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Editorial

The Metamorphosed Meta-Arteriole-Angiosarcoma

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Angiosarcoma is an extensively infiltrative, malignant neoplasm composed of sheet-like tumour configuration or irregular, anastomosing vascular channels exhibiting an inadequately defined perimeter. Vascular articulations are coated with multi-layered endothelial cells which demonstrate prominent nuclear atypia. Focal necrosis and elevated mitotic activity is observed.

Tumefaction exhibits morphological or phenotypic evidence of endothelial differentiation. Commonly, angiosarcoma incriminates cutis of head and neck, diverse viscera, soft tissues, bone or retroperitoneum.

Classically, angiosarcoma depicts upregulation of vascular specific receptor tyrosine kinases as TIE1, KDR, TEK or FLT genes. Overexpression of upstream regulators of VEGF as HIF1 alpha and HIF2 beta can be delineated [1,2].

Radiation induced and chronic lymphedema associated angiosarcoma display genomic amplification of c-MYC gene which can be detected with FISH. Certain neoplasms harbour repetitive mutations of genes implicated in angiogenesis as PTPRB or PLCG1 [1,2].

Characteristically, primary cutaneous angiosarcoma emerges within elderly subjects secondary to significant actinic exposure. However, secondary angiosarcoma may infrequently ensue [1,2].

Cutaneous angiosarcoma commonly emerges within head and neck and is exceptionally confined to trunk or extremities [1,2].

Angiosarcoma of salivary glands or oral cavity is extremely infrequent. Prognostic outcomes of salivary gland angiosarcoma remain undetermined [1,2].

Primary angiosarcoma of breast may appear de novo. Secondary breast angiosarcoma is induced by therapy for preceding carcinoma breast or following postoperative radiotherapy or chronic lymphedema (Stewart-Treves) syndrome. Angiosarcoma may incriminate upper extremities at ~15 years following radical mastectomy and axillary lymph node dissection with accompanying chronic lymphedema (Stewart-Treves syndrome). Neoplastic cells display variable nuclear atypia and hyperchromatic nuclei with enlarged nucleoli. Mitotic figures are frequently discerned [1,2].

Hepatic angiosarcoma is an infrequent, primary hepatic neoplasm arising due to exposure to vinyl chloride, arsenic or thorium dioxide (Thorotrast) [1,2].

Primary pulmonary angiosarcoma is exceptionally discerned, manifests with respiratory symptoms as haemoptysis, cough or dyspnoea and exemplifies a significantly adverse prognosis [1,2].

Angiosarcoma of spleen is an infrequent, aggressive neoplasm with significant, proportionate distant metastasis and inferior prognosis. Symptoms as left upper quadrant pain, gastrointestinal haemorrhage, splenomegaly or haemo-peritoneum secondary to splenic rupture may be discerned [1,2].

Primary angiosarcoma of small intestine is extremely exceptional and exhibits a significantly unfavourable prognosis [1,2].

Ovarian angiosarcoma is commonly associated with abdominal pain or infrequent, distant metastases into pulmonary parenchyma or various organs. Neoplastic dissemination beyond ovary may concur with initial tumour representation. Disease progression may emerge within <one year following tumour detection [1,2].

Primary renal angiosarcoma, designated as renal hemangiosarcoma is an extremely exceptional neoplasm occurring within sixth or seventh decade [1,2].

Angiosarcoma exemplifies upregulation of vascular specific receptor tyrosine kinases as TIE1, KDR, TEK and FLT. Upregulation of aforesaid genes along with overexpression of VEGFR may induce angiogenesis, expansion of endothelial cells and increased vascular permeability.

Primary breast angiosarcoma demonstrates KDR genetic mutation, irrespective of radiation exposure. c-MYC genetic amplification ensues within radiation induced or lymphedema associated angiosarcoma.

Secondary angiosarcoma depicts genomic amplification of FLT4 gene [1,2].

Characteristically, the infiltrative angiosarcoma demonstrates rapid, extensive proliferation of vascular endothelial cells. Locally aggressive angiosarcoma is associated with significant regional lymph node and distant metastases [1,2].

Of obscure aetiology, angiosarcoma may occur post-irradiation or following lymphedema of extended duration (Stewart-Treves syndrome). Exposure to vinyl chloride, arsenic or thorium dioxide (Thorotrast) can induce the neoplasm [1,2].

Few instances concur with implanted foreign material, pre-existing haemangioma or vascular malformations or appear associated with preceding trauma or surgery [1,2].

Angiosarcoma can manifest as a component of diverse syndromes as neurofibromatosis or Maffucci syndrome. Exceptionally, tumefaction configures as heterologous components of various neoplasms as benign or malignant nerve sheath tumours [1,2].

Characteristically, rapidly progressive, macular, nodular or plaque-like, blue or purple lesions of significant duration appear upon scalp or face. Diffuse, intradermal tumour dissemination with indistinct perimeter induces significant, multi-centric lesions [1,2].

Angiosarcoma manifests as a bruised, purpuric cutaneous zone prone to haemorrhage upon exposure to trauma. Gradually, lesions enlarge and become painful or oedematous [1,2].

Advanced neoplasia may display focal haemorrhage or ulceration. Cervical lymphadenopathy can infrequently appear as an initial presenting symptom [1,2].

Upon gross examination, cutaneous lesions manifest as nodules or plaques with purple or maroon discoloration. Cut surface appears haemorrhagic with focal necrotic areas [1,2].

Neoplasia of breast may be cutaneous or intra-parenchymal. Cutaneous lesions emerge in concurrence with postsurgical lymphedema or secondary to irradiation of breast or chest wall [1,2].

Intra-parenchymal lesions manifest as solitary tumefaction or multiple nodules with purple discoloration of superimposed cutis. Deep seated lesions of soft tissue are enlarged, painful or gradually progressive and may concur with coagulopathy [1,2].

Upon microscopy, angiosarcoma exhibits a varied morphologic countenance. Tumour is markedly infiltrative and inadequately circumscribed [1,2].

The vasoformative tumour may be configured of bland cells. Alternatively, solid sheets of significantly pleomorphic cells are discerned with absence of definitive vascular articulations. Innumerable irregular, anastomosing, vascular channels are layered with atypical endothelial cells [1,2].

Typically, neoplastic cells are plump and pleomorphic. Mitotic activity is significant. Intra-tumour haemorrhage is frequently discerned.

Tumour cells appear as spindle- shaped, polygonal, epithelioid or primitive, spheroidal cells. Papillae or solid cellular nests may be configured within vascular lumens. Lymphoid aggregates may appear within intervening stroma [1,2].

Neoplastic vasculature ramifies within dermis and vascular intercalation through dermal collagen and subcutaneous soft tissue may ensue. Morphological evaluation of poorly differentiated angiosarcoma with solid pattern of tumour evolution can be challenging [1,2].

Ultrastructural examination exhibits Weibel-Palade bodies denominated as elongated, cylindrical or rod shaped bodies surrounded with a singular membrane. Microtubules confined to matrix can be delineated within cytoplasm of endothelial cells [1,2].

Tumour Differentiation	Description
1	Simulating normal adult mesenchymal tissue (low grade leiomyosarcoma)
2	Certain histological subtypes (myxoid round cell liposarcoma)
3	Soft tissue osteosarcoma, sarcomas as embryonal, Ewing's, synovial, primitive neuroectodermal or undifferentiated sarcoma
Mitotic activity	
1	0 - 9 mitosis/10 high power fields
2	10 - 19 mitosis/10 high power fields
3	≥ 20 mitosis/10 high power fields
Tumour Necrosis	
0	Absence of necrosis
1	< 50% necrosis
2	≥ 50% necrosis

Table 1: *Histologic grade of soft tissue sarcoma [2,3].*

Grading of soft tissue sarcoma is contingent to ascertained points and denominated as:

- Grade X: tumour grade cannot be assessed
- Grade I: total score of 2 or 3
- Grade II: total score of 4 or 5
- Grade III: total score of 6, 7 or 8.

Concurrence of histological grade and clinical outcomes appear debatable as gradation of angiosarcoma is not recommended [2,3].

Stage	T	N	M	Histological grade
IA	T1	N0	M0	GX,G1
IB	T2	N0	M0	GX,G1
	T3	N0	M0	GX,G1
	T4	N0	M0	GX,G1
II	T1	N0	M0	G2,G3
IIIA	T2	N0	M0	G2,G3
IIIB	T3	N0	M0	G2,G3
	T4	N0	M0	G2,G3
IV	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

Table 2: *TNM staging and prognostic groups (soft tissue sarcoma, trunk and extremities) [2,3].*

Angiosarcoma is immune reactive to various endothelial cell markers as CD31, CD34, ERG, FLI1, VEGF or factor VIII. Besides, epithelioid angiosarcoma is immune reactive to cytokeratin, EMA and CD30. Podoplanin with D2-40 immunoreactivity is variably encountered pertaining to focal lymphatic differentiation. Angiosarcoma is immune non-reactive to HHV8 [3,4].

Angiosarcoma requires segregation from neoplasms as atypical fibroxanthoma, Kaposi's sarcoma, retiform haemangioendothelioma, Kaposiform haemangioendothelioma, epithelioid haemangioendothelioma, spindle cell haemangioma, diverse reactive or benign vascular tumours as capillary haemangioma, juvenile haemangioma or strawberry nevus, cherry angioma, pyogenic granuloma, cavernous haemangioma, epithelioid haemangioma, vascular ectasias as nevus flammus or spider nevus, angiomatosis, post-irradiation atypical vascular lesion or solitary fibrous tumour. Angiosarcoma can be appropriately evaluated with clinical representation. Cogent tissue sampling with microscopic examination of the neoplasm appears confirmatory [3,4].

Mass effect of enlarged angiosarcoma may engender compression of critical organs as compression of ureter with consequent renal failure and associated biochemical abnormalities or anaemia of chronic disorder and elevated sedimentation rate [3,4].

Plain radiographs of angiosarcoma of bone represent with a destructive, lytic tumour configuration devoid of sclerotic perimeter [3,4].

Imaging techniques as computerized tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET-CT) can be adopted to assess tumour magnitude and anatomic localization. MRI of angiosarcoma of head and neck enunciates intermediate signal intensity upon T1 weighted imaging with possible hyper-intense areas indicative of haemorrhage [3,4].

Soft tissue angiosarcoma manifests as an irregular, enhancing, soft tissue mass discernible upon contrast enhanced CT [3,4].

Breast angiosarcoma appears nonspecific upon imaging. Mammography demonstrates a solitary, poorly defined, non-calcified tumefaction. MRI depicts heterogeneous neoplasm of low signal intensity upon T1 weighted imaging and enhanced signal intensity upon T2 weighted imaging [3,4].

Hepatic angiosarcoma is an aggressive, vascular neoplasm preponderantly delineating a hypo-attenuating tumefaction along with or devoid of hyper-attenuating foci upon non enhanced CT [3,4].

Heterogeneous tumour enhancement upon contrast enhanced CT indicates the presence of tumour necrosis and fibrosis [3,4].

Features such as tumour magnitude, discernible epithelioid component, enhanced mitotic activity and tumour cell aggregates within surgical perimeter are associated with adverse prognostic outcomes [3,4].

Surgical extermination of neoplasm is an optimal, recommended mode of treatment, in addition to chemotherapy and radiotherapy. Besides, targeted therapy and immunotherapy may be adopted as contemporary therapeutic measures [3,4].

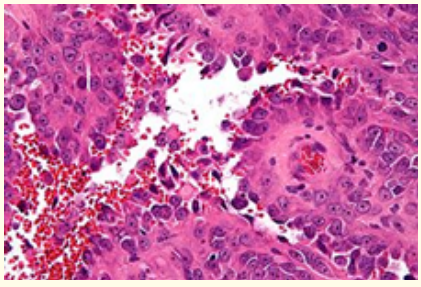

Figure 1: *Angiosarcoma depicting vascular articulations layered with neoplastic cells with indistinct cytoplasm, significant nuclear atypia and prominent nucleoli admixed with extravasation of red cells [5].*

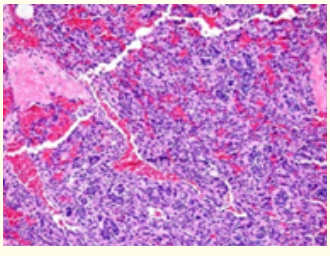

Figure 2: *Angiosarcoma demonstrating sheets of spindle-shaped and elliptical endothelial cells configuring vascular articulations incorporated with significant quantities of red cells. Cellular and nuclear atypia, nuclear pleomorphism and indistinct cytoplasm is observed [6].*

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5. Image 1 Courtesy: Libre Pathology.
6. Image 2 Courtesy: Science direct.

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