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An extremely rare neoplasm, histiocytic sarcoma: A report of two cases with an aggressive clinical course

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ABSTRACT

Histiocytic sarcoma (HS) is an extremely rare malignant neoplasm accounting for less than 1% of all hemato-lymphoid neoplasms. Sixty percent of all cases are metastatic at presentation and the prognosis is poor.

Two cases of HS with an aggressive clinical course are presented.

The first case was a 58-year-old man admitted to our hospital with back pain and paresthesia of the lower extremities. Magnetic resonance imaging (MRI) of the thoracic spine revealed a mass measuring 48 × 15 mm between the T2–T5 paravertebral area, entering the spinal channel via the neural foramen and compressing the spinal cord. The mass was completely resected and pathological and immunohistochemical staining confirmed the diagnosis of HS. After three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and two cycles of carboplatin/paclitaxel, the patient died due to disease progression after 9 months.

The second case is a 48-year-old man who presented with fever and weight loss, and complained of back pain for 2 months. Thoracic vertebral MRI revealed a lesion destructing the T6, T7 and T9 vertebral corpus and a mass measuring 2.5 × 2 cm near the T6–T7 transverse process. Total-body fluorodeoxyglucose positron emission tomography (FDG-PET) imaging revealed bilateral inguinal hypermetabolic lymph nodes measuring 10 × 14 mm and osteolytic destructive bone lesions on the vertebral colon and pelvic bones. Pathological and immunohistochemical staining of bone marrow aspirate confirmed the diagnosis of HS. After three cycles of ifosfamide, carboplatin, etoposide (ICE) chemotherapy, the patient died due to disease progression after 3 months.

Conclusions: HS is an extremely rare malignant neoplasm of the monocytic/macrophage lineage, with no standardized chemotherapy regimen for multisystemic disease. Metastatic patients have a more aggressive clinical course than those with unifocal disease.

1. Introduction

Histiocytic sarcoma (HS) is an extremely rare malignant neoplasm accounting for less than 1% of all hemato-lymphoid neoplasms. It is derived from the monocytic/macrophage lineage and shows morphological and immunophenotypic features of mature tissue histiocytes. Neoplastic cells exhibit positivity for CD68 and CD163 and are negative for CD1a, CD21, CD35, CD30, and T-cell, B-cell and myeloid lineage markers. S-100 may be positive; however, Ki-67 is variable.[1] Sixty percent of all cases are metastatic at presentation and the prognosis is poor.[2] Here we present two cases of HS presenting with a paravertebral mass with an aggressive clinical course treated with standard chemotherapy protocols.

2. Case 1

A 58-year-old man was admitted to our hospital with back pain and paresthesia of the lower extremities. Physical examination revealed tenderness of the thoracic spine, weakened motor activity

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of the lower extremities (4/5) and numbness. Complete blood count, renal and liver function tests, and alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (B-HCG) levels were normal. Magnetic resonance imaging (MRI) of the thoracic spine showed a mass measuring 48 × 15 mm between the T2–T5 paravertebral area entering the spinal channel via the neural foramen and a compressed spinal cord. The mass appeared isointense in T1A series and hyperintense in T2A series with diffuse contrast enhancement. The mass was resected completely by a neurosurgeon. The pathology of the total excised mass showed polygonal cells with ovoid spindling and prominent nucleoli. Immunohistochemistry (IHC) of the tumor cells revealed the following: lysozyme^{+}, vimentin^{+}, CD68^{+}, CD163^{+}, CK7^{-}, CK20^{-}, TTF-1^{-}, CK^{-}, PLAP^{-}, CEA^{-}, CD34^{-}, CD117^{-}, and desmin^{-}. Histopathologic examination confirmed the diagnosis of HS. Postoperatively, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET)/computed tomography (CT) imaging revealed a large mediastinal mass (59 × 40 mm) and destruction of the right pedicle, lamina and transvers processes of the T2 and T3 vertebrae. Palliative radiotherapy was given to the operation field T2–T3–T4 area. The patient received systemic chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] regimen) consisting of cyclophosphamide, adriamycin and vincristine on day 1 and prednisone on days 1–5. After three cycles of chemotherapy, ^{18}F-FDG PET/CT imaging revealed regression of the mediastinal mass size, hypometabolic lytic destructive lesions of the T2, T3 and T4 vertebral pedicles and a new hypermetabolic mass (53 × 37 mm) on the right lower lobe of the lung. The chemotherapy regimen was changed to carboplatin (AUC = 5) and paclitaxel (175 mg/m^2) on day 1, each for 21 days. After two cycles of the carboplatin/paclitaxel regimen, the patient died due to disease progression 9 months after the initial diagnosis.

3. Case 2

A 48-year-old man presented with fever, weight loss and complaints of back pain for 2 months. Physical examination revealed enlarged lymph nodes in the axillary and inguinal areas, with the largest mass measuring 2 × 1 cm. Laboratory analyses showed microcytic anemia, with a hemoglobin level of 7.6 g/dL. Gastrointestinal endoscopy was normal. Thoracic vertebral MRI showed a lesion destructing the T6, T7 and T9 vertebral corpus and a mass (2.5 × 2 cm) near the T6–T7 transverse process. ^{18}F-FDG PET/CT imaging revealed bilateral inguinal hypermetabolic lymph nodes measuring 10 × 14 mm and osteolytic destructive bone lesions on the vertebral colon and pelvic bones (Fig. 1a). Bone marrow aspirate showed neoplastic cells with an abundant eosinophilic cytoplasm and a round nucleus with prominent nucleoli. The IHC phenotype was as follows: CD68^{+}, lysosyme^{+}, vimentin^{+}, panCK^{-}, B-catenin^{-}, SMA^{-}, MPO^{-}, CD43^{-}, S100^{-}, Melan-A^{-}, HMB45^{-}, Tdt^{-}, kappa^{-}, lambda^{-}. The diagnosis of HS was confirmed with these pathologic and IHC results (Fig. 2). Three cycles of an ifosfamide, carboplatin, etoposide (ICE) chemotherapy regimen consisting of etoposide on days 1–3, and ifosfamide, mesna and carboplatine on day 2 were given. ^{18}F-FDG PET/CT imaging revealed progression on the previous bone lesions, new peritoneal and pleural effusion and a hypermetabolic spleen (Fig. 1b). The patient died after 3 months due to disease progression.

4. Discussion

HS is an extremely rare malignant neoplasm of the monocytic/macrophage lineage with no standardized chemotherapy regimen for multisystemic disease. Metastatic patients have a more aggressive clinical course than those with unifocal disease. ICE or CHOP regimens are preferred for advanced disease[3] and were therefore given to our patients. Previous lesions were responsive to the CHOP regimen in the first patient but a new lesion appeared on the lung. Since the second-line ICE regimen would be more aggressive, we began carboplatin/paclitaxel treatment. After two cycles of carboplatin/paclitaxel, the patient died 9 months after the initial diagnosis. The survival of the second patient was shorter (3 months) after receiving three cycles of ICE.

HS has been diagnosed in all age groups but is more common in adults. The median age in case series at presentation is 46 years. Our patients were also in their 4th and 5th decades (both patients were men in the 5th decade of life). The clinical presentation of HS varies according to organ involvement. The most commonly involved organs are the skin, soft tissues and intestinal tract. Both patients presented with paraspinal masses compressing the nerve roots. Some case reports present with a mediastinal, non-seminomatous germ cell tumor.[4] In our first case, the patient had a mediastinal mass but his AFP and B-HCG levels were normal; therefore, we did not take a biopsy.

HS has some diagnostic characteristics that can be examined by IHC. Tumor cells typically express CD4, CD163, CD68 and lysozyme. The tumor cells examined herein were positive for lysozyme, CD163 and CD68 in the first case, and positive for CD68 and lysozyme in the second case. The cells were negative for T-cell, B-cell and myeloid cell markers.

HS may be a sporadic disease or may be related to a synchronous or metachronous hematologic malignancy, such as acute lymphoblastic leukemia or follicular lymphoma. A bone marrow biopsy may yield a leukemia diagnosis in such instances; however, in our second case, the HS diagnosis resulted from a bone marrow aspiration biopsy. This was the second report of an HS diagnosis resulting from bone marrow aspiration; the first is described in.[7]

In patients presenting with a paraspinal mass, although it is rare,

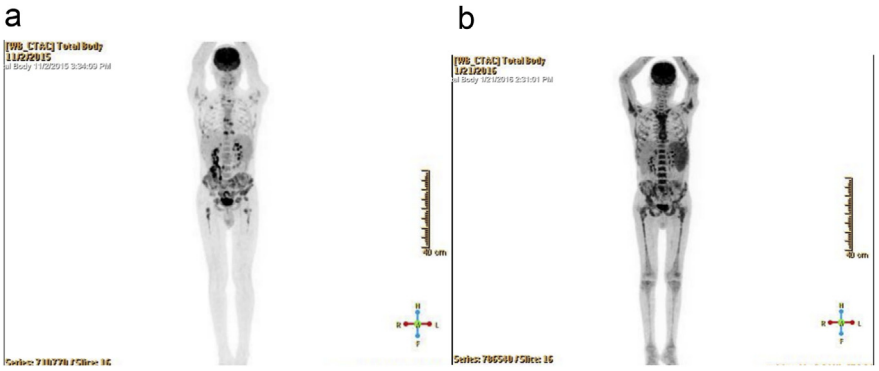

Fig. 1. (a) Abnormal FDG uptake on bilateral inguinal enlarged lymph nodes and bone lesions. (b) new bone, pleural and splenic FDG uptake on 18F-FDG-PET/CT imaging.

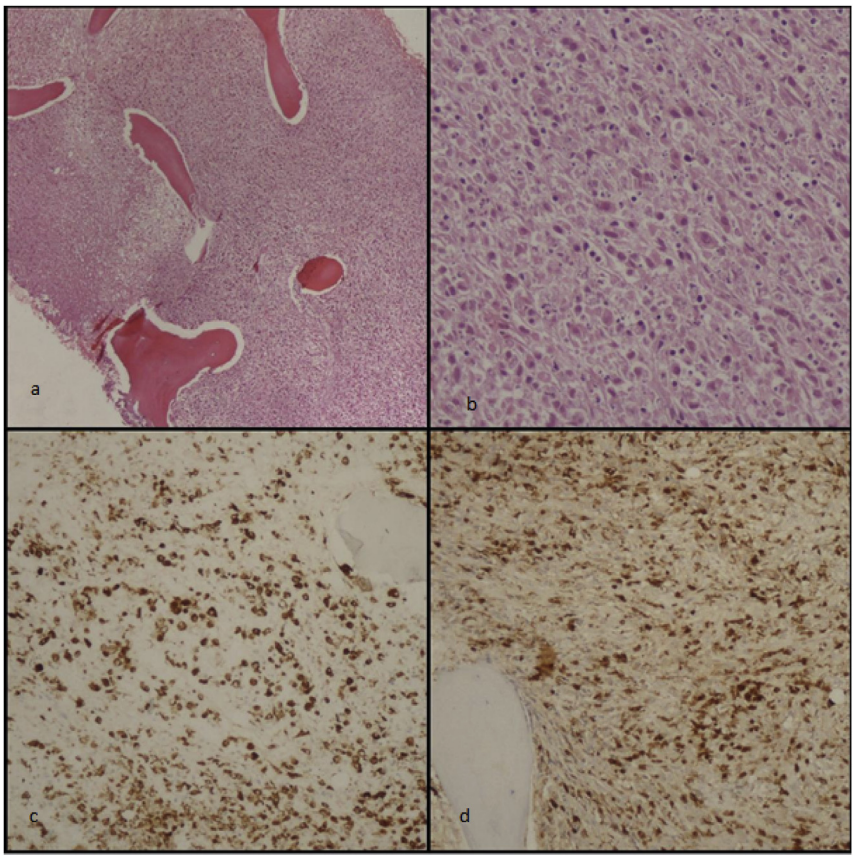

Fig. 2. (a) Diffuse neoplastic infiltrate in the hypercellular bone marrow (H&E, × 40). (b) Diffuse, non-cohesive neoplastic cell infiltrate resembling tissue histiocytes (H&E, × 200). (c) CD68-positive neoplastic cells (CD68, × 100). (d) Lysozyme-positive neoplastic cells (lysozyme, × 100).

HS must be considered during diagnosis. Pathologic examination must be confirmed by immunohistochemical staining. Patient survival with standard chemotherapeutic agents is very poor in metastatic disease. Therefore, clinical trials need to define new therapeutic approaches.

The BRAF V600E mutation was detected in six of eight (62.5%) cases of HS in a Korean trial.[5] The BRAF pathway may play a role in the carcinogenesis of histiocytic neoplasms. A loss of tumor suppressor genes PTEN and INK4a/ARF in mice causes premalignant expansion of biphenotypic myelolymphoid cells followed by the development of HS.[6] In contrast, Gatalica et al. reported no BRAF V600E mutation, but instead saw a PTEN mutation (a splice site mutation that abolishes the conserved splice region in exon 7 of PTEN) and 100% programmed cell death ligand 1 (PD-L1) expression in HS.[8] **In a study of 4 HS cases different molecular targets as platelet derived growth factor receptor, vascular endothelial growth factor receptor and epidermal growth factor receptor has detected and based on these marker profiles imatinib, sorafenib and bevacizumab has given to patients. But for the absolute effectiveness of these targeted therapies we need prospective randomized trials with high number of patients.**[9]

It is imperative to understand the pathogenesis of HS in prospective trials to guide the treatment of metastatic HS.

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