Case Report

Histiocytic sarcoma arising in the liver: a case report and review of the literature

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Abstract: Background: Histiocytic sarcoma (HS) is a rare and controversial hematopoietic neoplasm. The etiology of the disease is unclear and the pathologic diagnosis is challenging. We describe an unusual case of HS arising in the liver of a patient. Case presentation: A 28-year-old female, without pertinent past medical history, presented with an abdominal mass and non-specific symptoms. Abdominal CT and MRI imaging revealed multiple heterogeneous masses in the liver. The patient underwent partial hepatectomy. The specimen consisted of a predominantly gray, solid, moderately firm mass measuring 9.0×6.0×5.0 cm. Histological examination revealed a highly undifferentiated neoplasm comprised of markedly atypical large cells with eosinophilic to vacuolated cytoplasm, showing occasional hemophagocytosis. Immunohistochemistry showed strong positive tumor staining for CD4, CD68, CD163 and lysozyme, and negative staining for CD3, CD5, CD20, CD138, and CD30. Conclusion: Here we discuss different diagnostic considerations and establish a final diagnosis of HS with integration of histological, immunohistochemical and genetic testing. This case provides a systematic diagnostic approach to HS.

Keywords: Histiocytic sarcoma, immunohistochemistry, lymphoma, myeloid sarcoma, case report

Background

Histiocytic sarcoma (HS) is a rare hematopoietic neoplasm, demonstrating morphologic and immunophenotypic features of histiocytes [1]. The tumor shows wide age distribution (median 52 years) and can arise in any site, including lymph nodes, liver, and skin. At the present time, the World Health Organization (WHO) defines HS as a malignancy with morphologic and immunophenotypic features that resemble those of mature tissue histiocytes. The diagnosis of HS mainly relies on the lineage of histiocytes and the exclusion of other poorly differentiated large-cell malignant tumors [2]. Even though several studies have been published for attempting to identify reliable phenotypic and genotypic characteristics, the diagnosis is still challenging and uncertain [3, 7]. Comprehensive consideration of imaging, histological, and immunohistochemical results, our reports parallel some previous reports that presented specific histologic manifestation of HS.

Case report

A 28-year-old female presented to the Hospital of DongGuan for an evaluation of a solitary liver mass, which had initially manifested with non-specific symptoms (fever, abdominal pain). The patient provided no pertinent past medical history. CT and MRI imaging of the abdomen revealed a heterogeneous mass involving the liver, but no abdominal lymphadenopathy or splenomegaly was seen (Figure 1). CT showed a low density mass in the liver S4, which was clearly enhanced in arterial-phase and decreased in portal and late phases (Figure 1A). MRI showed a long T1/T2 mass in the liver S4, with high signal in DWI (b=800) and low signal in ADC, which was clear and uneven enhancement in arterial-phase, decreased in portal
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phase and annular enhanced in late phase (Figure 1B). Ultrasound (US) showed a hypoechoic mass (Figure 2A). Color doppler flow imaging (CDFI) showed rich blood supply signals in the mass (Figure 2B). A partial hepatectomy was then performed. Grossly, the surface of tumor was gray, solid, and moderately firm, measuring 9.0×6.0×5.0 cm. Microscopically, the lesion was comprised of scattered and occasionally clustered large cells that were pleomorphic, 3-4 times the size of hepatocytes, with abundant eosinophilic to vacuolated cytoplasm, round nuclei, coarse chromatin, and multiple prominent eosinophilic nucleoli (Figure 3). Large multinucleated forms were also seen. Many of these large cells were engorged with nuclear debris and degenerating inflammatory cells. Increased numbers of neutrophils were seen intermixed with the tumor cells to the point of obscuring the tumor cells. Scattered atypical mitotic figures and areas of necrosis were identified. An extensive panel of immuno-

Figure 1. CT and MRI imaging of the abdomen. A. CT scan images show a low density mass in the liver S4. B. MRI imaging show a long T1/T2 mass in the liver S4.

Figure 2. Ultrasonic imaging features. A. US show a hypoechoic mass. B. CDFI show a rich blood supply signals in the mass.
histochemical stains was performed in order to rule out other large cell neoplasms such as large cell lymphoma, melanoma, and carcinoma. IHC showed that the tumor cells were positive for CD68, lysozyme, CD163, and CD4 (Figure 4), and negative for CD3, CD5, CD20, CD138 and CD30. Polymerase chain reaction (PCR) and sequencing for IGH gene rearrangement and fluorescence in situ hybridization (FISH) studies for BCL2 rearrangement were both negative. The immunohistochemical staining profile, in combination with morphology and genetic studies supported the diagnosis of histiocytic sarcoma. During the patient’s subsequent hospital course, the patient was scheduled to receive a brief treatment of L-asparaginase inhibitor. Five months later, the patient exhibited complete resolution and no evidence of recurrent disease or remnants on regular follow-up.

Discussion

Histiocytic sarcoma (HS) is a rare hematopoietic neoplasms characterized by malignant proliferation of cells showing morphologic and immunophenotypic features similar to those of mature tissue histiocytes [4]. Clinically, the tumors, which show wide age distribution, could arise in any area of the body. According to previous reports, about one-half of HS occurs in soft tissue, one-third in the GI tract and other relatively infrequent locations such as the nasal cavity or the lung. Lesions arising in the soft tissue often presents as painless enlargements without other specific signs and symptoms, while those in GI tract present as abdominal masses associated with pain and weight loss, as well as frequent secondary involvement of lymph nodes or the liver [5].

Based on the revised classification proposed by the Histiocyte society about histiocytoses and neoplasms of the macrophage-dendritic cell lineages, HS, including primary malignant and secondary malignant histiocytoses, belongs to the “M” group [6]. Primary malignant histiocytoses often arise from malignant transformation of tissue macrophages, and the diagnosis is based on morphological assessment and exclusion of other entities. It is recommended to term the various histiocytic neo-
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plasms as “Malignant Histiocytoses”, and further subclassify by immunophenotypic assessment (i.e. histiocytic, interdigitating, Langerhans, etc.). Unlike primary malignant histiocytes, secondary malignant histiocytoses occur following with other hematopoietic neoplasm and associated with follicular lymphoma (FL), B lymphoblastic leukemia (B-ALL), and chronic lymphocytic leukemia (CLL). A comparison of the clinical manifestation, morphology and immunophenotype of histiocytic sarcoma and myeloid sarcoma has reported in WHO classification of tumors of hematopoietic and lymphoid tissues. Unlike myeloid sarcoma or follicular lymphoma, whose prognosis depends on genetics or grading, respectively, primary HS has a very poor prognosis. Therefore, differentiating between these entities is paramount. Although the two tumors were very similar in immunohistochemistry including CD4, CD68, lysozyme, MS may express myeloid antigens more frequently like MPO, CD11B/C, CD13 and CD33 [6]. Above all, the differentiation is based on morphology and clinical features.

Utilize the morphology supported by amount immunophenotypic analysis to identify histiocytic cell lineage and exclude other poorly differentiated, large cell neoplasms are foundation for the diagnosis of HS. The main differential diagnosis of HS includes dendritic cell sarcoma, diffuse large B cell lymphoma, anaplastic large T-cell lymphoma, myeloid sarcoma/AML, undifferentiated carcinoma, and malignant melanoma. The morphologic features of this tumor are isolated large neoplastic cells, one or more large pleomorphic nuclei, significant nucleoli, and large number of eosinophilic vacuoles and necrosis were commonly seen [1, 4]. Our case demonstrated all the above features including prominent hemophagocytosis.
Moreover, like other hematologic malignancies, immunohistochemistry plays an important role in the diagnosis of HS due to overlapping morphologic features. The diagnosis of HS strictly requires the neoplastic cells must express at least two specific macrophage-associated antigens including CD68, CD163, lysozyme, and typically lack of B-cell (CD20, CD79a, PAX5) and T-cell (CD3, CD5, CD7, CD8) markers and Langerhans cells (CD1a, CD207, S100), follicular dendritic cells (CD21, CD23, CD35, podoplanin), and epithelial (PAN-CK, EMA, CK18), muscle cell markers (SMA, Desmin), and myeloid (CD33, CD34, CD61, CD117, MPO, vWF) markers [6, 7]. It is worth noting that occasional expression of CD45 and CD4, Langerhans cell markers CD1a and S100 and the follicular dendritic cell marker podoplanin (D2-40) are expressed by a subset of HS. More importantly, the hemoglobin scavenger receptor-CD163, which has been identified as a new differentiation marker on macrophages, showed higher specificity compared with other histiocytic markers such as CD68. In a study of 19 cases previously reported as HS, upon further review, only 5 of 19 were diagnosed as true HS. All of five cases demonstrated expression of CD163 strongly, indicating that CD163 may have significant diagnostic utility [8]. In our case, the absence of expression of CD3, CD5, CD7, CD8, PAX-5, TIA1, CD20, CD79a, PAX, OCT1, CD138, CD30, S100, CD21, CD34, CD117, MPO, PAN-CK, EMA, SMA, Desmin and other immunohistochemical targets excludes common hematopoietic neoplasms and other tumors of epithelial and soft-tissue origin. Positive expression of CD4, CD68, CD163 and lysozyme strongly supports a diagnosis of histiocytic sarcoma.

Genetic and molecular testing also plays a vital role in the differential diagnosis along with morphology and immunohistochemistry. Although the diagnosis of HS no longer strictly requires the absence of clonal IGH or TCR gene rearrangement, these studies are crucial in differentiating primary and secondary HS. In accordance with a study of seven cases including 1 LCS, 2 HS, and 4 IDCS, all patients had clonal IGH gene rearrangement [9]. Moreover, a study of 23 histiocytic/dendritic cell sarcomas indicated the high frequency of clonal immunoglobulin receptor gene rearrangement since 9/23 cases showed clonal IGH gene rearrangement, 2/23 cases showed clonal IGH gene rearrangement and 1/23 showed t(14;18) IGH/BCL2 by PCR and FISH [10]. By comparing genetic features of patients with follicular lymphoma and histiocytic sarcoma, it has been suggested that there is transdifferentiation of the former neoplasm into the latter [11]. The presence of a BRAF V600E mutation, which is seen in >50% of LCH and Erdheim-Chester Disease, may be a clue to suspect secondary transformation from these lesions [7].

Histiocytic sarcoma is an aggressive neoplasm and most patients die of progressive disease within 2 years. There is no standard treatment for histiocytic sarcoma, and the optimal radiation dose and treatment volume remain to be determined. ICE (ifosfamide, carboplatin, and etoposide with mesna) and CHOP are systemic chemotherapeutic regimens often used to treat patients diagnosed with aggressive lymphomas. However, their efficacy in the treatment of systemic histiocytic sarcoma has not been evaluated [12]. Therefore, further investigation is necessary to obtain a systematic understanding of the clinical, immunophenotypic, and molecular features in order to develop effective treatments.

Conclusions

Histiocytic sarcoma (HS) is a rare hematopoietic neoplasms. The diagnosis of HS is based on morphology supported by an extensive immunophenotypic analysis to establish histiocytic lineage and the exclusion of other, poorly differentiated, large cell malignancies. Here we discussed different diagnostic considerations and established a final diagnosis of HS with integration of histological, immunohistochemical, and genetic testing. Our case provides a systematic diagnostic approach to HS.

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Disclosure of conflict of interest

None.
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Abbreviations

HS, histiocytic sarcoma; CT, computed tomography; MRI, magnetic resonance imaging; CD, cell differentiation; WHO, World Health Organization; DWI, diffusion weighted imaging; US, Ultrasound; CDFI, color doppler flow imaging; IHC, immunohistochemistry; PCR, polymerase chain reaction; FISH, fluorescence in situ hybridization; GI, gastrointestinal; LCS, Langerhans cell sarcoma; IDCS, interdigitating dendritic cell sarcoma; LCH, Langerhans cell histiocytoses.

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References