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Angiosarcoma, Classification, Histological Differentiation: Review

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Abstract: **In this review we aim to give an overview of angiosarcoma from pathological aspects, we intended to focus of classification and pathogenesis and histological differentiation of each subtype, also to discuss the staging method of this type of soft tissue tumors. Databases: PubMed/ MIDLINE, and EMBASE were searched for articles published in English language with human subject up to January 17 2017. Literature search was performed to identified pathological studies that discussing the classification, pathogenesis, and histological differentiation of angiosarcomas. In addition to that, references found in identified articles were searched for more relevant studies. AS stem from any structural site in the body, many frequently the head and also neck, and breast cutaneous cells. Previous irradiation, harmful chemical exposure, as well as chronic lymphedema are determined as particular risk factors. Angiosarcoma could emerge in any type of soft-tissue structure or viscera as well as cutaneous angiosarcomas commonly entail the head and also neck, particularly the scalp. Angiosarcomas are of endothelial cell origin and tumours emerging directly from significant capillary or the heart are uncommon.**

Keywords: **Angiosarcoma, classification, histological differentiation.**

1. INTRODUCTION

Angiosarcomas (AS) are rare malignancies of endothelial origin. These carcinomas are classified as; cutaneous, body organs (visceral), and soft tissue subtypes. Histologically, angiosarcomas range from well-differentiated tumors with variable endothelial atypia to top-quality spindle cell malignancies. Conventional appearance of angiosarcomas, a special morphologic subtype of angiosarcoma, in which the malignant endothelial cells have a mainly (or specifically) epithelioid look, has actually been defined as epithelioid angoisarcoma consisting of less than 1% of soft tissue sarcomas which in turn account for 1% of adult strong malignancies [(1,2)]. Existing understanding of AS natural history, management, and result stems from little AS accomplice reports. AS stem from any structural site in the body, many frequently the head and neck, and breast cutaneous tissues [(3)]. Previous irradiation, toxic chemical exposure, and chronic lymphedema are identified as particular risk factors [(4,5)]; however, most cases are erratic [(3)]. AS typically are extremely aggressive, with a tendency for remote transition and poor total survival [(6)]. Scientifically AS is unforeseeable; nevertheless, current insights suggest that it may make up a cluster of vascular malignancies linked by a typical pattern of endothelial cell distinction, rendering the identification of unique AS-therapeutic targets even more difficult [(2,6)].

Angiosarcoma is an aggressive sarcoma with distinction to blood or lymphatic endothelium. The tumor can emerge at any anatomic area including, a lot of typically, the scalp, the breast and the extremities [(7)]. The disease represents approximately 2% of all soft tissue sarcomas2 and the occurrence is rising, probably connected to increased use of radiotherapy in the treatment of breast and other cancers [(8)]. Known risk factors for developing angiosarcoma consist of prior radiation, polyvinyl chloride, arsenic and thorium dioxide direct exposure, chronic lymphedema, familial syndromes

and perhaps UV direct exposure, provided the greater frequency of scalp angiosarcoma [7,9]. Angiosarcomas are prone to locoregional reoccurrence, far-off and nodal metastases, and have infamously poor prognoses. The reported rates of advanced/metastatic disease at discussion differ from 16 to 44%, and the general disease-specific survival is reported as approximately 30 - 40% in contemporary series [10,11,12].

Cutaneous angiosarcoma of the head and neck regions seems to be a distinct neoplasm with characteristic clinicopathologic features that differ from angiosarcoma in other structural locations. Medical diagnosis of cutaneous angiosarcoma is frequently delayed, due to its putatively innocous scientific appearance [14]. There is general agreement that the poor prognosis of cutaneous angiosarcoma of the head and neck regions is not influenced by the histologic grade and mitotic activity, as it holds true with angiosarcoma in other structural areas. Tumor size, depth of tumor invasion, and completeness of surgical resection are more trustworthy prognostic indications [14,15].

In this review we aim to give an overview of angiosarcoma from pathological aspects, we intended to focus of classification and pathogenesis and histological differentiation of each subtype, also to discuss the staging method of this type of soft tissue tumors.

2. METHODOLOGY

Databases: PubMed/ MIDLINE, and EMBASE were searched for articles published in English language with human subject up to January 17 2017. Literature search was performed to identified pathological studies that discussing the classification, pathogenesis, and histological differentiation of angiosarcomas. In addition to that, references found in identified articles were searched for more relevant studies.

Finally, Principle investigator “Tawfiq Zuhair Al Laylah” has to decide at the end for which study to be included in this review.

3. RESULTS

- **Pathogenesis of AS:**

Angiosarcoma is thought to emerge from vascular endothelium. A selection of factors may be involved in the pathogenesis and also progression of angiosarcoma [16,17]. Vascular endothelial growth factor (VEGF) is associated with the law of endothelial cell expansion, angiogenesis, and also vascular leaks in the structure [18,19]. VEGF-D belongs to the VEGF family of glycoproteins as well as has been located to be upregulated in the tumor cells of some malignancies. One research [18] examined the lotion VEGF-D degrees in 11 patients with cutaneous angiosarcoma of the face and scalp and also 18 healthy and balanced controls. Product VEGF-D degrees were found to be substantially elevated in angiosarcoma patients compared with the controls; VEGF-D degrees enhanced with increasing level of disease in the former group [18]. The various research study with the very same writers [19] also assessed the product angiopoetin 2 degrees in the exact same parts of controls and also patients. Angiopoetin 2 promotes a fast boost in capillary diameter, renovation of the basal lamina, proliferation and migration of endothelial cells, and also new member’s vessel development [19]. As was observed with VEGF-D, angiopoetin 2 degrees were dramatically raised in angiosarcoma patients as well as enhanced with phase of disease [19]. 3rd research performed by Yamamoto et al [20] assessed pole cell density, the expression of stem cell factor (a growth factor cytokine), and kit receptor in the primary sore of 7 patients with angiosarcoma. Biopsies from the tumor exhibited raised mast cell thickness compared with biopsies from typical skin; package receptor was revealed on pole cells infiltrating around the tumor cells. Stem cell factor (SCF) was found in tumor cells as well as was believed to, in part, induce boosted numbers of pole cells that could add to neovascularization and tumor cell expansion. Zeitz and also colleagues evaluated Fas (a cell surface area receptor of the nerve development factor/tumor death factor superfamily) and also Fas ligand (Fas-L) expression and also tumor penetrating lymphocytes (TILs) in 40 patients with angiosarcoma [17]. Fas and also Fas-L contribute in controling apoptosis within the body immune system. Fas was detected in the less than 50% of tumors and was unassociated to TILs or survival. On the other hand, Fas-L was discovered in over 70% of tumors as well as the number of Fas-L positive cells correlated inversely with the numbers of CD3 and also CD8 favorable TILs and also survival, recommending that Fas-L positive cells may induce apoptosis in TILs thus blunting the immune feedback as well as detrimentally affecting survival. Endotheliotropic human herpes virus 8 (HHV-8) has been found in a selection of conditions including Kaposi sarcoma, human immunodeficiency virus (HIV) linked lymphoproliferative conditions, multicentric Castleman disease, as well as primary effusion lymphoma [16]. Schmid as well as Zeitz assessed specimens from 40 patients with angiosarcomas and found that they did not contain HHV-8 DNA sequences or healthy proteins indicating that it does not contribute in the pathogenesis of this neoplasm [16]. Vascular endothelial cadherin (VE

cadherin) is expressed on the endothelial adherens joints in typical blood vessels [21]. Tanioka as well as coworkers analyzed samples from the primary tumor as well as metastases from a patient that died of angiosarcoma and also discovered absent expression for VE cadherin in both [21]. In contrast, intercellular joints in the endothelia of regular dermal vessels stained positively for the VE cadherin monoclonal antibody. The lack of VE cadherin in the tumor could be related to decreased cell-cell adhesiveness that could be connected to promotion of regional intrusion as well as metastases.

- **Angiosarcomas etiology:**

A lot of angiosarcomas occur spontaneously, but there are a few reports of malignant improvement within pre-existing benign vascular sores [22]. A number of well-defined risk factors exist (**Table1**). Chronic lymphoedema of any beginning is associated with the growth of angiosarcoma; a phenomenon referred to as Stewart-Treves syndrome. Lymphoedema is one causal aetiological consider the development of bust angiosarcomas after therapy for bust cancer [23]. Lymphoedema brought on by Milroy's disease as well as chronic infections, such as filariasis,1 have also been linked to the advancement of angiosarcomas. Radiotherapy is an independent risk factor. Although the organization in between radiotherapy and also subsequent angiosarcoma is ideal defined for breast cancer therapy, it is not exclusive to bust sores. A huge epidemiological study of bust cancer patients using Surveillance of Epidemiology as well as End Results (SEER) data revealed an increased risk of soft-tissue sarcomas (especially angiosarcomas) after adjuvant radiotherapy, with a peak incidence 5 - 10 years after treatment [24]. Nonetheless, this link is disputed, and the increased risk might arise from concurrent lymphedema [25,26].

TABLE 1: Causes and risk factors of angiosarcomas

a) Radiation
b) Chronic lymphoedema (Stewart-Treves syndrome)
Postsurgery or radiotherapy
Milroy's syndrome
Other types of chronic lymphoedema
c) Exogenous toxins
Vinyl chloride
Thorium dioxide
Arsenic
Anabolic steroids
Foreign bodies
a) Familial syndromes
Neuro bromatosis *NF-1*
Mutated *BRCA1* or *BRCA2*
Ma ucci syndrome
Klippel-Trenaunay syndrome

- **Classification:**

Angiosarcomas are subdivided into **A)** cutaneous angiosarcoma, **B)** lymphoedema-associated angiosarcoma, **C)** radiation-induced angiosarcoma, **D)** primary-breast angiosarcoma, and **F)** soft-tissue angiosarcoma, and also the majority of records consist of numerous angiosarcoma subtypes. There is some proof that tumor practices may depend upon site of beginning [3,13,27].

- **Histological differentiation of AS:**

Well-differentiated angiosarcomas are made up of well-formed, irregular vascular networks, commonly lined by squashed endothelial cells. Such tumors are identified from hemangiomas by their so-called "collagen breakdown pattern," anastomosing design, and the formation of papillae. Reasonably separated tumors have even more largely jam-packed vessels, and also vascular channels are lined by numerous layers of irregular endothelial cells that commonly exhibit intraluminal proliferation [3,28]. Inadequately differentiated angiosarcomas are much less common in the skin, and also might carefully look like carcinomas or other soft tissue sarcomas. Some poorly differentiated angiosarcomas might have

evident vasoformative locations, helping with the diagnosis. Others are composed exclusively of pleomorphic spindled or epithelioid cells with prominent mitotic activity and also just refined vascular lumen formation. Histologic quality is not as accurate in forecasting outcome in cutaneous angiosarcomas as it is with other soft tissue sarcomas.

The histological attributes of angiosarcoma can differ both within and in between situations. Morphological distinctions can be subtle, and also identifying a malignant vascular tumor from a benign proliferative or inflammatory sore with light microscopy can be hard [(29)]. Angiosarcomas are infiltrative as well as do not have a capsule or a clear border dividing normal from unusual tissue. Abnormal, pleomorphic, malignant endothelial cells are the characteristic of angiosarcoma as well as can be rounded, polygonal, or fusiform as well as could have an epithelioid appearance. In well separated areas, unusual endothelial cells develop working vascular sinusoids continuous with regular vascular channels. These vascular sinusoids study between collagen bundles and also are often connected with areas of monocyte seepage (**Figure 3**) [(3)]. With progressively hostile disease, the style comes to be much more chaotic, with less plainly defined vascular rooms. Instead of a solitary endothelial-cell lining, the unusual cells come to be multilayered and also form papillarylike projections into the vascular lumen. Mitotic bodies prevail, as are little clusters of erythrocytes within the cytoplasm of the uncommon endothelial cells. In badly distinguished areas the malignant endothelial cells develop constant sheets, usually with an epithelioid morphology, and with locations of haemorrhage and also necrosis, which could make differentiation from anaplastic carcinoma or melanoma hard [(30,31)]. Angiosarcomas typically share endothelial markers consisting of von Willebrand factor, CD34, CD31, Ulex europaeus agglutinin 1, and vascular endothelial development factor (VEGF). Immunohistochemistry is as a result vital in validating the medical diagnosis. Von Willebrand factor, U europaeus agglutinin 1, and CD31 are the most helpful markers in badly set apart situations [(32)].

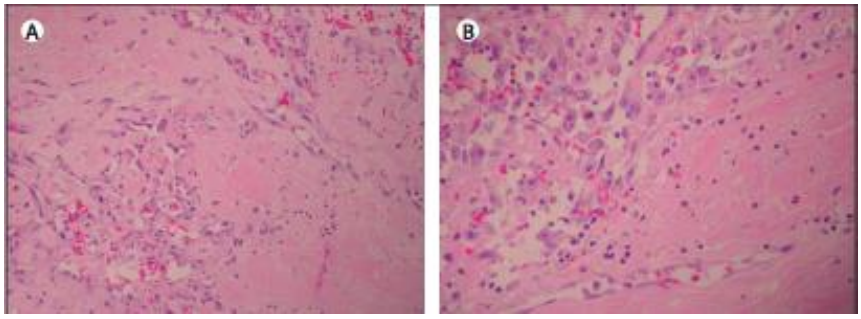

Figure1: Haematoxylin-eosin stained sections of angiosarcoma [(3)]

- **Angiosarcoma of bone:**

Angiosarcoma of bone is rare, making up less than 1% of all primary bone sarcomas as well as it is connected with a poor prognosis [(33,34)]. Although any kind of age can be affected, the occurrence is highest possible in between 50 - 70 years old [(33,35)]. Angiosarcoma of bone might offer as unifocal or multifocal disease [(34,35,36,37)]. The most common places of unifocal tumor are the lengthy and also brief tubular bones, complied with by the pelvis, as well as trunk [(35)]. Histologically, angiosarcomas of bone are composed of anastomosing vascular networks lined by atypical endothelial cells with enlarged centers, prominent nucleoli, and also enhanced mitoses. Inflammatory cells, mainly eosinophils, could exist (**Figure 2**) [(34)].

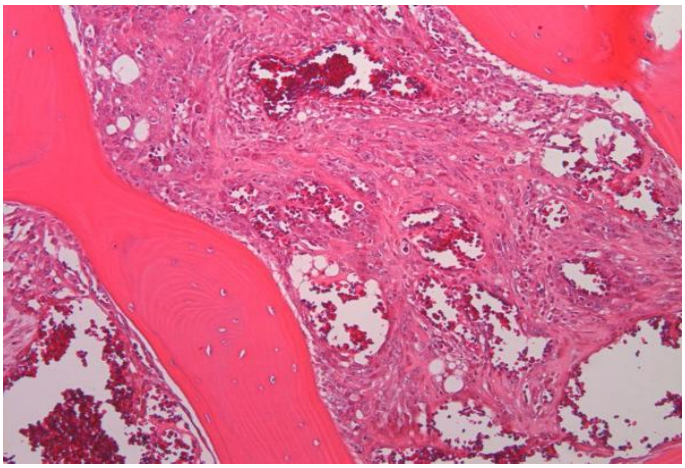

Figure 2: Microscopic anatomy of bone angiosarcoma [(34)]

- **Cutaneous angiosarcoma (endothelial type):**

Cutaneous angiosarcoma is an uncommon hostile tumor of lymphatic and also capillary endothelial cell origin. It provides as multiple purple and red papules, and blemishes on the head and neck or the extremities [38]. Angiosarcomas of the skin are unusual and also constitute less than 1% of all sarcomas [39]. It mostly happens in men (sex ratio of 3:1), at an average age ranging from 60 to 80 years [40]. Cutaneous angiosarcoma takes place exclusively in 3 scientific settings particularly idiopathic angiosarcoma of face, neck as well as scalp; angiosarcoma related to chronic lymphedema (Stewart-- Treves syndrome); and also postradiation angiosarcoma [40,41]. Differential medical diagnosis of cutaneous angiosarcoma includes intravascular papillary endothelial hyperplasia, Kaposi sarcoma (multiple hemorrhagic sarcoma), Kaposi-like hemangioendothelioma, angiolymphoid hyperplasia, Kimura's disease, and also amelanotic melanoma [42]. Absence of awareness of this entity and also its variable discussion can cause diagnostic delay [43].

Epithelioid angiosarcoma most often occurs in the deep soft tissues (usually intramuscular) of the extremities, but a range of primary sites, consisting of the thyroid gland, skin, adrenal glands, and also bone, are come across [44,45]. Subsequently, most situations of epithelioid angiosarcoma are soft cells angiosarcomas, with a minority falling into the cutaneous and natural categories.

Epithelioid angiosarcoma has a male preference as well as, although separated pediatric instances have actually been reported, they usually occur in grown-up life, with the highest possible occurrence in the seventh decade [45,46]. A selection of medical discussions may be experienced, owing to the diversity of primary sites and also the extremely aggressive nature of the tumor. These range from uncomfortable, expanding soft cells masses to long bone cracks to arteriovenous shunting and succeeding high-output cardiac failing [47]. In one study, around one third of patients with soft cells angiosarcoma had actually grievances credited to a hypocoagulable state, including hemothoraces, peritoneal bleeds, ecchymosis, stomach bleeding, and persistent hematoma [46]. The nonspecific preliminary presentation depends on the size of the tumor, the tissue entailed, as well as its resultant disorder. Furthermore, sores occasionally take place within schwannomas, [48] or in association with foreign bodies/trauma, hematologic and also strong hatreds (condition postsurgical, radiation, and/or chemotherapeutic treatment), artificial vascular grafts, and orthopedic hardware/prostheses [46,49]. Computerized and angioradiographic tomographic studies aid recognize the lesion's area as well as its relationship to the native vasculature.

Epithelioid angiosarcoma typically shows early nodal and solid body organ metastasis, especially to the lungs, bone, soft cells, as well as skin. Within 2 to 3 years of diagnosis, more than 50% of patients are dead of disease, yet 20% to 30% of people are disease totally free [46,50]. Adverse prognostic factors include advanced age, increased tumor size, a retroperitoneal primary site, and also an enhanced proliferative index (MIB-1 $\geq$ 10%) [46]. Treatment methods vary among specific cases of angiosarcoma, however medical resection of the primary tumor as well as radiation therapy are normally made use of [51]. There is evidence that paclitaxel-based chemotherapeutic routines could enhance survival [52]. Additionally, records of remission after the combined use of adjuvant radiation treatment and also bevacizumab, complied with by surgery, have actually been explained [53].

Endothelial malignancies are derived from mesenchymal cells, which undertake blood vessel and/or lymphatic-endothelial distinction. Existing evidence sustains that specific epithelioid angiosarcomas adhere to either or both (lymphatic as well as vascular) endothelial cell lines [54,55]. The diversity of primary sites is credited to the ubiquity of blood vessels and also lymphatics throughout the body. Larger tissues with a huge lymphovascular supply (eg, deep soft cells) and also cells with high focus of endothelial cells (eg, adrenals as well as thyroid) appear to be at the highest risk for establishing these malignancies [55].

Epithelioid angiosarcoma consists of huge, slightly to moderately pleomorphic, rounded to polygonal epithelioid cells, with central to eccentrically located cores having prominent nucleoli. Within the core, the chromatin is peripherally marginated, generating a vesicular look. A lot of malignant endothelial cells are filled with abundant eosinophilic cytoplasm, however periodic cells with intracytoplasmic lumina including erythrocytes could typically be identified, helping in diagnosis. Architecturally, cells are largely set up in sheets, however cellular islands or cords may be seen (**Figure 3**) [56]. On hematoxylin-eosin (H&E) tarnished areas, focal locations of irregularly anastomosing vessel formation are normally existing; simply epithelioid lesions are unusual, however a completely epithelioid emphasis could be encountered with little biopsy product. In areas of deadly vasoformation, mobile stratification might create a papillary appearance. Sheeted locations consist of a scant amount of stroma, but in much less mobile regions it is usually abundant, with a desmoplastic to fibromyxoid appearance. Deadly endothelial cells are carefully approximated to pericytes, which

could be highlighted with α-smooth muscle actin. In improperly distinguished locations of sheeted epithelioid cells, there is actually exterior laminal cellular organization right into primitive tubules, in which the tumor recapitulates vascular frameworks doing not have canalization. This primary vasoformative style is clearly demonstrated with reticulin discoloration (**Figure 3**). Throughout the tumor, mitotic numbers many, and varying levels of necrosis and also hemorrhage are present (**Figure 3**). In epithelioid angiosarcoma of the bone, foci containing famous neutrophilic infiltrate (not related to death) have been defined (**Figure 4**) [(50)].

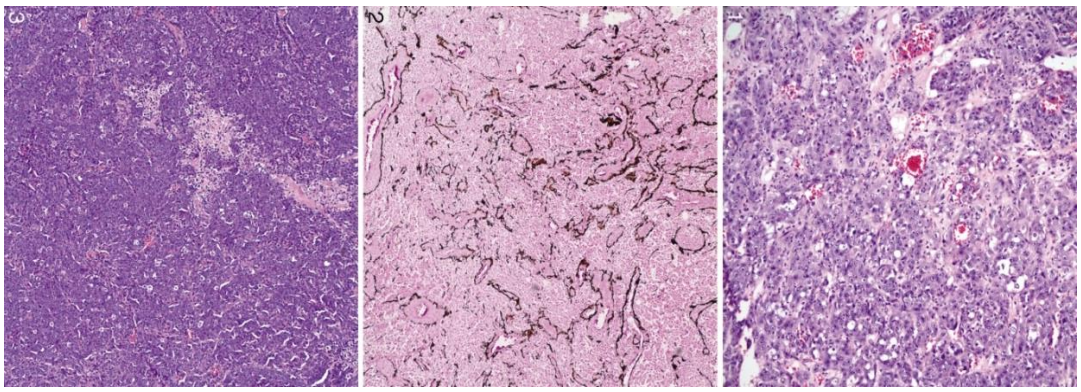

Figure 3: Epithelioid angiosarcoma [(50)]

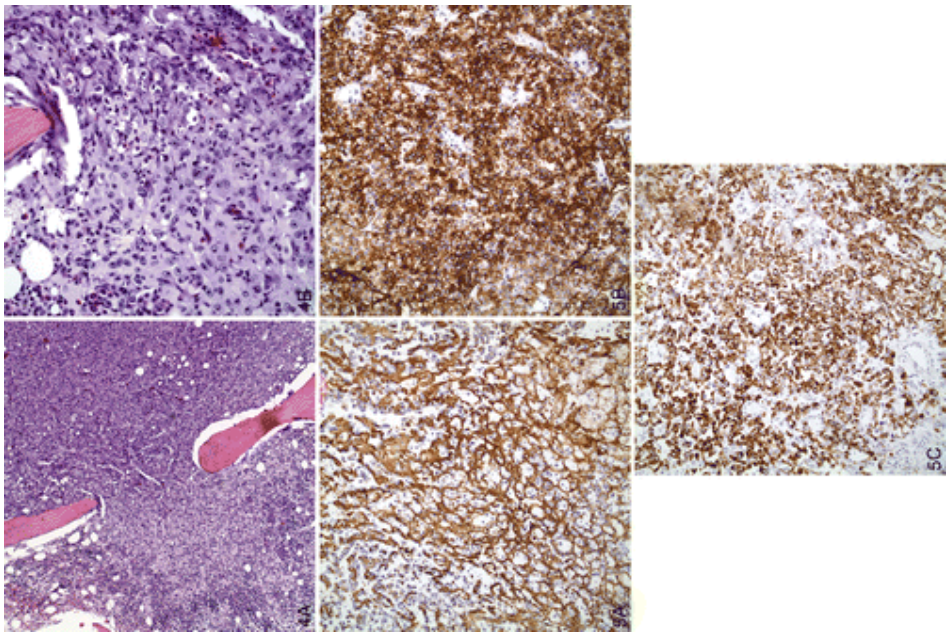

Figure 4: Sheets of malignant epithelioid cells fill the marrow cavity [(50)]

4. CONCLUSION

AS stem from any structural site in the body, many frequently the head and also neck, and breast cutaneous cells. Previous irradiation, harmful chemical exposure, as well as chronic lymphedema are determined as particular risk factors. Angiosarcoma could emerge in any type of soft-tissue structure or viscera as well as cutaneous angiosarcomas commonly entail the head and also neck, particularly the scalp. Angiosarcomas are of endothelial cell origin and tumours emerging directly from significant capillary or the heart are uncommon.

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