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BEYOND CARCINOMA: UNMASKING PRIMARY HISTIOCYTIC SARCOMA OF THE ESOPHAGUS

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ABSTRACT

Background: Histiocytic sarcoma (HS) is a rare and aggressive hematopoietic malignancy arising from mature histiocytes. Primary involvement of the esophagus is exceptionally uncommon and often poses significant diagnostic challenges because of its clinical and histopathological resemblance to high-grade carcinomas and other poorly differentiated malignancies.

Case Presentation: A 47-year-old woman presented with progressive dysphagia to solid foods for four months. Upper gastrointestinal endoscopy revealed an ulceroproliferative growth in the lower thoracic esophagus. Histopathological examination demonstrated a high-grade malignant neoplasm. Immunohistochemical analysis showed strong positivity for Vimentin, CD68, CD163, and CD4, with focal expression of EMA, PanCK, and LCA, while markers including p63, p40, S100, HMB45, SOX10, MPO, CD117, DOG1, and TdT were negative. These findings established the diagnosis of histiocytic sarcoma. Staging ^18F-FDG PET/CT demonstrated intensely FDG-avid circumferential mural thickening involving the lower thoracic esophagus and gastroesophageal junction (SUVmax 28.2) with metabolically active regional lymphadenopathy. The patient received CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone). Follow-up ^18F-FDG PET/CT after three cycles demonstrated complete metabolic response with resolution of FDG uptake at both the primary site and involved lymph nodes.

Conclusion: Primary histiocytic sarcoma of the esophagus is an exceptionally rare malignancy that may closely mimic high-grade carcinoma. Accurate diagnosis requires comprehensive immunohistochemical evaluation and correlation with imaging findings. This case highlights the diagnostic value of immunophenotyping and ^18F-FDG PET/CT and demonstrates a favorable response to CHOP chemotherapy. Reporting such rare cases contributes to the limited literature and may aid in developing future diagnostic and therapeutic strategies.

KEYWORDS: Histiocytic sarcoma; Esophagus; High-grade carcinoma; Immunohistochemistry; FDG PET/CT; CHOP chemotherapy; Case report.

INTRODUCTION

Histiocytic sarcoma (HS) is an exceptionally rare and aggressive hematopoietic malignancy characterized by the proliferation of malignant cells exhibiting morphologic and immunophenotypic features of mature histiocytes. According to the World Health Organization (WHO) classification, HS is a distinct neoplasm of the monocyte-macrophage lineage and accounts for less than 1% of all hematolymphoid malignancies[1,2]. The disease most commonly affects lymph nodes, skin, spleen, liver, and soft tissues, although extranodal involvement is frequently encountered. Primary involvement of the gastrointestinal tract is uncommon, and occurrence in the esophagus is exceedingly rare, with only a limited number of cases reported in the literature.The clinical presentation of esophageal HS is often nonspecific and may include progressive dysphagia, weight loss, odynophagia, or chest discomfort, closely resembling the symptoms of more common esophageal malignancies such as squamous cell carcinoma and adenocarcinoma. Consequently, diagnosis is frequently delayed or initially misinterpreted. Histopathologically, HS may present as a poorly differentiated high-grade malignant neoplasm with marked cellular pleomorphism, making distinction from carcinoma, melanoma, lymphoma, myeloid sarcoma, and other undifferentiated tumors particularly challenging.Accurate diagnosis relies heavily on immunohistochemical evaluation[3,4]. Tumor cells typically express histiocytic markers such as CD68, CD163, CD4, and lysozyme while lacking expression of epithelial, melanocytic, lymphoid, and myeloid lineage markers. Among these, CD163 is considered one of the most specific markers of histiocytic differentiation. Therefore, a comprehensive immunohistochemical panel is essential to establish the diagnosis and exclude potential mimics. In addition, ^18F-fluorodeoxyglucose positron emission tomography/computed tomography (^18F-FDG PET/CT) plays an important role in disease staging, assessment of nodal involvement, and monitoring treatment response due to the typically high metabolic activity of these tumors.Because of the rarity of HS, there are no standardized treatment guidelines, and management strategies are generally extrapolated from therapeutic regimens used for aggressive hematologic malignancies. Chemotherapy protocols such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) are commonly employed, although treatment outcomes remain variable. Reporting rare presentations of HS is important to improve understanding of its clinicopathological features, diagnostic

challenges, and therapeutic responses.Herein, we report a rare case of primary histiocytic sarcoma involving the lower esophagus and gastroesophageal junction in a 47-year-old woman presenting with progressive dysphagia. The lesion initially mimicked a high-grade carcinoma on histopathological examination but was ultimately diagnosed as histiocytic sarcoma through detailed immunohistochemical analysis. The patient demonstrated a complete metabolic response following CHOP chemotherapy. This case highlights the importance of considering histiocytic sarcoma in the differential diagnosis of atypical esophageal masses and underscores the critical role of comprehensive immunophenotyping in achieving an accurate diagnosis[5].

Research Gap

Primary histiocytic sarcoma of the esophagus is an exceptionally rare malignancy, with very few cases reported in the literature. Due to its rarity, the clinicopathological characteristics, optimal diagnostic approach, treatment strategies, and long-term outcomes remain poorly understood. Most available evidence is limited to isolated case reports and small case series, resulting in a lack of standardized management guidelines. Furthermore, esophageal histiocytic sarcoma frequently mimics high-grade carcinoma and other poorly differentiated malignancies, creating significant diagnostic challenges and increasing the risk of misdiagnosis. Limited data are also available regarding the role of immunohistochemical profiling and ^18F-FDG PET/CT in diagnosis, staging, and treatment response assessment. Therefore, reporting additional cases is essential to expand the existing knowledge base, improve diagnostic accuracy, and contribute to the development of evidence-based therapeutic approaches for this rare entity.

Case Presentation

A 47-year-old female presented to the Department of Medical Oncology with complaints of progressive dysphagia to solid foods for four months. The patient reported gradual worsening of swallowing difficulty without a history of hematemesis, melena, or significant comorbid illness. Physical examination was unremarkable, and no palpable peripheral lymphadenopathy was identified.Upper gastrointestinal endoscopy performed on June 7, 2025, revealed an ulceroproliferative growth located approximately 30 cm from the incisors involving the lower thoracic esophagus. Multiple biopsy samples were obtained for histopathological evaluation.Microscopic examination demonstrated a high-grade malignant neoplasm composed of large pleomorphic cells with abundant cytoplasm and prominent nucleoli. In view of the poorly differentiated morphology, an extensive immunohistochemical (IHC) panel was performed. Tumor cells showed strong positivity for Vimentin, CD68, CD163, and CD4, with focal expression of EMA, PanCK, and LCA. The neoplastic cells were negative for p63, p40, S100, HMB45, SOX10, MPO, CD117, DOG1, and TdT. Based on the morphologic and immunophenotypic findings, a diagnosis of histiocytic sarcoma was established.For disease staging, an 18F-FDG PET/CT scan was performed on June 14, 2025. The study revealed intensely FDG-avid heterogeneously enhancing circumferential mural thickening involving the lower thoracic esophagus and gastroesophageal junction with a maximum standardized uptake value (SUVmax) of 28.2. The lesion extended from D9 to D11 vertebral levels and demonstrated a maximum wall thickness of 2.4 cm. Multiple metabolically active lymph nodes were identified in the paraesophageal, retrocrural, periportal, and portocaval regions, with a maximum SUVmax of 13.4, suggestive of nodal metastasis.Considering the aggressive nature of the disease, the patient was initiated on CHOP chemotherapy comprising cyclophosphamide, doxorubicin, vincristine, and prednisone. Treatment was well tolerated. Following completion of three cycles, response assessment with FDG PET/CT demonstrated complete metabolic response, with no evidence of residual metabolically active disease at the primary site or previously involved lymph nodes.

Follow-Up

Following three cycles of CHOP chemotherapy, response assessment with ^18F-FDG PET/CT demonstrated a complete metabolic response. In view of the favorable response, the patient was advised definitive surgical management. However, she was subsequently lost to follow-up and did not undergo the planned surgery.Two months later, the patient re-presented with locally advanced locoregional recurrence. Restaging evaluation revealed recurrent disease that was considered surgically resectable. The patient subsequently underwent surgical excision. Histopathological examination of the resected specimen demonstrated residual disease with a pathological stage of ypT3N3. Unfortunately, following surgery, the patient was again lost to follow-up, and no further clinical or radiological outcome data were available.

Figure1: Image demonstrates the treatment response assessed by ^18F-FDG PET/CT imaging. The baseline PET/CT image (Figure 1A) shows intense FDG uptake in the lower thoracic esophagus and gastroesophageal junction, corresponding to the primary histiocytic sarcoma lesion. Following three cycles of CHOP chemotherapy, the follow-up PET/CT image (Figure 1B) reveals complete resolution of abnormal FDG uptake with no evidence of residual metabolically active disease, indicating a complete metabolic response to treatment.

Table 1. Comparison of the Present Case with Previously Reported Cases of Histiocytic Sarcoma

Parameter	Present Case (2025)	Findings from Global Literature	Reference
Age at presentation	47 years	Most patients present between 40–70 years of age	Shinohara et al., 2025 [1]

Parameter	Present Case (2025)	Findings from Global Literature	Reference
Sex	Female	Slight male predominance reported	Shinohara et al., 2025 [1]
Primary site	Lower esophagus and GE junction	Lymph nodes, skin, spleen, and GI tract are common; esophageal involvement is exceptionally rare	Vos et al., 2005 [2]; Shinohara et al., 2025 [1]
Presenting symptoms	Progressive dysphagia	Dysphagia, weight loss, abdominal pain, and obstructive symptoms depending on tumor location	Hornick et al., 2004 [3]
Initial diagnosis	High-grade malignant neoplasm	Frequently misdiagnosed as poorly differentiated carcinoma, lymphoma, melanoma, or sarcoma	Hornick et al., 2004 [3]
Histopathology	Pleomorphic high-grade tumor	Large atypical histiocytic cells with abundant eosinophilic cytoplasm and marked pleomorphism	WHO Classification, 2022 [4]
Positive IHC markers	CD68, CD163, CD4, Vimentin	CD68, CD163, CD4, and lysozyme commonly positive	Hornick et al., 2004 [3]
Negative IHC markers	p63, p40, S100, HMB45, SOX10, MPO, CD117, DOG1, TdT	Negative for epithelial, melanocytic, lymphoid, and myeloid markers	WHO Classification, 2022 [4]
PET/CT findings	SUVmax 28.2 with nodal involvement	HS typically demonstrates intense FDG avidity and widespread disease	Shinohara et al., 2025 [1]
Treatment	CHOP chemotherapy	No standard therapy; CHOP-based regimens commonly used	Shinohara et al., 2025 [1]
Outcome	Complete metabolic response after 3 cycles	Prognosis generally poor; responses vary according to stage and treatment	Shinohara et al., 2025 [1]

compares the clinical, pathological, and therapeutic characteristics of the present case with findings reported in the global literature. Similar to previously published cases, the patient presented with nonspecific symptoms and the lesion initially mimicked a high-grade carcinoma. The immunohistochemical profile was consistent with histiocytic sarcoma, showing positivity for CD68, CD163, and CD4. Notably, the present case demonstrated a complete metabolic response to CHOP chemotherapy after three cycles, highlighting the potential effectiveness of lymphoma-based chemotherapy regimens in selected patients with primary esophageal histiocytic sarcoma[table.1].

DISCUSSION

Histiocytic sarcoma (HS) is an exceptionally rare and aggressive hematopoietic neoplasm derived from mature histiocytes, accounting for less than 1% of all hematolymphoid malignancies. Primary involvement of the esophagus is exceedingly uncommon, with only a limited number of cases reported worldwide. Consequently, the clinicopathological characteristics, optimal treatment strategies, and prognostic factors of esophageal HS remain poorly defined.The present case illustrates the significant diagnostic challenges associated with this rare malignancy. The patient presented with progressive dysphagia, a common symptom of esophageal carcinoma. Endoscopic evaluation revealed an ulceroproliferative lesion, while initial histopathological examination suggested a high-grade malignant neoplasm. Similar diagnostic difficulties have been reported in the literature, where HS frequently mimics poorly differentiated carcinoma, melanoma, lymphoma, myeloid sarcoma, and other undifferentiated malignancies due to overlapping morphological features. Therefore, diagnosis based solely on routine histopathology may lead to misclassification and inappropriate management [6]. Immunohisto chemistry remains the cornerstone for establishing the diagnosis of HS. In the present case, the tumor demonstrated strong positivity for CD68, CD163, CD4, and Vimentin, with negativity for epithelial, melanocytic, and myeloid markers. CD163, in particular, is regarded as one of the most specific markers of histiocytic differentiation and played a crucial role in confirming the diagnosis. The immunophenotypic profile observed in our patient was consistent with previously reported cases and current diagnostic criteria for histiocytic sarcoma.^18F-FDG PET/CT was instrumental in both disease staging and treatment response assessment. The baseline scan demonstrated intense FDG uptake within the lower thoracic esophagus and gastroesophageal junction, along with metabolically active regional lymphadenopathy, reflecting the aggressive biological behavior of the tumor. Consistent with previous reports, PET/CT proved valuable in accurately defining disease extent and monitoring therapeutic response[7].Due to the rarity of HS, no standardized treatment guidelines currently exist. Management is generally extrapolated from therapeutic regimens used for aggressive hematologic malignancies. CHOP-based chemotherapy remains one of the most commonly employed treatment approaches, although surgery, radiotherapy, stem cell transplantation, and targeted therapies have been reported in selected cases. In the present case, CHOP

chemotherapy was administered as initial treatment.A noteworthy aspect of this case was the remarkable complete metabolic response achieved after only three cycles of CHOP chemotherapy, as demonstrated on follow-up PET/CT imaging. Such an early and profound response is clinically significant given the aggressive nature of histiocytic sarcoma. Although the patient was subsequently advised definitive surgical management, she did not undergo the planned procedure and was lost to follow-up. Two months later, she re-presented with locoregional recurrence, which remained surgically resectable and was managed with surgical excision. Histopathological examination revealed residual disease with a pathological stage of ypT3N3. Unfortunately, the patient was again lost to follow-up after surgery[8,9].The clinical course observed in this patient highlights two important aspects of histiocytic sarcoma. First, the excellent initial response suggests substantial chemosensitivity of the tumor to CHOP-based chemotherapy. Second, the development of locoregional recurrence despite an earlier complete metabolic response underscores the aggressive biological behavior of the disease and indicates that metabolic remission may not necessarily translate into durable disease control. These findings emphasize the importance of timely definitive local treatment and close surveillance following systemic therapy[10].Comparison with the available literature reveals several similarities. Like previously reported cases, the present patient presented with nonspecific symptoms and was initially suspected to have a high-grade esophageal carcinoma. The diagnosis was ultimately established through comprehensive immunohistochemical evaluation. However, unlike many reported cases with rapidly progressive disease and poor outcomes, our patient demonstrated an exceptional initial response to chemotherapy, thereby contributing valuable information regarding the potential effectiveness of CHOP-based regimens in selected patients with esophageal HS. Given the extreme rarity of primary esophageal histiocytic sarcoma, each additional case contributes important evidence regarding its clinical presentation, diagnostic approach, treatment response, and disease behavior. Accumulation of further case reports and multicenter experiences will be essential for improving diagnostic accuracy and establishing evidence-based management strategies for this rare malignancy.

Limitations

The present report is limited by the incomplete follow-up of the patient. Despite achieving an initial complete metabolic response following CHOP chemotherapy, the patient did not undergo the planned definitive surgical intervention and was subsequently lost to follow-up. She later presented with locoregional recurrence requiring surgical resection; however, postoperative follow-up data were unavailable due to loss to follow-up. Consequently, the long-term clinical outcome, progression-free survival, overall survival, and durability of treatment response could not be determined. Additionally, as this is a single case report, the findings cannot be generalized to all patients with primary esophageal histiocytic sarcoma**.**

Recommendations

Additional multicenter studies and case reports are needed to improve understanding of the clinical behavior, diagnostic features, and treatment outcomes of primary esophageal histiocytic sarcoma. Comprehensive immunohistochemical and molecular analyses should be incorporated whenever possible to enhance diagnostic accuracy and identify potential therapeutic targets. Long-term follow-up studies are also required to establish evidence-based management guidelines for this rare malignancy.

CONCLUSION

Primary esophageal histiocytic sarcoma is an extremely rare malignancy that may mimic high-grade carcinoma and requires comprehensive immunohistochemical evaluation for accurate diagnosis. Although our patient achieved a complete metabolic response following CHOP chemotherapy, subsequent locoregional recurrence underscored the aggressive nature of the disease. This case highlights the diagnostic value of immunophenotyping and PET/CT imaging, the potential chemosensitivity of histiocytic sarcoma, and the importance of definitive treatment and long-term follow-up.

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