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Commentary

Bellicose and Contentious-Histiocytic Sarcoma

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Histiocytic sarcoma emerges as a malignant neoplasm delineating cellular proliferation which simulates morphological and immuno-phenotypic features of mature histiocytic cells. Additionally designated histiocytic medullary reticulosis, malignant histiocytosis, true histiocytic lymphoma or true histiocytic sarcoma, histiocytic sarcoma configures as a malignant neoplasm engendered from mature histiocytic cells. However, dendritic cell neoplasms, Langerhans cell neoplasms and myeloid sarcomas with monocytic differentiation do not categorize as histiocytic sarcoma.

Preponderantly extra-nodal, tumefaction may arise within diverse cutaneous surfaces, soft tissues, pulmonary parenchyma or central nervous system. Few neoplasms appear confined to regional lymph nodes.

Tumour cells are significantly pleomorphic or spindle shaped and may recapitulate cells of pleomorphic sarcoma or spindle cell sarcoma. Histiocytic sarcoma may arise from dedifferentiated B cell lymphomas, myeloid neoplasms and exceptionally T cell lymphomas. A subset of lesions may depict tumour cells with BRAF V600E genetic mutation and clonal IGH or TRG genomic rearrangements.

The infrequently discerned histiocytic sarcoma exemplifies < 1% of hematolymphoid neoplasms. Adults are commonly implicated with median age of disease emergence at ~61 years. A mild male preponderance is observed with male to female proportion of 5:3 [1,2].

Histiocytic sarcoma is preponderantly extra-nodal and implicates sites as cutaneous surfaces, soft tissue, pulmonary parenchyma or central nervous system. Nearly ~17% lesions arise within regional lymph nodes [1,2].

Of obscure aetiology, roughly ~25% neoplasms occur due to trans-differentiation of B cell lymphomas as small lymphocytic lymphoma/chronic lymphocytic leukaemia, follicular lymphoma, mantle cell lymphoma, extra-nodal marginal zone lymphoma or diffuse large B cell lymphoma [2,3].

Exceptionally, neoplasms may be associated with B cell or T cell lymphoblastic lymphoma/acute lymphoblastic leukaemia, myeloid neoplasms and mediastinal non-seminomatous germ cell tumours.

A subset of histiocytic sarcomas depict clonal rearrangements within IGH and TRG genes. Besides, neoplasms emerging from dedifferentiated lymphomas may delineate aforesaid genomic rearrangements. Lesions delineating trans-differentiation of B cell lymphomas depict genetic alterations encountered within preceding B cell lymphomas as chromosomal translocation t(14;18) observed within follicular lymphoma and del(13q) arising within small lymphocytic lymphoma or chronic lymphocytic leukaemia [2,3].

An estimated ~63% neoplasms depict BRAF V600E genetic mutation. Exceptionally, lesions concordant with mediastinal non-seminomatous germ cell tumours delineate iso-chromosome 12p [2,3].

Majority of neoplasms demonstrating advanced disease expound B symptoms as pyrexia, fatigue and weight loss. Upon physical examination, regional lymphadenopathy, hepatosplenomegaly and cutaneous lesions may be discerned [3,4].

Histiocytic sarcoma may exemplify lytic bone lesions. Central nervous system may be exceptionally involved. Median overall survival emerges at 6 months [3,4].

Upon cytological assessment, histiocytic sarcoma may be indicated by occurrence of mature histiocytic cells demonstrating variable cellular and nuclear pleomorphism [3,4].

Upon microscopy, a diffuse infiltration of tumour cells within circumscribing soft tissue may ensue. Characteristically, tumefaction exhibits sinusoidal infiltration within regional lymph nodes, spleen and hepatic parenchyma. Nodal architecture appears effaced. Besides, expansion of lymph node sinuses with sparing of follicles is commonly observed [4,5].

Tumour cells are permeated with abundant eosinophilic cytoplasm which is frequently foamy or vacuolated. Tumour cell nuclei appear elliptical, irregular or eccentric and are pervaded with vesicular chromatin, enlarged nucleoli and occasional nuclear grooves. Enlarged tumour cells appear to simulate mature histiocytic cells although display variable cellular and nuclear pleomorphism [4,5].

Tumour cells are entangled within a mixed inflammatory cell infiltrate composed of quantifiably variable reactive lymphocytes, plasma cells, benign histiocytic cells and eosinophils [4,5].

Exceptionally, multinucleated tumour giant cells, foci of erythrophagocytosis or focal aggregates of spindle shaped cells may be observed. Enhanced mitotic activity, apoptotic cells and focal tumour necrosis may be observed.

Ultrastructural examination depicts significant surface activity and occurrence of microfilaments and short segments of rough endoplasmic reticulum along with disseminated 'haloed' granules. Tumour cells appear to lack Birbeck granules [4,5].

Plasmacytoid dendritic cell neoplasms
Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm
Blastic plasmacytoid dendritic cell neoplasm
Langerhans cell and other dendritic cell neoplasms
Langerhans cell neoplasms
Langerhans cell histiocytosis
Langerhans cell sarcoma
Other dendritic cell neoplasms
Indeterminate dendritic cell tumour
Interdigitating dendritic cell sarcoma
Histiocytic neoplasms
Juvenile xanthogranuloma
Erdheim-Chester disease
Rosai-Dorfman disease
ALK+ histiocytosis
Histiocytic sarcoma

Table: *WHO classification of dendritic and histiocytic neoplasms 5th edition [4].*

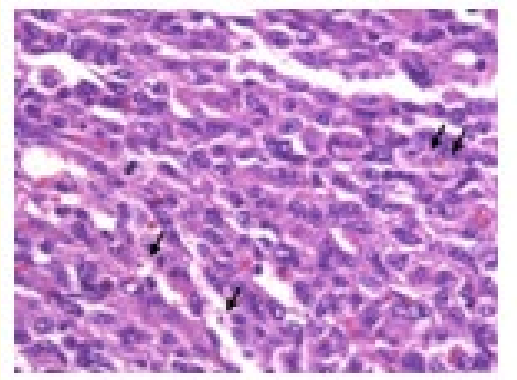

Figure 1: *Histiocytic sarcoma demonstrating histiocytic cells imbued with abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli. An admixture of reactive lymphocytes, plasma cells, benign histiocytic cells and eosinophils is observed [9].*

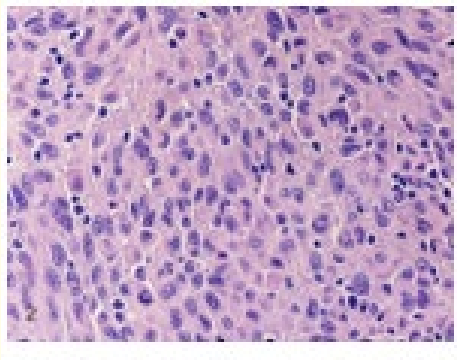

Figure 2: *Histiocytic sarcoma expounding cells impregnated with abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli. Commingling of reactive lymphocytes, plasma cells, benign histiocytic cells and eosinophils is encountered [10].*

Histiocytic sarcoma appears immune reactive to histiocytic markers as CD68, CD163, lysozyme, CD45, CD4, HLA-DR, CD14, CD15 and α-1 antitrypsin.

Tumour cells appear immune non reactive to B cell markers, T cell markers, follicular dendritic markers as CD21, CD23 and CD35 or Langerhans cell markers as CD1a and CD207. Neoplasm is immune non reactive to S100 protein, CD34, CD30, human melanoma black 45 (HMB45) antigen, myeloperoxidase (MPO) and cytokeratin [5,6].

Histiocytic sarcoma requires segregation from neoplasms as diffuse large cell lymphoma, anaplastic large cell lymphoma, Rosai-Dorfman disease, Langerhans cell histiocytosis, metastatic carcinoma, distant metastasis from malignant melanoma, myeloid sarcoma with monocytic differentiation or reactive histiocytosis and storage diseases.

Besides, distinction is required from myeloid sarcoma delineating monocytic differentiation, Langerhans cell neoplasms and various histiocytic lesions [6,7].

Appropriate neoplastic discernment necessitates concurrence of histopathological features with confirmation of cell of origin with specific techniques [6,7].

Localized unifocal disease may be appropriately alleviated by surgical extermination of the neoplasm with subsequent adjuvant radiotherapy and chemotherapy [6,7].

Disseminated disease necessitates intense regimens of chemotherapy with agents as ifosfamide, carboplatin and etoposide or CHOP-like (cyclophosphamide, doxorubicin, vincristine and prednisone) drugs. Besides, autologous hematopoietic stem cell transplantation appears beneficial [6,7].

Lesions arising within central nervous system may be managed with surgical intervention, chemotherapy and focal radiation therapy. Neoplasms demonstrating activation of RAS/MEK/ERK pathway may be managed with administration of MEK inhibitor, trametinib [7,8].

Singular surgical intervention or combination of surgical resection with radiotherapy is associated with extended overall survival, especially within subjects demonstrating cutaneous and connective tissue disease.

Singular surgical extermination expounds insignificant amelioration of overall survival in subjects with lesions confined to gastrointestinal tract or pulmonary parenchyma [7,8].

Neoplasms implicating hematopoietic and reticuloendothelial system expound inferior prognostic outcomes, despite the commencement of systemic chemotherapy [7,8].

In contrast to *de novo* neoplasms, secondary histiocytic sarcomas exhibit an aggressive clinical course and decimated overall survival [7,8].

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9. Image 1 Courtesy: Nature.com.

10. Image Courtesy: Diagnostic Pathology- Biomed Central.

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