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Case Report

Histiocytic sarcoma of paranasal sinus; report of the first case with emphasis on potential diagnostic pitfalls and differential diagnosis

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ABSTRACT

Introduction: Histiocytic sarcoma is a very rare hematopoietic malignancy of mature histiocytes with an aggressive clinical course, arising as a primary neoplasm or less commonly as a secondary neoplasm from pre-existing indolent lymphoma or rarely after therapy for other neoplasms. Most patients present at advanced stage with metastasis and hence have poor prognosis.

Case Report: A 70 year old female presented with difficulty in breathing and epistaxis. There was no pain, fever, weight loss and other systemic manifestations. On examination, there was a tumour in the nasopharynx. Based on the characteristic morphological features and an extensive panel of Immunohistochemistry markers, a diagnosis of histiocytic sarcoma was rendered.

Discussion: It usually occurs in extra nodal sites and the most common locations being the gastrointestinal tract, skin, various soft tissue sites, liver and spleen. To the best of our knowledge, rare case arising in nasal cavity has been reported, but tumour from paranasal sinus has not been reported in literature, so far. We report the first case of Histiocytic sarcoma arising from Ethmoid in an elderly female, also discuss the differential diagnosis, potential pitfalls and highlight the importance of immunohistochemistry.

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1. Introduction

Histiocytic sarcoma (HS) is an uncommon neoplasm accounting for less than 1% of all hematopoietic malignancies.¹ HS is characterised by proliferation of malignant cells exhibiting morphology and immunophenotype of mature tissue histiocytes.² On the basis of limited number of cases described in literature, most cases occur in adults with the median age of presentation about 52 years and some studies have shown a slight male predominance.³ HS generally presents at an extranodal location, as a solitary and painless mass. However, systemic symptoms such as fever, weight loss and night sweats are very common in these patients.⁴ Sometimes patients can present with hepatosplenomegaly, intestinal obstruction, skin rash,

skin tumour, lymphadenopathy or pancytopenia.⁵ HS can arise De novo or from transdifferentiation of low grade lymphomas like follicular lymphoma, chronic lymphocytic leukaemia /small lymphocytic lymphoma, extranodal marginal zone lymphoma^{6–8} or after chemotherapy for germ cell malignancies in the sites like gonads and mediastinum.⁹ The classic morphology include sheets of large cells with well defined cell borders, abundant eosinophilic cytoplasm, round to oval folded nuclei with vesicular chromatin and prominent nucleoli and exhibiting nuclear pleomorphism.¹⁰ Cytoplasmic vacuoles, xanthomatous cytoplasm, giant cells, frequent mitoses, foci of necrosis, hemophagocytosis or emperipolesis by tumour cells and a mixed inflammatory background can be observed.¹⁰

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2. Case Presentation

A 70-year-old female presented with difficulty in breathing and epistaxis. There was no pain, fever, weight loss and other systemic manifestations. On examination, there was a tumour in the nasopharynx. Computerized tomography revealed a large and moderately aggressive tumour, arising in the left ethmoid and involving the nasopharynx. Biopsy was performed and the sample was sent in 10% neutral buffered formalin solution. Routine processing of the tissue was done and haematoxylin & eosin stained sections showed sheets of pleomorphic large cells with abundant eosinophilic cytoplasm, enlarged round to oval vesicular nuclei with prominent eosinophilic nucleoli (Figure 1A). Giant cells (Figure 1B), foci of necrosis and a mixed inflammatory background was observed.

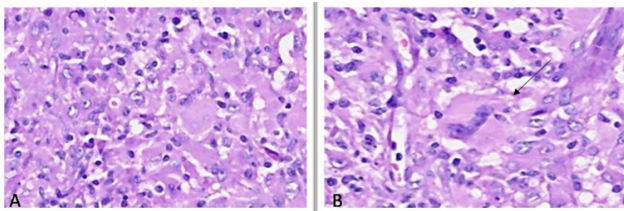


Fig. 1: (A) The neoplasm is composed of cells with abundant cytoplasm, enlarged vesicular nuclei with prominent nucleoli (H&E, magnification X40). (B) Few multinucleated giant cells (Black arrow) is also seen admixed (H&E, magnification X40)

Immunohistochemistry (IHC) was performed on automated Roche Ventana Benchmark GX. Initially pan cytokeratin and S100 IHC markers were run. The neoplastic cells were negative for Pancytokeratin (clone AE1/AE3) (Figure 2A), and showed diffuse positivity for S100 (clone 4C4.9) (Figure 2B).

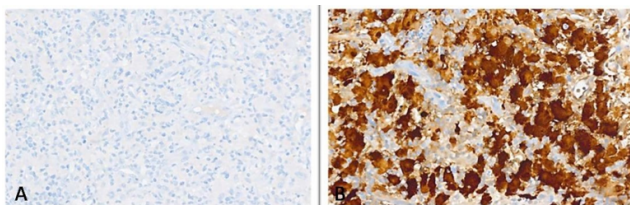


Fig. 2: (A) Immunohistochemical stain for Pancytokeratin (magnification X40) showing neoplastic cells are negative. (B) Immunohistochemical stain for S100 (magnification X40) show a strong diffuse staining in neoplastic cells.

Subsequently a panel of IHC markers were run, which included HMB45 (clone HMB45), Melan A (clone A103), CD1a (clone EP80), Leucocyte common antigen (LCA) (clone 2B11+PD7/26), CD68 (clone kP1), CD15 (clone MMA), CD23 (clone EP75). The neoplastic cells showed a diffuse membranous positivity with LCA, a diffuse cytoplasmic positivity with CD68 and were negative

for all the other markers (Figure 3A to Figure 3D), establishing the histiocytic origin of the neoplastic cells.

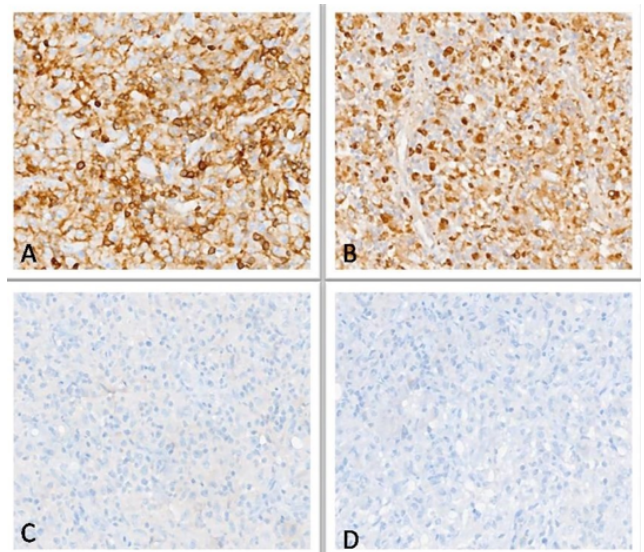


Fig. 3: Immunohistochemical staining: (A) The Neoplastic cells show diffuse membranous positivity with LCA (magnification X40). (B) Diffuse cytoplasmic positivity with CD68 (magnification X40). (C) Neoplastic cells are negative for Melan A (magnification X40). (D) Neoplastic cells are negative for CD1a (magnification X40).

CD23 and CD15 were focally positive in the reactive dendritic cells and B cells respectively, but were negative in the large neoplastic cells (Figure 4A and Figure 4B)

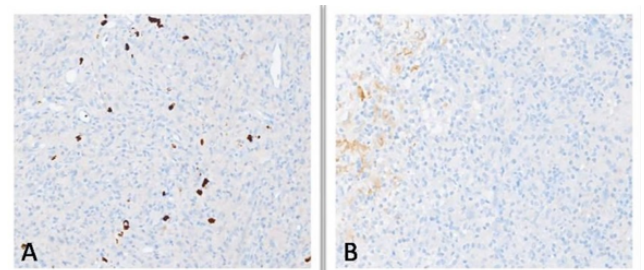


Fig. 4: (A) Immunohistochemical staining for CD15 (magnification X40), show intermingled positive inflammatory cells and the neoplastic cells are negative. (B) Immunohistochemical staining for CD23 (magnification X40), reveal few admixed dendritic cells and the neoplastic cells are negative.

3. Discussion

HS has a mild male preponderance and based on cases reported in the literature, has median age at diagnosis as 51 years and occurs in a wide range of age group from one to 89 years.³ The case presented here is an elderly female of age 70 years.

HS usually presents clinically with non-specific systemic symptoms such as lesions in the skin, lymphadenopathy or hepatosplenomegaly.¹¹ Our case presented with unusual symptoms like difficulty in breathing and epistaxis.

The usual extra nodal sites of presentation include skin, various soft tissue sites gastrointestinal tract, liver and spleen.¹² We present the first case report of HS arising in paranasal sinus. Our patient had the tumour originating in ethmoid sinus, infiltrating into and involving the nasal cavity.

It can arise *denovo* or as a secondary malignant neoplasm after treatment for other neoplasm or may occur following indolent neoplasms like follicular lymphoma or germ cell tumours or conditions like Idiopathic myelofibrosis and myelodysplastic syndromes.¹³ Our case was a *denovo* neoplasm and there was neither history of previous neoplasm nor any treatment.

Histological findings in HS vary according to the site of involvement. In lymph nodes, it can either totally efface or partially efface the architecture with a paracortical pattern of involvement. While occurring in extra nodal sites, they mostly have infiltrative borders and necrosis in few cases. Cytomorphologically, the neoplastic cells are pleomorphic, large, round to oval, have abundant amounts of eosinophilic cytoplasm and large, irregularly shaped or round to oval nuclei with finely dispersed chromatin and conspicuous nucleoli. Mitosis is consistently present, but variable in case to case. In some cases, the neoplastic cells can have spindled appearance simulating a sarcoma or can possess foamy cytoplasm and have multinucleated cells, thus imparting a xanthomatous appearance.¹⁰

By Immunophenotyping, these neoplastic cells, usually stain positive for CD4, CD31, CD45, CD68, CD163, fascin, HLA-DR and lysozyme.¹⁴ According to Classification of World health organisation (WHO), expression of one or more of the Histiocytic markers by immunophenotyping is essential for a case to be diagnosed as HS.

The potential diagnostic pitfall includes presence of mixed inflammatory background, giant cells and emperipolesis, which can lead to misdiagnosis of benign histiocytic disorders like Rosai-Dorfman disease. Nevertheless, careful attention to bland cytomorphological features and presence of sinusoidal pattern in nodal sites and presence of abundant plasma cells, will give a clue to Rosai-Dorfman disease and large cells by immunohistochemistry show diffuse S100 positivity, variable CD68 expression, Cd1a negativity and HLA-DR negativity that helps in confirming the diagnosis.¹⁵

The differential diagnosis include Interdigitating Dendritic Cell Sarcoma, Follicular Dendritic Cell Sarcoma, syncytial variant of nodular sclerosis Hodgkin Lymphoma, Anaplastic large cell lymphoma, metastatic melanoma, metastatic carcinoma and Langerhans cell sarcoma.

Interdigitating dendritic cell sarcoma may have epithelioid appearing large neoplastic cells and mixed inflammatory cell background, similar to HS. The cells having convoluted and lobulated irregular nuclei, indistinct cell borders, possessing long dendritic processes and Immunohistochemically having abundance of S100 staining, when compared to CD68 staining will clinch the diagnosis.¹⁶

The neoplastic cells of Follicular dendritic cell sarcoma can also be large, epithelioid, with indistinct cell borders and oval nuclei, along with presence of multinucleated giant cells. However, the immunohistochemistry for CD23, CD21, clusterin or fascin will reveal the positivity in at least one of the follicular dendritic cell markers, thus helpful in arriving at a definitive opinion.¹⁶

Classical Hodgkin's lymphoma (CHL), especially the syncytial variant of Nodular sclerosis subtype, can have large cells, which are variant Reed Stenberg cells arranged in sheets or clusters. Nonetheless, immunohistochemistry will aid in confirming CHL as the large cells are CD15 positive, CD30 positive and are negative with histiocytic markers.¹⁷

Anaplastic large cell lymphoma (ALCL), by morphology has sheets of large cells with abundant cytoplasm, admixed with inflammatory infiltrates and histiocytes, resembling HS. The presence of hallmark cells and large cells exhibiting a diffuse, membranous CD30 positivity, EMA positivity and ALK positivity (in cases of ALK positive ALCL), by immunohistochemistry will confirm the diagnosis of ALCL.¹⁸

Some cases of Metastatic carcinoma can have large cells and rarely hemophagocytosis, thus simulating HS.¹⁹ However, the presence of pan cytokeratin positivity will help in concluding the diagnosis as carcinomatous deposits and ruling out HS.

Metastatic melanoma can sometimes have cells morphologically resembling HS and in addition, S100 positivity in large cells will be misleading. Another potential pitfall is that rare cases of melanoma are CD68 positive as well.²⁰ Still, additional Immunohistochemical markers are extremely helpful in arriving at correct diagnosis, as the melanoma cells will be positive for Melan A and HMB 45.

Langerhans cell sarcoma (LCS), by morphology show large pleomorphic cells in a mixed inflammatory background, resembling HS. Yet, presence of numerous eosinophils, occasional cells with grooved and folded nuclei resembling 'twisted towel' and immunohistochemistry showing positivity for S100, CD1a and langerin along with negative expression of CD68, CD21 and CD35 will settle the diagnosis in favour of LCS.²¹

HS, being a very aggressive neoplasm with poor prognosis, the management options, depend on the stage of tumour and include a combination of chemotherapy,

surgery and radiotherapy. Our patient underwent surgery, but unfortunately was lost for follow up.

4. Conclusion

Pathologists must be aware of such rare aggressive neoplasms, presenting in unusual locations. A stringent morphological assessment along with judicious immunohistochemical panel is mandatory to avoid pitfalls and misdiagnosis. Considering the fact that HS has a very poor prognosis with average median survival of only two years, reporting all such cases will add to epidemiological data, can shed light on etio-pathogenesis, clinical features and course of progression, to unveil the mysteries of this rare neoplasm.

5. Conflicts of Interest

All contributing authors declare no conflicts of interest.


6. Source of Funding

None.

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