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Editorial

Schematic and Sanguine-Epithelioid Hemangiendothelioma

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Epithelioid hemangioendothelioma emerges as a malignant neoplasm arising from endothelial cells. Tumefaction commonly implicates soft tissue, bone, pulmonary parenchyma, hepatic parenchyma or various cutaneous surfaces.

Neoplasm is associated with localized tumour aggression and may exhibit distant metastasis.

Definitive subtypes are discerned

- Classic epithelioid hemangioendothelioma delineating CAMTA1 gene and associated with WWTR1-CAMTA1 genetic rearrangement Tumours depicting WWTR1-CAMTA1 genetic rearrangement are composed of cords or miniature nests of enlarged endothelial cells imbued with abundant eosinophilic cytoplasm wherein tumour cells are embedded within a myxohyaline stroma and appear immune reactive to CAMTA1.
- Tumefaction associated with TFE3 gene and demonstrating YAP1-TFE3 genetic rearrangement. Neoplasms with YAP1-TFE3 genetic rearrangement is constituted of solid sheets, nests or pseudo alveolar configurations of epithelioid cells entangled within a fibrous stroma. Tumour cells appear immune reactive to TFE3.

Tumefaction incriminates adult subjects although may appear from infancy to the ninth decade. A female predilection is observed with female to male proportion of 1.5%:1 [1,2].

Commonly, epithelioid hemangioendothelioma occurs within soft tissue, bone, pulmonary parenchyma, hepatic parenchyma or various cutaneous surfaces. However, no site of disease emergence is exempt. Frequently, multifocal lesions appear within bone or diverse viscera. Nearly 50% instances are concurrent with or emerge from a vein [1,2].

Of obscure aetiology, neoplasm is preponderantly triggered by various genetic fusions. Tumefaction exhibits repetitive genomic fusions within WWTR1-CAMTA1 or YAP1-TFE3 genes [2,3].

Chromosomal translocations are associated with genetic fusion of CAMTA1 gene situated upon chromosome 1p36.23 with WWTR1 gene confined to chromosome 3q25.1. Besides, genetic fusion of exon 1 of YAP1 gene with exon 4 of TFE3 gene may emerge [2,3].

Cogent clinical representation is contingent to localization of the neoplasm. Pain is frequently encountered.

Tumefaction arising from a vein may delineate symptoms of vascular occlusion as oedema or thrombophlebitis. Localized tumour reappearance is observed. Distant metastasis into regional lymph nodes and pulmonary parenchyma may ensue [3,4].

Cytological examination exhibits moderately to abundantly cellular smears composed of singularly dispersed and clusters of polygonal cells delineating moderate nuclear atypia. Also, components as epithelioid cells or plasmacytoid cells may be discerned. Tumour cells are pervaded with delicate cytoplasm, elongated, tapering, cytoplasmic tails, fine nuclear chromatin with intra-nuclear inclusions, nuclear grooves and conspicuous nucleoli.

Blister cells or multi-nucleated cells with multi-lobated nuclei may appear. Cellular moulding may occur. Enlarged cells are pervaded with biphasic cytoplasm. Red blood cells appear impacted within intracytoplasmic lumens. Stromal fragments encompass the cellular component [3,4].

Frozen section exhibits a hyper-cellular tumefaction constituted of aggregates of epithelioid cells embedded within a myxohyaline stroma. Grossly, an inadequately circumscribed, firm, grey/white to tan tumefaction is observed. Tumour magnitude is variable and may extend to up to 18 centimetres [3,4].

Upon microscopy, classic epithelioid hemangioendothelioma demonstrating WWTR1-CAMTA1 genetic fusion delineates:

- Cords, strands or miniature nests of enlarged endothelial cells permeated with abundant eosinophilic cytoplasm, spherical, clear intracytoplasmic vacuoles representing miniature vascular lumens impregnated with erythrocytes and vesicular, spherical to ovoid, indented nuclei. Tumour cells are enmeshed within a myxohyaline stroma.

Neoplasm depicting YAP-TFE3 genomic fusion expounds:

Cellular Category	Cyto-morphology
Benign hepatocytes	Polygonal cells with granular, pigmented cytoplasm, round to ovoid nuclei, coarse chromatin discernible nucleoli.
Histiocytes	Foamy, vacuolated cytoplasm with intracytoplasmic debris, reniform, round or ovoid nucleus. Cytoplasmic tail or intra-nuclear inclusions absent
Mesothelial cells	Flattened sheets of enlarged cells with cytoplasmic rim as 'lacy skirt' and intercellular windows
Poorly differentiated adenocarcinoma	Cellular clusters with acinar pattern, cells with foamy, vacuolated cytoplasm, intracytoplasmic mucin, hyperchromatic nuclei. Focal necrosis and mitosis.
Hepatocellular carcinoma	Clusters of cells with granular cytoplasm, bile pigment, endothelial cell rimming, traversing vessels and granular background with innumerable naked nuclei
Malignant melanoma	Cell clusters with intracytoplasmic melanin pigment, bi-nucleated cells with mirror image nuclei and cherry red macro-nucleoli. Focal necrosis, marked pleomorphism
Mesothelioma	Hyper-cellular smears with morular architecture. Cells with increased N/C ratio, prominent nucleoli and intercellular windows
Epithelioid angiosarcoma	Hyper-cellular smears with cells displaying hyperchromatic nuclei. Significant nuclear and nucleolar pleomorphism, mitotic figures, apoptotic bodies and focal necrosis

Table: *Cytological mimics of epithelioid hemangioendothelioma [3].*

- Solid sheets, nests or pseudo-alveolar configuration of epithelioid cells. Tumour cells are pervaded with abundant, densely eosinophilic cytoplasm with vascular spaces and infrequent intracytoplasmic vacuoles. Neoplastic cells are enmeshed within a fibrous tissue stroma. Mitotic activity, cellular and nuclear atypia or focal necrosis is minimal.

Nearly 10% neoplasms exhibit features of malignant metamorphosis as significant nuclear pleomorphism, elevated mitotic activity, solid pattern of tumour evolution or tumour necrosis. Aforesaid neoplasms morphologically simulate epithelioid angiosarcoma and manifest an aggressive biological behaviour [3,4].

Epithelioid hemangioendothelioma is immune reactive to ERG, CD31, CD34, podoplanin (D2-40), FLI1 or von Willebrand factor.

Neoplasms depicting WWTR1-CAMTA1 genetic rearrangements appear immune reactive to CAMTA1. Tumours delineating YAP-TFE3 genomic rearrangements appear immune reactive to TFE3.

Tumour cells appear immune non reactive to S100 protein, SOX10, desmin, keratin, smooth muscle actin (SMA) or epithelial membrane antigen (EMA) [5,6].

Epithelioid hemangioendothelioma requires segregation from neoplasms as epithelioid angiosarcoma, epithelioid sarcoma, malignant melanoma diverse carcinomas or distant metastasis associated with various carcinomas [5,6].

Hepatic lesions require distinction from benign reactive cells, hepatocellular carcinoma, haemangioma, angiosarcoma or cholangiocarcinoma. Fluid effusions may delineate aggregates of benign mesothelial cells or neoplasms as mesothelioma or adenocarcinoma which mandate a demarcation.

Segregation is necessitated from soft tissue lesions as metastasis from poorly differentiated carcinoma, signet ring cell carcinoma, epithelioid angiosarcoma, pleomorphic liposarcoma, malignant melanoma or granulation tissue [5,6].

Neoplasm may be appropriately ascertained with radiographic imaging and histological assessment of surgical resection specimens with pertinent immunohistochemistry and molecular assay.

Computerized tomography expounds an inadequately circumscribed lesion delineating ground glass appearance [5,6].

Localized surgical extermination of the neoplasm with broad perimeter of uninvolved tissue is optimal and recommended mode of therapy. Tumour reoccurrence may ensue. Distant metastasis into pulmonary parenchyma or hepatic parenchyma occurs in ~30% neoplasms.

Disease associated mortality in neoplasms demonstrating metastasis into pulmonary parenchyma is ~65% [5,6].

Morphological features associated with aggressive biological behaviour appear as > 3 mitotic figures per 50 high power fields and tumour magnitude > 3 centimetres. Aforesaid neoplasms expound 5 year disease specific survival at ~59%. Generally, benign or low grade neoplasms are devoid of tumour associated mortality [5,6].

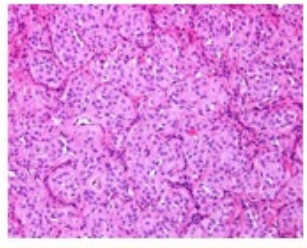

Figure 1: *Epithelioid hemangioendothelioma demonstrating cords and strands of epithelioid endothelial cells impregnated with eosinophilic cytoplasm, spherical nuclei surrounded by myxohyaline stroma [7].*

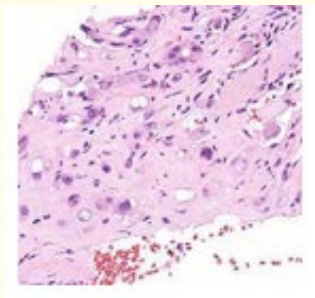

Figure 2: *Epithelioid hemangioendothelioma delineating cords and nests of epithelioid cells with abundant, eosinophilic cytoplasm and ovoid nuclei encompassed within a myxohyaline stroma [8].*

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7. Image 1 Courtesy: Science photo library.

8. Image 2 Courtesy: Libre pathology.

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