Case Report
A case report of disseminated histiocytic sarcoma

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Abstract: Background: Histiocytic sarcoma (HS) is an extremely rare and aggressive malignant neoplasm. Most of the HS cases reported before are now considered to be T-lineage-associated hematolymphoid neoplasms. This report describes a case of pathological verified HS. Main observations: A 59-year-old Chinese man presented to the clinic with complains of weight loss and hypodynamia. Histopathological examination revealed a predominant population of large non-cohesive cells with bizarre pleomorphic shape, lobulated nuclei and abundant foamy cytoplasm. Immunohistochemistry was positive for KP-1 (CD68), CD14, lysozyme, Vim, LCA and S100, but negative for CD1a, CD21, CD35, CD3, CD56, CD30, EMA, ALK, SOX-100 and HMB45. The clinical presentation of enlarged lymph nodes and malignant mass within retroperitoneum, as well as the H&E and a panel of immunohistochemical staining made the diagnosis of histiocytic sarcoma. Conclusion: We describe a case report of HS which is verified by immunohistochemical examination and discuss the clinical and pathological presentations, diagnosis, therapy and genetic alterations underlying this uncommon neoplasm. Invasive progression and lack of effective treatment methods of HS deprive the survival chance of this patient. Early diagnosis methods and novel therapies are urgent be developed.

Keywords: Histiocytic sarcoma, immunohistochemical, case

Introduction
Histiocytic sarcoma (HS) is an extremely rare and aggressive malignant neoplasm derived from histiocytes which are part of the mononuclear phagocyte system. The abnormal histiocytes typically affect the liver, spleen, lymph nodes, and bone marrow [1]. The tumor cells are characterized by the positive histiocytic markers (KP-1 (as known as CD68), CD163, or lysozyme), negative T/B cell markers (CD3, CD20), negative dendritic cell markers (CD21, CD35), negative Langerhans cell markers (CD1a, langerin), and lack of Birbeck granules under electron microscopy [2, 3]. Most of the HS cases reported before are now considered to be T-lineage-associated hematolymphoid neoplasms, such as diffuse large B-cell lymphoma or anaplastic large cell lymphoma because the overlapping histologic features and inadequate phenotypic data [4]. This report describes a case of immunohistochemically verified HS.

Case report
A 59-year-old Chinese man presented to our hospital after experiencing weight loss and hypodynamia over the past half year. He had no other symptoms. Laboratory findings in other clinic were as follows: hemoglobin 9.8 mg/dl, fasting blood-glucose 6.1 mmol/L, glycosylated hemoglobin 7.5%, decrease of serum iron, total iron binding force, ferritin and iron saturation and thyroid function was normal. Abdominal ultrasound showed multiple low echo masses in upper abdomen. A computed tomography scan showed a nodular shadow in the right lobe of liver near diaphragm. Hypoferric anemia, diabetes, carcinoma were suspected. He subsequently started on chalybeate, but improvement was little. Physician considered the anemia was attributed to chronic diseases, and bone marrow aspiration was suggested, but he refused. Persistent complaining of hypodynamia and the high blood-glucose led him walk to the endocrinologist’s clinic, and he was admit-
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Figure 1. Enlarged lymph node localized in neck (A), groin (B) and supraclavicular fossa (C, D) measuring 11×7 mm to 27×15 mm with dot blood flow signal.
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There were no positive findings on physical examination after admission. Abnormal laboratory findings were as follows: transferrin 1.4 g/L, ferritin 3708.3 μg/L, unsaturated transferrin 23.6 μmol/L, serum iron 4.2 μmol/L, total iron binding capacity 27.8 μmol/L, pro-BNP 1118.0 pg/mL, CPK30 U/L, CK-MB29 U/L, LDH353 U/L, AST38 U/L, Na134 mmol/l, Ca2.01 mmol/l, Hb96 g/L, neutrophils percentage 92.9%, lymphocyte percentage 4.9%, eosinophils percentage 0.3%.

Abdominal ultrasound imaging after admission showed splenomegaly. Bone marrow aspiration was performed several times, but failed to aspirate bone marrow. The marrow films revealed that it was actually peripheral blood cells with toxic granules in granulocytes. Lymphatic ultrasonic Imaging showed multiple abnormal lymphadenectasis localized in neck, groin, and supraclavicular on both sides and the left armpit. Some lymph nodes show blood flow signals (Figure 1).

Then the lymph node biopsy was performed. After that patient's condition deteriorated suddenly and rapidly, with his direct bilirubin concentration rising from 8.8 to 171 μmol/L, hepatosplenomegaly, pancytopenia, hallucination, poor appetite and

### Table 1. Immunohistochemistry results

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Major cell specificity</th>
<th>Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK</td>
<td>Epithelial cell (Keratin)</td>
<td>-</td>
</tr>
<tr>
<td>EMA</td>
<td>Epithelial cell (Epithelial membrane)</td>
<td>-</td>
</tr>
<tr>
<td>Vim</td>
<td>Mesenchymal tissue</td>
<td>+++</td>
</tr>
<tr>
<td>S100</td>
<td>Melanocytes, histiocytes</td>
<td>+++</td>
</tr>
<tr>
<td>CD1a</td>
<td>Langerhan’s cell</td>
<td>-</td>
</tr>
<tr>
<td>CD21</td>
<td>Dendritic cell</td>
<td>-</td>
</tr>
<tr>
<td>CD35</td>
<td>Dendritic cell</td>
<td>-</td>
</tr>
<tr>
<td>CD3</td>
<td>T lymphocytes</td>
<td>-</td>
</tr>
<tr>
<td>CD20</td>
<td>B lymphocytes</td>
<td>+</td>
</tr>
<tr>
<td>MPO</td>
<td>Myeloid cell</td>
<td>-</td>
</tr>
<tr>
<td>CD56</td>
<td>NK cell</td>
<td>-</td>
</tr>
<tr>
<td>CD34</td>
<td>Blood vessel</td>
<td>++</td>
</tr>
<tr>
<td>CD117</td>
<td>Gastrointestinal stromal cell</td>
<td>-</td>
</tr>
<tr>
<td>HMB45</td>
<td>Melanocytes</td>
<td>-</td>
</tr>
<tr>
<td>LCA (CD45)</td>
<td>Leukocyte</td>
<td>+++</td>
</tr>
<tr>
<td>KP-1 (CD68)</td>
<td>Histiocytes/macrophage</td>
<td>+++</td>
</tr>
<tr>
<td>lysozyme</td>
<td>Histiocytes/macrophage</td>
<td>+++</td>
</tr>
<tr>
<td>CD14</td>
<td>Mainly histiocytes/macrophage</td>
<td>+++</td>
</tr>
<tr>
<td>SMA</td>
<td>Smooth muscle cell</td>
<td>-</td>
</tr>
<tr>
<td>P63</td>
<td>Tumor suppressor gene</td>
<td>-</td>
</tr>
<tr>
<td>CD30</td>
<td>Anaplastic large cell</td>
<td>-</td>
</tr>
<tr>
<td>ALK</td>
<td>Anaplastic large cell</td>
<td>-</td>
</tr>
<tr>
<td>CD138</td>
<td>Bone marrow plasmaocyte</td>
<td>-</td>
</tr>
<tr>
<td>SOX-10</td>
<td>Melanocytes, Neurologic tumor cells</td>
<td>-</td>
</tr>
</tbody>
</table>

+++ Strong reactivity. ++ Moderate reactivity. + Weak reactivity. -, No reactivity.

![Figure 2](image_url). H&E staining at ×20 and ×40 magnifications showed fragments of lymph node infiltrated by numerous pleomorphic giant cells with hyperchromatic nuclei and large, prominent nucleoli. Cytoplasm is eosinophilic occasionally filled with vacuole (black arrow). Scattered abnormal mitotic figures were observed. A capillary was shown in the pathological section (white arrow).
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Symptomatic and supportive treatment like reduce the bilirubin, protect the liver function, bring down the fever etc. was used. The pathological analysis of the lymph node demonstrated the diagnosis of histiocytic sarcoma. His family members gave up chemotherapy according to his bad situation and poor effect of treatment. He died on the second day after the pathological results reported.

Pathological findings

A predominant population of large non-cohesive cells with bizarre pleomorphic shape, lobulated nuclei and abundant foamy cytoplasm were shown in microscopic examination. Small lymphocytes and occasional multinucleated cells scattered and admixed within the atypical cells. Mitoses could be identified within the abnormal morphology cells. The pathological section showed a capillary which demonstrated the abundant blood supply of the tumor (Figure 2). Immunohistochemical analysis (Table 1) was carried out, with the tumor cell staining strongly positive for the histiocytic markers KP-1, LCA, Vim, CD14, lysozyme, S100 (Figure 3) and negative for the Langerhan's cell markers CD1a, dendritic cell markers CD21 and CD35, anaplastic large cell markers CD30 and ALK. Although the immunoreactive of S100 may indicated melanocytes, but the anti-body
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of melanocytes HMB45 was negative which ruled out melanoma. They showed weakly positive for B cell marker CD20 and negative for T cell marker CD3, epithelial membrane antigen EMA. The Ki-67 proliferation labeling index was 50%+ in the histiocytic proliferation supporting a neoplastic process.

We here discuss the definition, epidemiology, pathogenesis, clinical diagnosis, treatment, prognosis, and mechanism of histiocytic sarcoma.

Discussion

Histiocytic sarcoma (HS) is an extremely rare, aggressive tumor of hematopoietic origin, accounting for less than 1% of all neoplasms arising in the lymph nodes or soft tissues [5]. HS was originally described in 1939 by Scott and Robb Smith as histiocytic medullary reticulosis which then was designated in 1966 as malignant histiocytosis. But the term histiocytic sarcoma was introduced in 1970 by Mathe et al. [6]. Lacking available ancillary techniques (immunohistochemistry) made the definitive lineage determination hard. Thus many cases described as histiocytic sarcoma or malignant histiocytosis are now recognized to be other histiocytic and dendritic cell disorders such as reactive histiocytic proliferations, dendritic cell neoplasms, and Langerhans cell histiocytosis, as well as non-Hodgkin lymphomas, especially diffuse large B cell lymphoma and anaplastic large cell lymphoma. Literature review demonstrates a clear association between HS and various malignancies, like follicular lymphoma, acute monocytic leukemia, hairy cell leukemia, diffuse large B-cell lymphoma, acute lymphoblastic lymphoma, chronic lymphocytic leukemia and chronic myelomonocytic leukemia. HS frequently occurs as a secondary event following these hematolymphoid malignancies [7]. It characterizes the same molecular or cytogenetic abnormalities as the primary malignancy. HS affects all age groups but it is seen more common in the second and third decade of people. Its morbidity doubles in men.

Clinical presentation of HS varies greatly, depending on its location. Some patients especially those with progressive disseminated disease show systemic symptoms such as fever, fatigue, night sweats, weight loss and weakness. About 30% of patients with HS present cytopenias, so does this case report. The lymph node is the most common site, followed by the gastrointestinal tract, spleen, soft tissue, skin and central neuron system (CNS) [8]. Generally, some patients with localized nidus may benefit from surgery or chemotherapy, but most patients with disseminated sites die within two years [9] and most cases of primary HS in CNS have shown a very aggressive clinical course with a median survival of 4.5 months [10]. Staging workup, including imaging studies such as computed tomography (CT) or a combined positron emission tomography (PET/CT), should be performed at presentation to determine the extent of the disease. Excisional biopsy is the most accurate diagnostic modality.

HS has high cellularity composed of non-cohesive diffuse proliferation of large ovoid cells (diameter of >20 μm) [4]. The cytoplasm of the tumor cells is abundant and eosinophilic. The nuclei are large, pleomorphic, and eccentric with one or more distinct nucleoli. The chromatin is hyperchromatic, coarse, and granular. Mitotic figures are easily observed. The cytoplasm often contains numerous lysosomes and occasionally has a foamy appearance. Some tumors may contain a prominent inflammatory infiltrate and hemophagocytosis [11].

The diagnosis of HS relies predominantly on the verification of histiocytic lineage and the exclusion of other, poorly differentiated, large cell malignancies (i.e. lymphoma, carcinoma, and melanoma) by way of extensive immunophenotypic [12]. The best available immunohistochemical markers are CD163, CD68 (KP-1 or PG-M1) and lysozyme. In this case, the positive of Vim means these cells originate from mesenchymal tissue. Positive LCA means they are leukocytes. Strongly positive of KP-1, lysozyme and CD14 means these are histiocytes. S-100 protein in this case is strongly positive but HMB-45 is negative, so melanoma is ruled out. Some cases with activated normal macrophages can be S-100 protein positive [13]. The absence of dendritic cell markers (CD1a, CD21, and CD35), B-cell and T-cell related markers, anaplastic large cell markers (CD30, ALK), epithelial (pancytokeratin, EMA), melanocytic (HMB-45, Melan A) and myeloid cell (CD13, CD33, myeloperoxidase) markers ruled out cells of other lineages. We should emphasize
that the evaluation with a panel of antibodies in the context of the morphology is very important, because none of the antibodies is specific for histiocytic differentiation.

Clinically, there is no standard therapy for HS due to its rarity [14]. The choice of treatment is based on its location and extent. Preferred therapies in localized disease are surgical excision and adjuvant radiation. Most patients with histiocytic sarcoma show limited response to chemotherapy and a high mortality rate [15]. Actually, there has been no effective treatment of HS. Different regimens including CHOP, CHOP-E, BEAM, and MEAM had been tried in the past. CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) is the most popular therapy for HS. Novel approaches in using treatments such as thalidomide, alemtuzumab, and vemurafenib have also been tried in a few individual cases. With the discovery of driver mutations, targeted therapies to improve patient outcomes may be the standard in future, but as for now it is yet to be completely accepted.

Genetic findings are observed in several cases. J. M. Alonso-Dominguez et al. reported a case with trisomy 8, extra material on the short arms of chromosome 4, deletion of chromosome 3 at q11 and tetrasomy 8 and translocation t(3;5) (q25;q35) [16]. Liu et al. studied five histiocytic sarcomas. Three cases carried somatic mutations in BRAF [17, 18]. Reports demonstrate the tumor often harbored a BCL2 translocation [19]. As for secondary HS, Junaid Ansari et al. reviewed the fish analysis of 34 cases and the most common mutation is t(14,18). Bcl2 rearrangement, IGH/BCL2 16p del, CDKN2A del, 13q/17p del, CCND1-IGH also can be seen occasionally in some cases [7, 19, 20]. The secondary HS often evolved from hematopoietic malignancies, it may be explained by lineage switching. For example, PAX5 expression is critical in maintaining the B-cell phenotype, and the deletion of PAX5 may cause mature B cells to dedifferentiate to either macrophages or uncommitted precursors [21, 22]. The study of Xie et al. demonstrated that the inhibition of PAX5 expression and conjunction with forced expression of C/EBPα and β convert B cells to macrophages [21]. Sharing of BRAF V600E mutation in Langerhans cell histiocytosis and Erdheim-Chester disease, but also in HS could be explained on the basis of a common progenitor within this heterogeneous group [23, 24]. Some reported that the lost expression of tumor suppressors PTEN and p16INK4A caused by the deletion or promoter hypermethylation may be the mechanism of human HS [25].

Conclusion

Here we report a case of the rare HS and emphasize the important of the immunohistochemical examination in the diagnosis of HS. Diagnostic criteria include the positive marker of histiocytes (predominately positive on KP-1, LCA, CD163, CD14, lysozyme or S100) and the negative marker of other lineages. Due to the distinctive characteristics of tumor biology and variable clinical presentation, the mechanism and standardized treatment of HS remains unclear. Its highly malignancy and poor effect of treatment makes people despair. Therefore, more efforts should be made on molecular biology and genetic approaches to explore more comprehensive information about HS and development of a novel therapy in the future is top priority.

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Disclosure of conflict of interest

None.

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