A Case Report of Histiocytic Sarcoma in a 41-Year-Old Filipino Male*

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ABSTRACT

Histiocytic Sarcoma (HS) is a rare and aggressive hematopoietic neoplasm originating from the monocyte or macrophage bone marrow lineage. It has a poor outcome and pathogenesis is said to be caused by the transdifferentiation of one cell type to another of preexisting hematolymphoid tumors. Limited information both locally and internationally is due to its low incidence. Its rarity and overlap with diverse mimics makes it a clinical and diagnostic problem. This case report aims to discuss the pathologic findings of HS, explain the importance of immunohistochemistry (IHC) when dealing with poorly differentiated malignancies and review the current literature on its diagnosis. Presented here is a case report of a 41-year-old Filipino male who presented with abdominal pain and lymph node enlargement who subsequently underwent biopsy. His surgical pathology report revealed a poorly differentiated malignancy with the following considerations: hematologic malignancy and poorly differentiated carcinoma. An IHC panel (CD3, CD20, Ki67, Pan-Cytokeratin, S100, EMA, CD68 and CD163) was performed confirming the diagnosis of histiocytic sarcoma.

Key words: histiocytic sarcoma, immunohistochemistry, lymph node

It is believed that mononuclear phagocytic cells, such as dendritic cells and macrophages, are the source of histiocytic disorders. Histiocytic disorders are grouped into Langerhans's cell histiocytes (LCH) and non-LCH. The cause of the extremely rare non-LCH histiocytic malignancy known as histiocytic sarcoma (HS) is still unknown. It may manifest spontaneously or be constitutively connected to another hematologic malignancy, such as acute lymphoblastic leukemia or follicular lymphoma (ALL).[1,2]

Histiocytic sarcoma is a rarely reported disease with only a few hundred cases in the literature. In addition, there are no known environmental or hereditary genetic factors predisposing to the development and progression of the disease. Up to this day, there are no published articles made available in the Philippines regarding cases in Histiocytic Sarcoma. It has been diagnosed across all age groups, but is most commonly found in adults.[3]

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The pathologic analysis is used to make the diagnosis of histiocytic sarcoma, which should be connected with the clinical presentation. Due to its rarity, it can be challenging to identify because it can impact several organ systems and has a similar presentation to other disease entities. It must be separated from other histiocytic illnesses, dendritic cell disorders, metastatic solid tumors, primary familial lymphohistiocytic disorders, and acquired causes of hemophagocytic macrophage activation syndromes. Histiocytic disorders, such Langerhans cell histiocytosis and histiocytic sarcoma, can also affect several sites. Examining the two entities morphologically and immunohistochemically is necessary to distinguish them. Experts have agreed that tumors with pathologic characteristics resembling histiocytic sarcoma occurring in the setting of acute monocytic leukemia should not be regarded as such, although special consideration should also be given to these cases.[3]

Histiocytic Sarcoma (HS) is classified as a rare malignant neoplasm that shows morphologic and immunophenotypic features of histiocytes.[4] It is also known without origin that often manifests

as symptoms of singular or multiple extranodal malignancies.

Different lymphomas, other histiocytic and dendritic cell neoplasms, carcinomas, melanomas and pleomorphic sarcomas are included in the differential diagnosis of HS. The diagnosis of HS can be quite challenging and difficult due to its rarity and histologic overlap with numerous imitators. The diagnosis depends on the identification of morphological cues as well as the prudent application of immunohistochemical markers to validate its histiocytic lineage and to exclude imitators. HS can be mistakenly taken as other histiocytic disorders like Langerhans cell histiocytosis and Langerhans cell sarcoma.[4]

The diagnosis of HS is challenging due to its low prevalence and the potential for immunophenotypically and morphological overlap with other illnesses. It is decided upon after analyzing a biopsy sample taken from the affected area. Cytologic characteristics and improvements in the identification of histiocytic cell markers are the key to diagnosis.[5]

The objectives of the study were:

1. To present a case of histiocytic sarcoma and describe gross, microscopic and immunohistochemistry findings.
2. To discuss the importance of immunohistochemistry when dealing with poorly differentiated malignancies especially when histiocytic sarcoma is being considered.
3. To review the current literature on the diagnosis of histiocytic sarcoma.

THE CASE

This is a case of a 41-year-old male, who had lower abdominal pain one month prior to admission. It was described as crampy, non-radiating, with a pain scale of 9 to 10/10 with occasional chills. No other associated signs and symptoms such as nausea, vomiting, fever, dysuria, or changes in bowel movement. The patient sought teleconsultation and was advised to take Ibuprofen 400mg/tab three times a day and Buscopan with unrecalled dosage.

The patient was brought to a medical facility in Japan wherein initial diagnostics were requested. Ultrasound and radiographic imaging of the abdomen were unremarkable. However, a CT scan revealed an inflamed left inguinal lymph node. Hence, he was referred to Hematology department. He underwent an incision biopsy of the said lymph node which was diagnosed as a malignant tumor metastasis. It was suspected to be histiocytic sarcoma based on the results of morphology, infiltration pattern and immunostaining. Histopathologic and immunohistologic findings revealed large fine granular, broad sporangia, various unusual shapes, robust large nuclei of unequal size and polygonal atypical cells with large nucleolus with multiple nodular growths. Also seen were images of filling within the lymph sinuses. It was highly malignant with multiple fission images. Immunostaining revealed CD68 positive in large cells, EMA positive and negative for AE1/AE3, CK7, CK20, S-100, CD3 and CD20. Epithelial tumor metastasis, melanoma metastasis, malignant lymphoma, and Langerhans cell histiocytosis were not considered. He was advised to follow-up but he could not comply.

One week prior to admission in this institution, the patient arrived back in the Philippines and experienced colicky epigastric pain, radiating to the left flank, with a pain scale of 9 to 10/10. No other associated signs and symptoms such as nausea, vomiting, fever, icteria, dysuria and changes in bowel movement. He sought consult and was prescribed the following medications: Arcoxia 120mg/tab (completed for 7 days), Dolcet 1 tablet thrice a day, Rebamipide 100 mg thrice a day, and Omeprazole 20mg/tab twice a day. The patient brought up a concern that he noticed a left supraclavicular lymph node swelling. However, it was not addressed because it was unnoticeable.

Still with persistent abdominal pain, now with a pain scale of 5 to 6/10. The aforementioned left supraclavicular lymph node increased in size and was noted to be as big as a one peso coin. It was also observed to be smooth, firm and movable. No other associated signs and symptoms were noted. These prompted him to seek consult at this institution. He was subsequently admitted and underwent excision biopsy of the left cervical lymph node. Gross examination revealed several, irregularly shaped, tan-brown, rubbery pieces of tissue measuring 2.5cm x 1.8cm x 0.5cm in aggregate diameter. Microsection shows lymphoid tissues harboring a neoplasm arranged in sheets. The neoplastic cells are pleomorphic with hyperchromatic nuclei and prominent nucleoli (Figure 1). The tumor cells are seen almost completely replacing the lymph node. Diagnosis at the time was a poorly differentiated malignancy with the following considerations: hematologic malignancy and poorly differentiated carcinoma. The following immunohistochemical stains were suggested: CD3, CD20, Ki67, Pan-Cytokeratin, S100, EMA, CD68 and CD163.

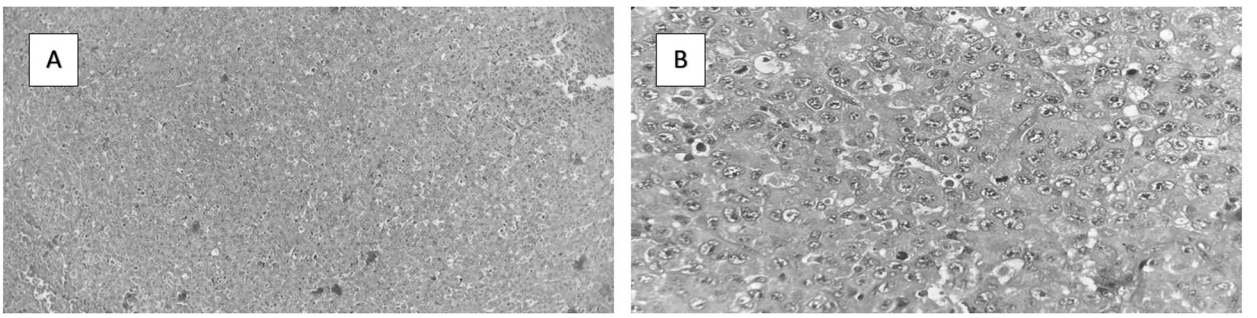

Figure 1. A, Low-power view showing lymphoid tissues harboring a neoplasm arranged in sheets. B, High-power view showing neoplastic cells are pleomorphic with hyperchromatic nuclei and prominent nucleoli.

Imaging studies were performed such as chest radiograph and plain CT scan of the whole abdomen. Chest radiograph findings were unremarkable. However, plain CT scan of the whole abdomen revealed a retroperitoneal mass and multiple intraperitoneal lymphadenopathies with some in aggregates.

JP drain insertion of the left chest was performed and pleural fluid cytology and cellblock revealed atypical cells suspicious for malignancy. The smears and microsection of the cellblock show several clusters and sheets of variably sized atypical cells with vesicular nuclei, prominent nucleoli admixed with scattered lymphocytes in a background of eosinophilic amorphous material (Figure 2). Immunohistochemical staining for LCA, CK, CD68, EMA and calretinin were suggested.

Suggested immunohistochemical stains were performed and showed the following: CD3- negative staining in the cells of interest, CD20- negativing staining in the cells of interest, Pan-Cytokeratin-negative staining in the cells of interest, S100-negative staining in the cells of interest, EMA-positive membranous staining in the cells of interest, CD68- positive staining in the cells of interest, CD163- positive staining in the cells of interest CD163- positive staining in the cells of interest and Ki67- high proliferative index (80%) (Figure 3). In conjunction with the histomorphologic findings and the immunostaining profile, the histomorphologic was signed out immunohistochemical profile compatible with histiocytic sarcoma.

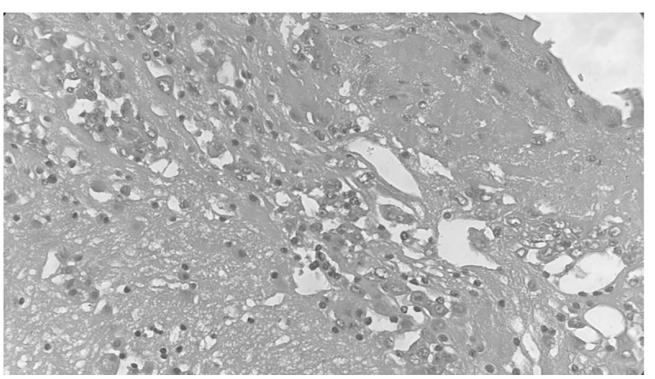

Figure 2. Microsection of the cellblock in high-power view showing several clusters and sheets of variably sized atypical cells with vesicular nuclei, prominent nucleoli admixed with scattered lymphocytes.

The patient was provided with conservative management and he expired on the thirty fourth hospital day due to complications of the disease.

DISCUSSION

The case is a 41-year-old male who presented with persistent abdominal pain and lymph node enlargement. CT scan of the whole abdomen revealed a retroperitoneal mass and multiple intraperitoneal lymphadenopathies with some in aggregates. His incision biopsy performed in Japan was diagnosed as a malignant tumor metastasis. Immunostaining revealed CD68 positive in large cells, EMA positive and negative for AE1/AE3, CK7, CK20, S-100, CD3 and CD20. It was suspected to be histiocytic sarcoma based on the results of morphology and immunostaining. Excision biopsy of the cervical lymph node done in our institution revealed a poorly differentiated malignancy with the following considerations: hematologic malignancy and poorly differentiated carcinoma. Suggested immunohistochemical stains were performed and showed positive staining for CD163, CD68, EMA and Ki67. On the other hand, CD3, CD20, Pan-Cytokeratin and S100 had negative staining in the cells of interest.

The World Health Organization (WHO) classifies tumors based on scientific data and include cancers

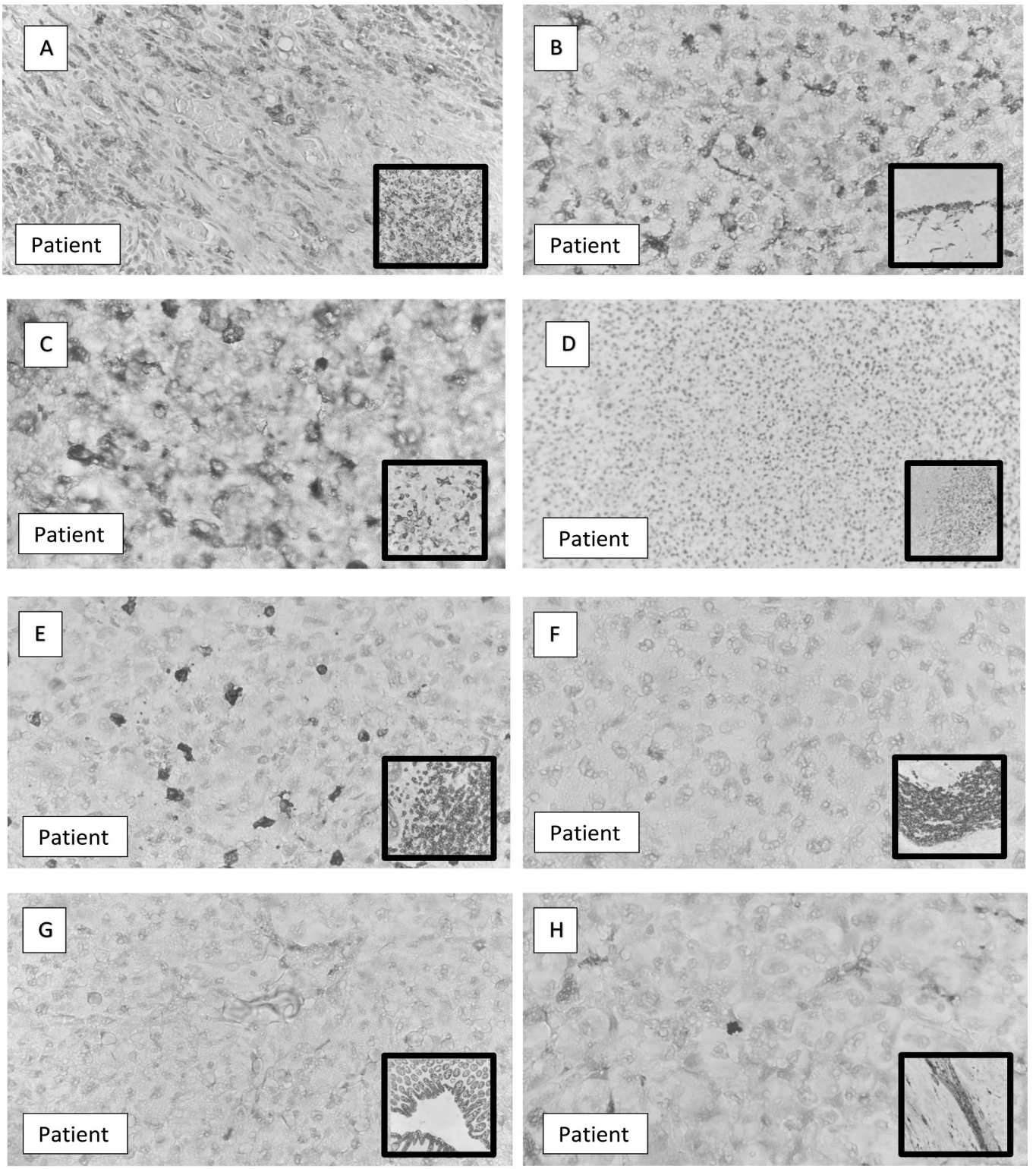

Figure 3. A, IHC of the present case showing a positive CD163 stain on cells of interest in comparison to the positive control (image inset). B, IHC of the present case showing a positive CD68 stain on cells of interest in comparison to the positive control (image inset). C, IHC of the present case showing a positive EMA stain on cells of interest in comparison to the positive control (image inset). D, IHC of the present case showing a positive Ki67 stain with high proliferative index of 80% in comparison to the positive control (image inset). E, IHC of the present case showing a negative CD3 stain on cells of interest in comparison to the positive control (image inset). F, IHC of the present case showing a negative CD20 stain on cells of interest in comparison to the positive control (image inset). G, IHC of the present case showing a negative Pan-Cytokeratin stain on cells of interest in comparison to the positive control (image inset). H, IHC of the present case showing a negative S100 stain on cells of interest in comparison to the positive control (image inset).

that affect different organ systems. A lineage-based framework underpins the classification structure, which flows broadly from benign to malignant and branches out into categories, families, types (disease/tumor), and subtypes. Where possible, a trinity of characteristics—lineage + dominant clinical + dominant biologic— was employed consistently.[6] With the 2016 revision of the World Health Organization classification, histiocytic sarcoma is recently classified within the category of the macrophage-dendritic cell lineage.[7] Dendritic cells, monocytes, and macrophages are members of the mononuclear phagocyte system whereas a histiocyte is a morphological term referring to tissue-resident macrophages.[8]

Histiocytic sarcoma shows morphologic and immunophenotypic features of mature tissue histiocytes. It is believed to be derived from monocytes/macrophages. Many inconsistencies in the terminology and diagnostic criteria of these lesions have complicated their recognition and characterization. These tumors were initially considered histiocytic in origin on the basis of morphology alone. The 2016 WHO classification has finally finalized its classification due to the merit of its morphological and immunophenotypic features.[9] HS most commonly occur in adults ages 46-55 years old mostly male according to SEER Surveillance.[8] There are risk factors that are associated with histiocytic sarcoma which can lead to different complications and development of more massive disease. Septic shock and failure of organs can be one of the highest possible risks that may be associated with HS specially in men. There are no known genetic or environmental factors that predispose people to developing HS. HS can arise alone or in conjunction with other hematologic neoplasms including acute lymphoblastic leukemia, myelodysplasia, or follicular lymphoma.[10] Histiocytic sarcoma has a median age at diagnosis estimated at 46 years with slight male predilection. Patients that are diagnosed have a history of lymphoma, MDS, or germ cell tumors.[11]

Manifestation of extranodal disease or diseases located outside a lymph node, lymphadenopathy or diseases affecting the lymph nodes are the presenting symptoms of Histiocytic Sarcoma. Skin lesions including plaques, nodules of tumors at any site of the body, intestinal obstruction and splenomegaly are samples of this disease's manifestations. Systemic symptoms such as fever, fatigue, night sweats and weight loss are common indication of Histiocytic Sarcoma.[12]

Extranodal sites, including the gastrointestinal tract, superficial and deep soft tissue, lung, and nasal cavity are the ones that are typically involved in Histiocytic Sarcoma. There are reports that Primary Histiocytic Sarcomas is manifested in lymph nodes, skin and brain. This disease is often presented as a fleshy mass with a well- circumscribed or a penetrative border and variable bleeding or necrosis (gangrene).[13] The case presented with persistent abdominal pain and lymph node enlargement.

Histiocytic sarcoma can be diagnosed when there is left over diagnosis after all other possible differential diagnoses have been excluded. To diagnose HS, there is a process of differentiating between HS and other conditions where both have similar signs and symptoms. HS can also affect bone marrow and spleen. It can also affect the central nervous system and gastrointestinal tract. Less than 20% of the cases reported are considered as primary HS. In addition, a systemic symptom of HS is weight loss.[14]

Transdifferentiation or conversion of one cell type to another of preexisting hematolymphoid tumor in some patients causes the arising of Histiocytic sarcoma. In histiocytic sarcoma,[11–15] Immunoglobulin H (IgH)–BCL2 fusion has been detected . Identical immunoglobulin gene rearrangement also happens in the histiocytic sarcoma. Cyclin D1–IgH fusion also is usually reported as histiocytic sarcoma. There is also a BRAF mutation V600E in this type of disease. Alterations in the MAP kinase pathway and chromatin regulation is the way of development of variety histiocytic neoplasms, including histiocytic sarcoma.[17]

On gross examination, HS is often solitary, fleshy and sometimes with hemorrhage and necrosis. Microscopic examination shows diffuse sheets of cells. The tumor cells are large, oval to round, sometimes spindle, with abundant cytoplasm. It can be eosinophilic with fine vacuoles. The nuclei are oval, indented, grooved, or irregularly folded, with vesicular chromatin and distinct. Nuclear pleomorphism is present. There are often admixed reactive inflammatory and stromal cells.[6] Mitotic figures and apoptotic cells are also frequently seen.[12,16] In the case presented, microsection of the lymph node revealed lymphoid tissues harboring a neoplasm arranged in sheets. The neoplastic cells are pleomorphic with hyperchromatic nuclei and prominent nucleoli.

Histiocytic Sarcoma, upon electron microscopy has abundant surface activity, microfilaments, short segments of rough endoplasmic reticulum and scattered brightened granules. Lymph nodes & spleen, non lymphoma, Lymph node & spleen-non lymphoid neoplasms, Histiocytic sarcoma.[15,16]

Cytopathologic findings include large epithelioid to pleomorphic cells with vacuolated cytoplasm and reniform nuclei, multinucleation, cytophagocytosis and inflammatory background. Since cytologic diagnosis can be challenging, immunohistochemistry is considered to be used for diagnostic confirmation.[6] Pleural fluid cytology and cellblock performed in the current case revealed atypical cells suspicious for malignancy. The smears and microsection of the cellblock show several clusters and sheets of variably sized atypical cells with vesicular nuclei, prominent nucleoli admixed with scattered lymphocytes in a background of eosinophilic amorphous material.

This disease is mostly recognized as diffuse large B cell lymphomas (DLBCL). The tumor cells are positive for CD68, CD163, lysozyme, CD11c and CD14 and are negative for myeloperoxidase, CD33 and CD34.[16] CD163+, a hemoglobin scavenger receptor (structurally unrelated membrane receptors), is a specific marker of Histiocytic Sarcoma.[17] Histiocytic sarcomas are very rare tumors that affect the hematopoietic (formation of blood cells) and lymphoid tissue. It resembles mature tissue histiocytes (normal immune cell that are found in many parts of the body especially in the bone marrow, the blood stream, the skin, the liver, the lungs, the lymph glands and the spleen.

It can involve multiple sites in the body and the tumors occur at any age.[13] Immunohistochemical markers are important for confirming diagnosis and ruling out differentials (Tables 1 & 2). Studies show that at least two of the following: CD163, CD68, KP-1, PGM-1, CD4 and lysozyme can be confirmatory for HS. CD163 is a hemoglobin receptor that is positive for monocytes or macrophages and CD68 is a lysosomal marker to identify histiocytic and monocytic cells. Immunohistochemical stains performed in the present case had the following results: CD3- negative staining in the cells of interest, CD20- negativing staining in the cells of interest, Pan-Cytokeratin- negative staining in the cells of interest, S100- negative staining in the cells of interest, EMA- positive membranous staining in the cells of interest, CD68- positive staining in the cells of interest, CD163- positive staining in the cells of interest CD163- positive staining in the cells of interest and Ki67- high proliferative index (80%).

Table 1. Showing the different differentials and immunohistochemical markers in comparison with histiocytic sarcoma.

Differentials[17]	Immunohistochemical Markers[17]
Histiocytic sarcoma	At least 2 of the following: CD163, CD68 (KP-1 and PGM- 1, the latter slightly more specific), CD4, lysozyme
	Absence of myeloid or lymphoid markers.
	Other adjuncts: PU.1, CD31, CD14, CD43, CD45RO, CD45, HLA-DR, fascin, factor XIIIa, a-1-antitrypsin
Langerhans cell histiocytosis	S100, CD1a, langerin
Anaplastic large cell lymphoma	CD30, EMA, T-cell markers (variable), ALK (subset)
Peripheral T-cell lymphoma	CD4 > CD8; antigen loss frequent (CD7, CD5, CD4/CD8, CD52)
High-grade	B-cell lymphoma B-cell markers and germinal center cell markers (variable)
Hodgkin lymphoma (syncytial variant of classical type)	CD30, CD15, PAX5, EBER (subset)
Metastatic carcinoma	Keratin, claudin-4, SMARCA4 (expression lost, subset)
Metastatic melanoma	S100, SOX10, HMB-45, MiTF, MART-1

Table 2. Showing the different differentials and immunohistochemical markers in comparison with the case.

	CASE	LCH	ALCL	HGBCL	HL	MC	MM
CD163	(+)	(-)	(-)	(-)	(-)	(-)	(-)
CD68	(+)	(+)	(-)	(-)	(-)	(-)	(-)
EMA	(+)	(-)	(+)	(-)	(-)	(-)	(-)
Ki67	(+)	(-)	(-)	(+)	(-)	(-)	(+)
CD3	(-)	(-)	(-)	(-)	(-)	(-)	(-)
CD20	(-)	(-)	(-)	(+)	(+)/(-)	(-)	(-)
Pan- Cytokeratin	(-)	(-)	(-)	(-)	(-)	(+)	(-)
S100	(-)	(+)	(-)	(-)	(-)	(-)	(+)

LCH, Langerhan's cell histiocytosis; ALCL, Anaplastic large cell lymphoma; HGBCL, High grade B Cell lymphoma; HL, Hodgkin lymphoma (HL); MC, Metastatic carcinoma; MM, Metastatic melanoma.

HS is an aggressive neoplasia managed using different types of treatment including surgery, radiotherapy, chemotherapy and combinations thereof, depending on the stage of the disease.[2,3] It is diagnosed based on a detailed pathological evaluation of involved tissue, interpreted in the clinical context. Being a rare disease with a lack of prospective randomized evidence, there is no standard of care for the treatment of these patients. Localized disease is usually treated with surgery with or without adjuvant radiation. The multisystem disease is treated with chemotherapy. Due to its aggressive nature, poor prognosis, and lack of a standard treatment regimen of choice, its management poses a challenge to the clinician.[4,12]

Histiocytosis necessitates a study to rule out an underlying neoplasm. Radical action, such as an extensive lymph node excision may be indicated and appropriate. The prognosis of HS is often aggressive with a fatal outcome; the stage the size of the tumor appear to be significant predictors of treatment plan.[2,15] The prognosis for histiocytic sarcoma is poor and its treatment is often ineffective. It may progress to malignant histiocytosis which can present as a disseminated disease and associated with systemic symptoms. Despite the bad prognosis, lymphoma-like treatment induces complete remissions in some patients and median survival is estimated at 2 years.[14,16,17]

SUMMARY

HS is a rare and aggressive malignancy. Presented here is a case of a 41-year- old Filipino male, who presented with abdominal pain and lymphadenopathy with histopathologic and immunohistochemical findings compatible with histiocytic sarcoma (HS). Excision biopsy of the cervical lymph node revealed a poorly differentiated malignancy with the following considerations: hematologic malignancy and poorly differentiated carcinoma. Immunohistochemical stains performed showed positive staining for CD163, CD68, EMA and Ki67 and was negative for CD3, CD20, Pan- Cytokeratin and S100. The histomorphologic diagnosis was signed out as immunohistochemical profile compatible with histiocytic sarcoma. Clinical correlation, histomorphologic features and IHC were all used to arrive with a diagnosis of HS. Its rarity and overlap with diverse mimics highlights the importance of IHC in diagnosing HS. Pathologic diagnosis through histopathology, cytology and immunohistochemical (IHC) staining are all crucial in arriving at the proper diagnosis.

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