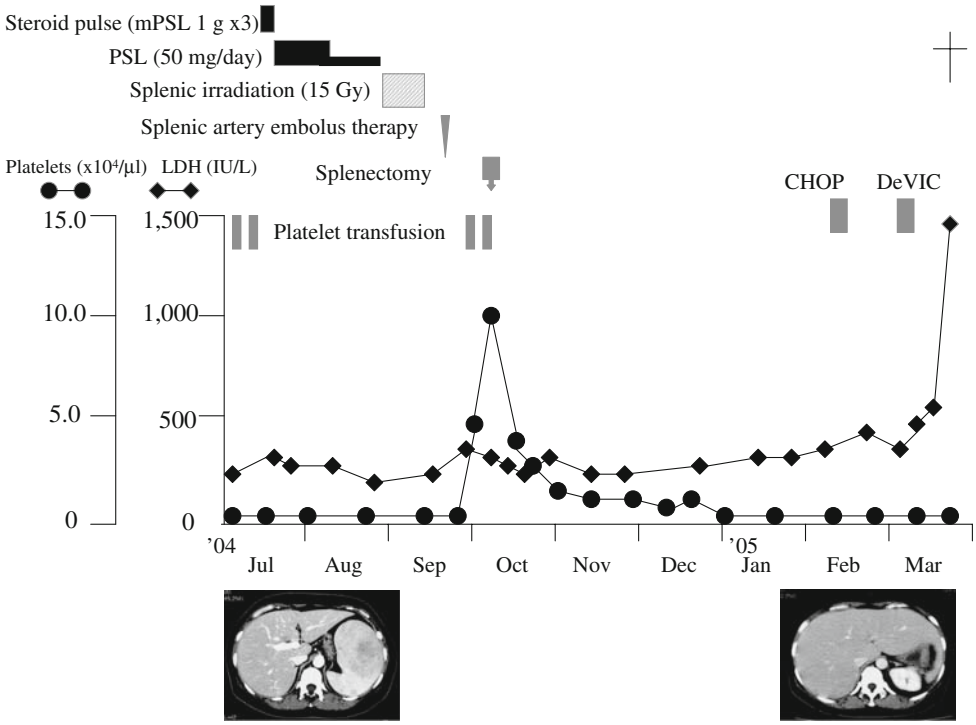

Fig. 2 Clinical course

[2–6]. In contrast to the frequent secondary splenic involvement of histiocytic sarcoma, especially at the terminal stage of the disease, primary splenic histiocytic sarcoma appears to be rare, with a rate of only 17% according, for example, to the International Lymphoma Study Group [2], and only a few cases have been described in detail [7–9]. One of the characteristic features of histiocytic sarcoma is the presence of hemophagocytic activity in histiocytes even after neoplastic transformation. Although this feature was observed in only one out of five patients with histiocytic sarcoma in a previous report [3], all the five patients with primary splenic histiocytic sarcoma were reported to exhibit hemophagocytic activity [7–9]. In our patient, thrombocytopenia was one of the most prominent and serious clinical features, to which neither corticosteroid therapy nor the infusion of platelets was effective. Splenic irradiation, which is one of the therapeutic options in chronic idiopathic thrombocytopenic purpura (ITP) with minor adverse effects [10], was not effective, either. Embolization of the splenic artery is used to improve thrombocytopenia by hypersplenism due to liver cirrhosis, thalassemia major, and chronic ITP, although complications such as splenic rupture and splenic abscess formation can rarely occur [11]. We, therefore, applied partial splenic embolization to our patient, and could achieve a significant enough improvement of the platelet count to perform splenectomy.

The neoplastic cells of our case were polymorphic, with abundant cytoplasm, and showed hemophagocytosis. They were immunohistochemically positive for CD68, lysozyme, and S-100 protein. In addition, they were negative for molecules related to B cells, T cells, accessory/dendritic cells (except for S-100 protein), myeloid cells, epithelial cells, and melanocytes. Furthermore, the clonal rearrangement of antigen receptor genes was not detected by Southern blot analysis. These features fulfill the criteria of histiocytic sarcoma put forward by the WHO [1]. Recently, CD163, a hemoglobin scavenger receptor, has been recognized as a new macrophage-related differentiation marker, which is more specific than the conventional histiocyte-related molecules, such as CD68 and lysozyme [3]. In our case, however, only some of the neoplastic cells, other than giant cells with bizarre-shaped and lobulated nuclei, expressed this molecule. The heterogeneous pattern of expression of CD163 among CD68-positive neoplastic cells might have been involved with the nonimmnunoreactivity of CD163 for splenic white pulp macrophages [12]. In other words, the pattern of CD163 expression may not be uniform in histiocytic sarcomas, although the molecule is rather specific to cells of the histiocytic lineage.

Clinically, it is generally accepted that most patients with histiocytic sarcoma show a limited response to chemotherapy, and a high mortality rate is a usual clinical outcome [1–6]. In the literature, all of the seven reported patients with a fatal outcome had progressive disease [2], while some of the patients presenting with skin or clinically localized disease showed a favorable long-term outcome [5]. A relationship between tumor

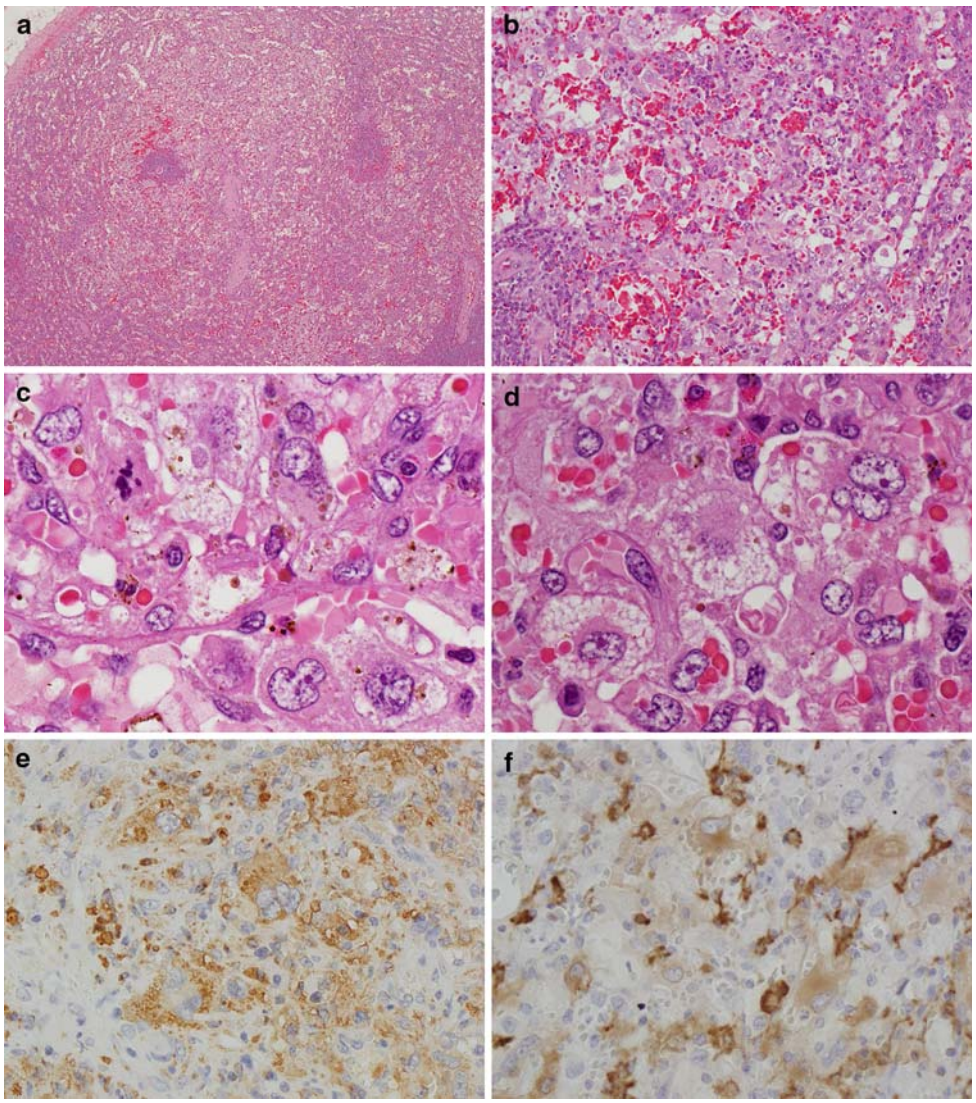

Fig. 3 Histological and immunohistochemical features of the resected spleen. **a** Several ill-defined, small nodules present in the splenic parenchyma; *white pulps* are spared in this image (H&E stain, ×4 objective). **b** The cells have proliferated rather loosely, with erythrocytes among them; *white pulp* is present (*lower left*) (H&E stain, ×20 objective). **c** At this higher magnification, the neoplastic cells are medium-sized to large and consist of irregular nuclei with clumped chromatin, more than one nucleolus, and abundant eosinophilic or foamy cytoplasm; hemosiderin granules can be seen in some of them; a cell undergoing mitosis is evident (*upper left*) (H&E stain, ×100 objective). **d** The neoplastic cells contain some erythrocytes in their foamy cytoplasm; a few eosinophils are also seen (*upper center*) (H&E stain, ×100 objective). **e** Atypical cells are positive for CD68 (PG-M1) in their cytoplasm (immunoperoxidase stain with hematoxylin counter-stain, ×40 objective). **f** Some of the atypical cells show weak, diffuse cytoplasmic positivity for anti-CD 163. Juxtanuclear, intense staining is noted in one of them (*upper center*) (immunoperoxidase stain with hematoxylin counter-stain, ×40 objective)

size and prognosis has also been pointed out [3]. It is of note that the prognosis of patients with primary splenic histiocytic sarcoma is characterized by a fatal clinical outcome in spite of splenectomy with/without chemotherapy [2, 7, 9]. Although an earlier diagnosis and initiation of treatment is mandatory for such a highly malignant neoplasm as histiocytic sarcoma, this approach is not generally applicable to primary splenic histiocytic sarcoma, in which an earlier diagnosis is hampered by difficulty in obtaining materials for histopathologic examination because of the frequent association of thrombocytopenia due to the hemophagocytic activity of neoplastic cells. When a patient shows splenomegaly of unknown etiology and hemophagocytosis, splenic histiocytic sarcoma should be included in the differential diagnosis. It is, therefore, important to accumulate cases of primary splenic histiocytic sarcoma to characterize the clinicopathologic features and to better modify the current treatment strategy, as well as to determine the pattern of CD163 expression.

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