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RESEARCH ARTICLE

DIAGNOSTIC PITFALL IN THE DIAGNOSIS OF A HISTIOCYTIC SARCOMAARISING IN GASTRO-INTESTINAL TRACT

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Abstract

Histiocytic sarcoma is a rare malignant tumor characterized by histiocytic morphologic and immunophenotypic features. It typically presents extranodally and has a poor clinical outcome, particularly in disseminated cases. Some patients have a history of hematolymphoid disorders, suggesting transdifferentiation from a preexisting hematolymphoid neoplasm. Diagnosis is challenging due to its rarity and histological overlap with various other neoplasms. Judicious use of immunohistochemical markers is essential to confirm its histiocytic lineage and exclude differential diagnoses. Recent molecular studies have identified recurrent alterations in the MAP kinase pathway and chromatin regulators, offering potential new therapeutic targets.

Introduction:-

Histiocytic disorders are derived from mononuclear phagocytic cells, such as macrophages and dendritic cells, collectively known as histiocytes. These disorders are categorized into Langerhans cell histiocytoses (LCH) and non-LCH groups. Histiocytic sarcoma (HS) is an exceedingly rare non-LCH histiocytic malignancy of unknown origin. HS can present as an isolated condition or may be clonally related to other synchronous or metachronous hematologic malignancies, including follicular lymphoma or acute lymphoblastic leukemia (ALL). [1-2]

The diagnosis of histiocytic sarcoma (HS) is particularly challenging due to its clinical and histopathological characteristics.

The objective of this work is to report a case of a rare tumor in the gastrointestinal tract diagnosed as histiocytic sarcoma (HS). Additionally, it aims to describe the clinical, radiological, and histological features, and to discuss the differential diagnoses of this uncommon malignancy.

Case Report:

52-year-old gentleman presented with progressive dysphagia over two months. His medical history includes well-controlled hypertension and type 2 diabetes managed with oral medication. He is a smoker with moderate alcohol consumption.

Upper gastrointestinal endoscopy revealed an ulcero-proliferative lesion and a contrast-enhanced CT scan of the thorax identified an intramural soft tissue mass in the gastric region, nearly obstructing the esophageal lumen

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Endoscopic biopsy demonstrated histiocytoid tumor (Figure 1)cells in nests of atypical cells with moderate to abundant eosinophilic cytoplasm and irregular nuclei within an inflammatory background.

Immunohistochemical staining (Figure 2A, B) indicated these cells were cytokeratin-negative but positive for CD163, CD68, and vimentin, markers of a histiocytic lineage. The Ki-67 proliferation index was about 30%, indicating moderate cellular proliferation.

Treatment involved esophageal stenting to relieve obstruction, followed by chemotherapy with cisplatin and 5-fluorouracil, and concurrent radiotherapy. Due to the advanced stage of the tumor, surgical resection was not feasible.

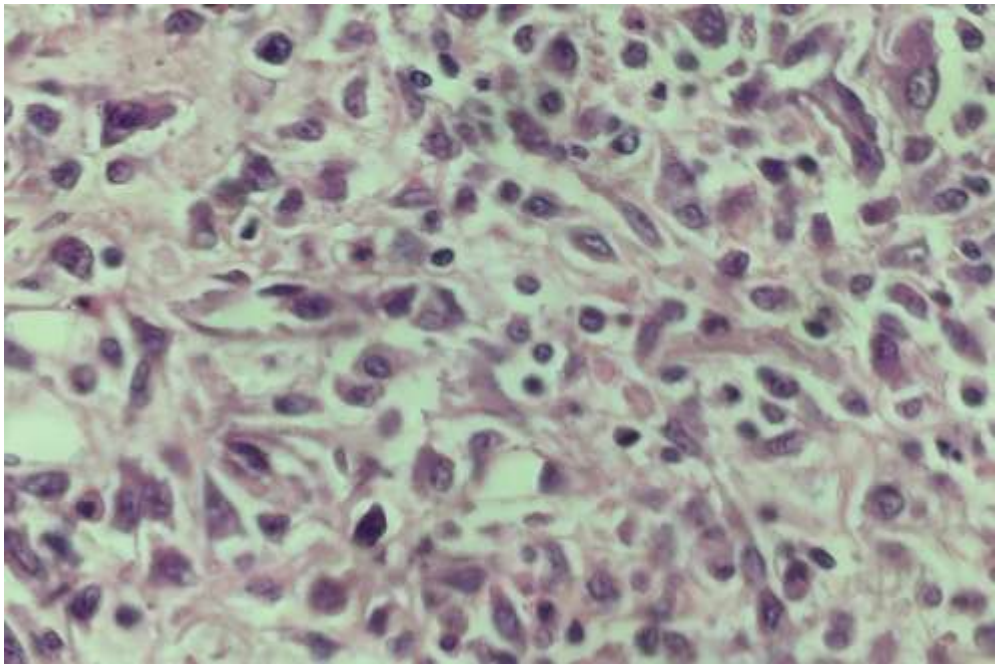

Figure 1:- Histiocytic sarcoma, characterized by sheets of epithelioid tumor cells, with eosinophilic cytoplasm, variably prominent nucleoli, and admixed neutrophilic inflammation.

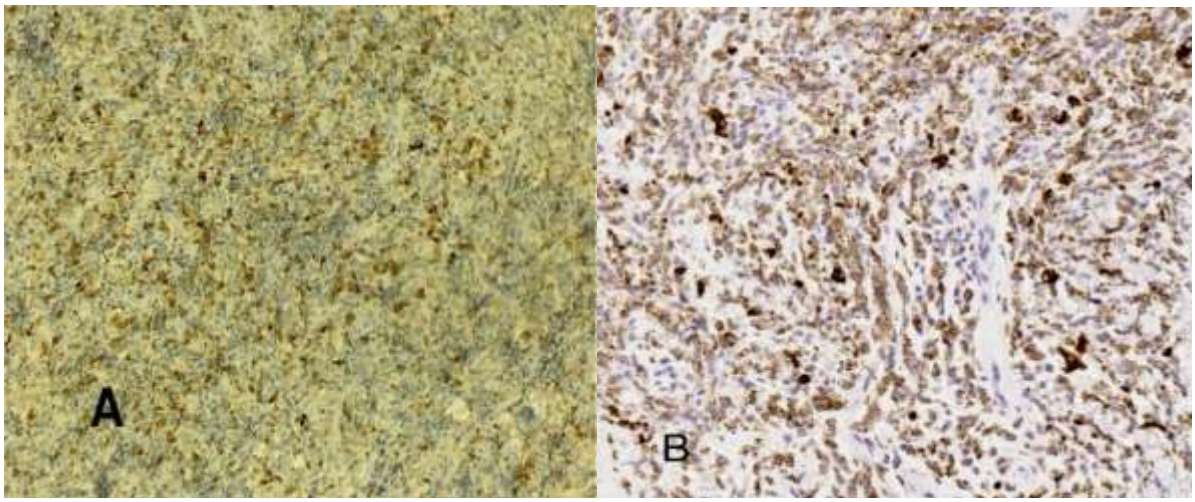

Figure 2.A:- Immunohistochemical stain for CD68 shows diffuse membranous/cytoplasmic staining in histiocytic sarcoma**B,** Immunohistochemical stain for CD163 shows diffuse cytoplasmic immunoreactivity in histiocytic sarcoma.

Discussion:-

Histiocytic sarcoma (HS) is a malignant neoplasm of mature histiocytes, which excludes myeloid sarcoma with monocytic differentiation and dendritic cell neoplasms.[3–5]

Clinical Features

Histiocytic sarcoma presents with a wide age distribution and slight male predominance.[6,7,8] While it occurs principally in adults, pediatric histiocytic sarcoma cases have been reported.[9] Histiocytic sarcoma typically involves extranodal sites, including the gastrointestinal tract, superficial and deep soft tissue, lung, and nasal cavity.[8] Primary histiocytic sarcomas of lymph nodes,[10] skin,[11] and brain[12] have also been reported. Patients with histiocytic sarcoma have variable clinical presentations, ranging from localized disease with a solitary mass to widely disseminated disease. A subset of patients with histiocytic sarcoma has a history of hematolymphoid disorder such as follicular lymphoma,[13,14] chronic lymphocytic leukemia/small cell lymphoma,[15] marginal zone lymphoma,mantle cell lymphoma,[16] hairy cell leukemia,[17] and multiple myeloma.[18] Association with germ cell tumor in the adult setting[19] and autoimmune lymphoproliferative syndrome in the pediatric setting has also been reported.[9]

Pathologic Features

The involved lymph nodes can show diffuse, sinusoidal or paracortical involvement, while extranodal sites are involved diffusely. The neoplastic cells are often very large, and are reminiscent of large cell or anaplastic large cell lymphoma, except that the cytoplasm is typically eosinophilic and voluminous. The cytoplasm in some cells often shows fine vacuoles. The nuclei are eccentrically located, with round, oval, irregular, or grooved contour, and delicate or coarse chromatin. Nucleoli are often small. The degree of cellular pleomorphism is variable. Multinucleated cells can be seen. Phagocytic activity is rare, but can be present. There can be variable admixtures of lymphocytes, plasma cells, neutrophils, and eosinophils, and the inflammatory component can be so prominent that the neoplastic cells are masked, especially for histiocytic sarcoma involving the central nervous system.[20] In rare cases, a myxoid or sarcomatoid growth pattern can be observed.

Immunohistochemistry plays a crucial role in diagnosing histiocytic sarcoma by confirming true histiocytic differentiation through positive markers and excluding morphological mimics with negative markers.

For positive markers, most histiocytic sarcomas express CD68, CD163, and PU.1 with a subset of cases also expressing CD31, CD4 (cytoplasmic), and CD45RO.[6] Expression of at least 2 of the following markers (CD68, CD163, CD4, and lysozyme) has been recommended as a diagnostic criterion in histiocytic sarcoma.Although a-1-antitrypsin, lysozyme, and CD68 (clones KP-1 and PGM-1) were used in earlier studies, each of these markers can be expressed in various neoplasms such as melanoma and is thus not specific for the histiocytic lineage alone.[10] CD163 and PU.1 have been increasingly used in the diagnosis of histiocytic sarcoma and other histiocytoses. Compared to CD68, CD163 is more specific for the histiocytic lineage and for the diagnosis of histiocytic sarcoma.The transcription factor PU.1, a marker for the macrophage lineage, can be particularly helpful to visualize and confirm the nuclear immunoreactivity in the tumor cells amidst the extensive background inflammation.[18] Aside from the markers discussed above, a subset of histiocytic sarcoma can also variably express CD15, CD45, human leukocyte antigen DR-isotype (HLA-DR), fascin, and factor XIIIa.[21]

In addition to expressing histiocytic markers, histiocytic sarcoma is expected to be negative for Langerhans cell (CD1a, langerin), follicular dendritic cell (CD21, CD35), myeloid cell (CD13, MPO), melanocytic (SOX10, HMB-45, MART-1), epithelial (keratin, EMA), vascular (ERG), and specific B-cell and T-cell(CD20,Pax5,CD3) markers.

Molecular Pathology

Although the presence of IG or TR gene rearrangement was previously considered to be incompatible with adiagnosis of histiocytic sarcoma, recent studies have shownthat clonal IG rearrangement, and rarely TR rearrangement,can occur in up to 50% of cases.[22,23]This phenomenon is observed in sporadic cases as well as cases that develop subsequent to or concurrent with B-lymphoblastic or T–lymphoblastic leukemia/lymphoma or low-grade B–cell lymphoma (especially follicular lymphoma and CLL/ SLL).1630,[22–27]In the latter scenario, the histiocytic sarcoma often shares the clonal markers of the lymphoma, such as IGH rearrangement, BCL2

rearrangement, and clonal cytogenetic aberrations, suggesting trans differentiation from neoplastic lymphoid cells to neoplastic histiocytic cells.[22,25,26,28]

A proportion of cases show BRAF or MAP2K1 mutation. The rare cases of histiocytic sarcoma associated with mediastinal germ cell tumor show the same isochromosome 12p genetic change as the latter.

Differential Diagnosis

The differential diagnoses include various large cell neoplasms, such as lymphoma (especially large B-cell lymphoma and anaplastic large cell lymphoma), Langerhans cell sarcoma, follicular dendritic cell sarcoma, melanoma, carcinoma, and undifferentiated pleomorphic sarcoma. A relatively non-cohesive growth pattern and an abundance of eosinophilic cytoplasm are clues to the diagnosis of HS, which has to be further supported by expression of the relevant immunohistochemical markers

Treatment

Due to the rarity of the disease and lack of large prospective trials, there is no standard treatment regimen for HS. The stage of disease usually determines the choice of therapeutic options among systemic chemotherapy, surgery, and/or radiotherapy [29]. Patients with unifocal/localized disease are treated with surgical resection with or without radiotherapy. Patients with the multisystem, multifocal disease usually have a more aggressive clinical course and are treated with combination systemic chemotherapy regimens. Data regarding treatment are limited to small case series and case reports. Most clinicians use regimens designed for patients with clinically aggressive lymphomas. The most commonly used regimens are cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), ifosfamide, cisplatin, and etoposide (ICE), or doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD).

Prognosis

HS is aggressive and most patients present at advanced clinical stage. The patients generally have a poor response to therapy with a median overall survival of 6 months.[30,31] A small subset of patients have localized disease, associated with a more favorable outcome. One case had an excellent response to MEK inhibition with trametinib and tyrosine kinase inhibition with imatinib.[32]

Conclusion:-

The diagnosis of histiocytic sarcoma is extremely challenging due to its rarity and histologic overlap with various other conditions. Identifying morphologic clues and carefully using immunohistochemical markers to confirm histiocytic differentiation and rule out mimics are essential. Recent discoveries of recurrent genetic alterations in the MAP kinase pathway and chromatin regulators in the pathogenesis of histiocytic sarcoma have highlighted potential therapeutic targets. Some of these targets are currently being investigated in clinical trials and may offer new treatment options for this aggressive disease.

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