Angiosarcoma

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Definition

Angiosarcoma (AS) is a malignant tumor of vascular origin. It is also known as hemangiosarcoma, malignant hemangioendothelioma, malignant angioendothelioma, lymphedema-associated angiosarcoma, and lymphangiosarcoma.

Epidemiology and Presentation

AS accounts for 1–3% of all soft tissue sarcomas and can affect patients of all ages although the incidence peak in the seventh decade of life, with a male predominance. Its annual incidence has been estimated to be one case for every million people.

The primary sites of angiosarcoma include the skin (the most frequent site, the head and neck being the most common cutaneous site), breast (→ see section entitled "Breast Angiosarcoma"), soft tissue, viscera (especially liver and spleen; → see section entitled "Hepatic Angiosarcoma"), and bone. Clinical presentation varies considerably depending on the primary site: cutaneous AS presents as bruise-like patches, violaceous nodules, or plaques, whereas AS of soft tissue presents as an enlarged painful mass of deep muscles of the lower extremities (approximately 40% of cases) or as a mass of retroperitoneum, mediastinum, or mesentery; the clinical presentation of visceral AS is variable depending on the organ involved. Since extensive hemorrhage is commonly present, the lesion can be confused with a hematoma.

Etiology and Predisposition

Although its etiology is unknown in most cases (**primary angiosarcoma**), a subset of AS is associated with specific risk factors (**secondary angiosarcoma**). In particular, secondary AS is associated with exposure to ionizing radiation (mainly

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breast AS after radiotherapy for breast carcinoma, which has been reported to occur in approximately 1 out of 1000 cases even 20 years after exposure), ultraviolet radiation (occurs mainly on the scalp of elderly men), chronic lymphedema (due to lymphadenectomy or lymphatic diseases such as filariasis; the AS lymphedema association is known as Stewart-Treves syndrome), and chemicals such as vinyl chloride (utilized in the production of PVC; it has been associated with the development of hepatic AS) and thorotrast (utilized as contrast agent in radiology, it has been associated with hepatic AS).

Li-Fraumeni syndrome (LFS) has been associated with an increased risk of angiosarcoma in multiple locations such as the liver, spleen, breast, head and neck, and (rarely) heart. In most cases (80%), LFS is triggered by the germline mutations in the TP53 tumor suppressor gene (encoding the p53 protein). The estimated prevalence of causal deleterious germline TP53 mutations is approximately 1/20,000. The lifetime risk of cancer in LFS is about 70% for men and close to 100% for women. Typical cancers observed in LFS include early-onset breast cancer, adrenal cortical carcinoma, soft tissue and bone sarcomas (especially rhabdomyosarcoma and osteosarcoma), and brain tumors (choroid plexus carcinoma, astrocytoma, medulloblastoma, and glioblastoma). LFS is inherited in an autosomal dominant pattern; most patients with LFS inherit an altered copy of the gene from an affected parent: In 7–20% of cases, however, the altered gene is the result of a new mutation in the gene that occurred during the formation of reproductive cells or very early in development. For a cancer to develop in LFS, a somatic mutation involving the other copy of the TP53 gene must occur, according to the classical Knudson two-hit hypothesis.

Recently, a germline missense variant (p.R117C) in the POT1 gene (encoding protection of telomeres 1, a protein involved in telomere maintenance) has been proven to be responsible for cardiac angiosarcoma, a very rare malignant tumor that represents <10% of cardiac malignancies.

Pathology

Macroscopically it usually presents as multinodular hemorrhagic and necrotic nodules. Microscopically AS shows a variety morphological appearances ranging from areas of well-formed anastomosing vessels with limited cell atypia to solid sheets of high-grade epithelioid or spindled cells without clear formation of vessels composed of high-grade spindled and epithelioid cells (multiple patterns may be present in the same lesion, which calls for accurate tumor sampling). An AS with predominant epithelioid cells is called epithelioid angiosarcoma, which can be misdiagnosed as a carcinoma because of morphological and immunophenotypical commonalities. Most AS are high-grade tumors with brisk mitotic activity, coagulative necrosis, and marked nuclear atypia.

Differential diagnosis may be needed with other vascular lesions such as atypical post-radiation vascular proliferations (relatively common in radiated skin, can form an erythematous lesion, consists of dilated round or angulated vessels in the

dermis lined by a single layer of endothelium that shows mild/absent cytological atypia without mitoses), Kaposi sarcoma (HHV8 positive), and papillary endothelial hyperplasia (also known as Masson tumor, a non-neoplastic benign intravascular lesion only, with papillary formations with hyaline or fibrous stalks, anastomosing vascular channels, plump endothelial cells; no necrosis, no atypia, no atypical mitotic figures).

Biomarkers

AS expresses typical vascular biomarkers (e.g., CD34, CD31, ERG, FLI1) and occasionally lymphatic biomarkers (e.g., podoplanin). Epithelioid AS can coexpress epithelial antigens (e.g., cytokeratins, EMA), which should be kept in mind for differential diagnosis with carcinomas. Immunostaining for HHV8 is negative (which is helpful to differentiate AS from Kaposi sarcoma).

AS has not been associated with specific genetic alterations except for high-level **MYC gene amplification** (chromosome 8q24),[1] which is a consistent hallmark of radiation-induced and lymphedema-associated AS.

Prognosis

AS is a high-grade malignancy associated with high rates of disease recurrence (70%) and mortality (50%), representing the most aggressive type of all vascular malignancies (once metastasized the median survival is 4–12 months). Negative prognostic factors are the following: older age, retroperitoneal location, large size, high mitotic rate, necrosis, and epithelioid subtype. In the light of the high metastatic potential, thoraco-abdominal computed tomography scan coupled with central nervous system magnetic resonance imaging is suggested for staging purposes.

Therapy

Surgery (wide excision) is the mainstay of treatment for localized primary AS, although ill-defined margins can make radical surgery a challenging task; in order to maximize the curative intent, large skin removal may be needed, which may require plastic surgery techniques to repair cutaneous defects. In order to improve local disease control, adjuvant **radiotherapy** is often delivered. Definitive

[1] MYC: this is a proto-oncogene and encodes a nuclear phosphoprotein (c-Myc) that plays a key role in cell cycle progression, apoptosis, and cellular transformation. The encoded protein forms a heterodimer with the related transcription factor MAX: then, this complex binds to the E-box DNA consensus sequence and regulates the transcription of specific target genes. Amplification of this gene is frequently observed in numerous human cancers, including radiation-induced angiosarcoma. Translocations involving this gene are associated with Burkitt lymphoma and multiple myeloma.

radiotherapy has been also utilized as the only treatment for patients unsuitable for surgery; the combination of radiotherapy plus chemotherapy has been proposed as an alternative to surgery. Other **locoregional treatments** such as electrochemotherapy and isolated limb perfusion are available for the control of localized disease not amenable to surgery.

Patients with locally advanced or metastatic disease are treated with systemic **chemotherapy**; beside the "pan-sarcoma" doxorubicin (which—however—has not been evaluated in prospective studies dedicated to AS), there is prospective non-randomized evidence supporting the use of paclitaxel (often considered as first-line treatment). **Targeted therapy** with multikinase small molecule inhibitors such as sunitinib[2] and sorafenib[3] has been tested in the clinical setting with some benefit. Despite some promising results in non-randomized studies of bevacizumab[4] as a single agent, a randomized trial of paclitaxel with or without bevacizumab showed no difference between the study arms. Pazopanib[5] is approved for the second-line treatment of metastatic soft tissue sarcomas based on the results of the PALETTE randomized controlled trial that included patients with AS. Attempts to identify biomarkers predictive of response to target therapy are underway. PIK3CA-activating mutations[6] have been recently reported in AS, which suggests a therapeutic rationale for the use of PI3K inhibitors already available in the clinical setting (e.g., alpelisib, currently approved for breast cancer treatment). Also in the light of the high tumor mutation burden that can be found in this tumor, **immunotherapy** with anti-PD1 checkpoint inhibitors is being tested in patients with AS, with some encouraging results.

Suggested Readings

Agulnik (2013) An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol 24(1):257–263

Calvete (2015) A mutation in the POT1 gene is responsible for cardiac angiosarcoma in TP53-negative Li-Fraumeni-like families. Nat Commun 6:8383

[2] Sunitinib: tyrosine kinase inhibitor targeting the following: PDGFR, VEGFR, KIT, FLT3, CSF1R, RET.

[3] Sorafenib: tyrosine kinase inhibitor targeting the following: BRAF, KIT, RET, FGFR1, FLT3, VEGFR1, VEGFR2, VEGFR3, PDGFRB.

[4] Bevacizumab: monoclonal antibody blocking VEGFA (vascular endothelial growth factor A).

[5] Pazopanib: tyrosine kinase inhibitor targeting the following: VEGFR, PDGFR, KIT.

[6] PIK3CA: this gene encodes for phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, the catalytic subunit of phosphatidylinositol 3-kinase (PI3K) that phosphorylates phosphatidylinositol to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3), which is dephosphorylated by the protein product of tumor suppressor gene PTEN (a negative regulator of the PI3K-AKT pathway). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility, and morphology in response to various growth factors (e.g., EGF, insulin, IGF1, VEGFA, and PDGF). PIK3CA is the most recurrently mutated gene in breast cancer and has been found to important in a number of cancer types (PIK3CA is considered an oncogene).

Campana (2016) Angiosarcoma on lymphedema (Stewart-Treves syndrome): a 12-year follow-up after isolated limb perfusion, limb infusion, and electrochemotherapy. J Vasc Interv Radiol 27(3):444–446
Campana (2019) Electrochemotherapy for advanced cutaneous angiosarcoma: a European register-based cohort study from the International Network for Sharing Practices of electrochemotherapy (InspECT). Int J Surg 72:34–42
Fletcher (2020) WHO classification of tumours of soft tissue and bone, 5th edn
Florou (2019) Angiosarcoma patients treated with immune checkpoint inhibitors: a case series of seven patients from a single institution. J Immunother Cancer 7(1):213
Fujisawa (2014) Chemoradiotherapy with taxane is superior to conventional surgery and radiotherapy in the management of cutaneous angiosarcoma: a multicentre, retrospective study. Br J Dermatol 171(6):1493–1500
Guida (2016) Local treatment with electrochemotherapy of superficial angiosarcomas: efficacy and safety results from a multi-institutional retrospective study. J Surg Oncol 114(2):246–253
Habeeb (2019) The molecular diagnostics of vascular neoplasms. Surg Pathol Clin 12(1):35–49
Italiano (2012) Comparison of doxorubicin and weekly paclitaxel efficacy in metastatic angiosarcomas. Cancer 118(13):3330–3336
Kollár (2017) Pazopanib in advanced vascular sarcomas: an EORTC soft tissue and bone sarcoma group (STBSG) retrospective analysis. Acta Oncol 56(1):88–92
Mito (2019) Radiation-associated sarcomas: an update on clinical, histologic, and molecular features. Surg Pathol Clin 12(1):139–148
Momen (2019) Dramatic response of metastatic cutaneous angiosarcoma to an immune checkpoint inhibitor in a patient with xeroderma pigmentosum: whole-genome sequencing aids treatment decision in end-stage disease. Cold Spring Harb Mol Case Stud 5(5):a004408
Painter (2020) The angiosarcoma project: enabling genomic and clinical discoveries in a rare cancer through patient-partnered research. Nat Med 26(2):181–187
Papke (2020) What is new in endothelial neoplasia? Virchows Arch 476(1):17–28
Penel (2008) Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX study. J Clin Oncol 26(32):5269–5274
Radaelli (2014) Emerging therapies for adult soft tissue sarcoma. Expert Rev Anticancer Ther 14(6):689–704
Ravi (2016) Antitumor response of VEGFR2- and VEGFR3-amplified angiosarcoma to Pazopanib. J Natl Compr Cancer Netw 14(5):499–502
Ray-Coquard (2015) Paclitaxel given once per week with or without bevacizumab in patients with advanced angiosarcoma: a randomized phase II trial. J Clin Oncol 33(25):2797–2802
Rombouts (2019) Assessment of radiotherapy-associated angiosarcoma after breast cancer treatment in a Dutch population-based study. JAMA Oncol 5(2):267–269
Shon (2019) Epithelioid vascular tumors: a review. Adv Anat Pathol 26(3):186–197
Steininger (2019) Masson's tumor of the breast: rare differential for new or recurrent breast cancer-case report, pathology, and review of the literature. Breast J 26(4):752–754
van der Graaf (2012) Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 379(9829):1879–1886
Weidema (2019) Targeting angiosarcomas of the soft tissues: a challenging effort in a heterogeneous and rare disease. Crit Rev Oncol Hematol 138:120–131
Yamamoto (2010) Histological type of thorotrast-induced liver tumors associated with the translocation of deposited radionuclides. Cancer Sci 101(2):336–340