Retroperitoneal Angiosarcoma

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Hai Liu and Chengli Miao

1 Introduction

Angiosarcoma is a malignant tumor originated in the vascular or lymphatic endothelium. As described in the literature under various names, angiosarcomas were previously called vascular endothelial tumor, ductal sarcoma, angiosarcoma, malignant hemangioendothelioma, and lymphatic sarcoma. It is now known as angiosarcoma, including vascular endothelial derived hemangiosarcoma and lymphangiosarcoma. Hemangiosarcoma cannot be differentiated from lymphangiosarcoma due to lack of reliable morphologic parameters and immunohistochemical features, so they are collectively referred to as angiosarcoma. Angiosarcoma is a rare tumor, commonly seen in skin and soft tissue, accounting for approximately 1–2% of soft tissue sarcoma. Retroperitoneal angiosarcoma is extremely rare as reported in the literature. In this chapter, etiological causes, histopathological features, immunohistochemical markers, clinical manifestation, treatment strategies, therapeutic efficacy, and prognostic factors of angiosarcoma will be briefly described.

H. Liu (✉)
The Third Xiangya Hospital of Central South University, Changsha, China
e-mail: minisurgery@126.com

C. Miao
Peking University International Hospital, Beijing, China

2 Etiology

It is now widely accepted that chronic lymphedema, ionizing radiation history, chemical exposure history, trauma history, and chronic infections may contribute to the development of angiosarcoma.

Angiosarcoma is developed on the basis of long-term chronic edema, lymphatic expansion, and malignant proliferation of endothelial cells, which is originated in the following pathologic conditions: a. post-mastectomy lymphedema in the upper extremities of patients with breast cancer; b. abdominal wall of patients with penile cancer following lymphadenectomy; c. extremities of patients with congenital, idiopathic, or traumatic lymphedema; and d. filariasis lymphedema. It was first described in 1948 by Stewart and Treves (1948) in a series of 6 cases of lymphangiosarcoma after chronic post-mastectomy lymphedema, and later called Stewart–Treves syndrome, accounting for about 6% of all angiosarcoma. Since then, 14 cases of angiosarcoma resulted from chronic edema of the upper extremity secondary to mastectomy, and 2 cases induced by chronic congestion and edema of the lower extremities have been reported by Maddox and Evans (1981). Angiosarcoma has a longer latency period (range: 4–27 years; median: 10 years)

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after breast cancer treatment. Chronic lymphedema causes malnutrition of connective tissue and plays a significant role in the onset of angiosarcoma (McConnell and Haslam 1959).

Radiation tumorigenesis must meet the following three criteria: (a) tumor occurs within the radiation field; (b) pathological type of tumor is inconsistent with the primary, and (c.) the interval between the onset of two tumors is relatively longer (usually more than 10 years). Naka et al. (1996) reported that 4/5 cases of cervical cancer developed angiosarcoma in the radiation field of abdominal wall and hip following radiotherapy at an average interval of 13 years. Among18 cases of head and neck angiosarcoma, 4 met the above criteria for radiation-induced tumorigenesis (Lydiatt et al. 1994). Angiosarcoma commonly occurs in the head, face, and skin of Caucasians, related to long-term exposure to the sunlight. Mutations in the tumor suppressor genes (e.g., p53) may play a role in the pathogenesis of radiation-induced tumors.

Chemical stimulation has a major effect on the carcinogenesis of angiosarcoma. A study was carried out in America from 1964 to 1974 to investigate the pathogenesis of hepatic angiosarcoma (Falk et al. 1981). 25% of the cases had been exposed to poly vinyl chloride, thorium coagent (thoratrast), and inorganic arsenic. The high incidence of liver angiosarcoma was firstly found in workers with long-term exposure to polyvinyl chloride (PVC). Thorium is a mixture of 25% of thorium dioxide latex, which had been previously widely used as radiographic enhancer in clinical practice, and now abandoned due to non-uniform deposition in various organs of the human body (72% in liver, 12% in spleen, and 8% in bone marrow). Long-term stimulation of thorium agent can induce hepatic angiosarcoma. In recent years, arsenic compounds induced tumors in animal models have been reported.

It has been reported that patients with angiosarcoma usually have a previous history of trauma. Girard et al. (1970) found that 3/28 cases of angiosarcoma had a previous history of trauma at the occurrence site. In a study conducted by Naka et al. (1996) in Japan, 21 out of 99 cases of angiosarcoma (21%) had obvious incentives. For example, 5 patients had history of bumps, which was considered as a common risk factor, only second to chronic tuberculous pleurisy (6 cases) (Naka et al. 1996). Clinical manifestation of angiosarcoma is similar to that of bruise caused by bump, thus supporting its trauma origin.

Chronic inflammation is closely related to angiosarcoma. Chronic tuberculous pleurisy is the most common predisposing factor (Naka et al. 1996). Pleural angiosarcoma may develop in 15–40 years (median: 33 years) after the onset of pleurisy. The present study suggests that long-term inflammation is subject to angiosarcoma based on the clinical and pathological features of pleural angiosarcoma.

3 Pathogenesis and Pathobiology

Histologically, angiosarcoma can be classified as well-differentiated, moderately differentiated, and poorly differentiated subtypes. The histological findings of tumor vessels are very similar to those of normal lymphatic vessels in patients with well-differentiated angiosarcoma. Sometimes, the capillary vessels can be found in the lesion, with the lumen either void or filled with protein liquid and red blood cells.

Under the light microscope, the tumor is composed of various atypia endothelial cells in spindle-, cubic-, or irregular-shape, with obvious nuclear atypia and short stubby chromatin, and numerous mitotic figures. Irregular and mutually anastomotic lumen tubules are formed by endothelial cells. Lumen tubules of varying sizes and shapes are mutually anastomotic, so cutting of the dermis collagen results in separation of the fascia from subcutaneous fat tissue. In well-differentiated areas, luminal tubules are prominent, either slit-shaped or dilated into sinusoid-shaped, lined by flattened endothelial cells. The proliferated endothelial cells pile up in multiple layers and even block lumen or form nipples that protrude into the lumen. Nuclear atypia still exists, and mitotic figure is rare. In poorly differentiated areas, endothelial cells are arranged in a diffuse pattern to form solid nests, with inconspicuous lumen. The endo-

thelial cells are obviously atypia with a large deeply stained prominent nucleoli and numerous mitotic figures. Occasionally hyperkeratosis or parakeratosis exists, and frequently intratumoral necrosis occurs.

Under electron microscope, the tumor exhibits typical lumen in which malignant endothelial cells are arranged, accompanied by pinocytotic bubbles, intact or fragmental basement membrane, and intercellular tight junction, but lack of desmosomes. Occasionally flagellar microtubules-like bodies are visible; however, no definite Weibel–Palade bodies can be seen. Since Weibel–Palade bodies present only in endothelial cells but not in lymphatic endothelial cells, angiosarcoma cells that don't contain these bodies may have lost the ability to differentiate into the specific structure in the malignant process or arise from lymphatic endothelium.

A variety of molecular markers, such as FVIII-RA, UEA-1, CD31, cytokeratin, EMA, HMB 45, VEGF and p53, have currently been used for the diagnosis and differentiation of angiosarcoma. FVIII-RA is widely distributed in endothelial cells of the arteries, capillaries, and veins, such as lymphatic vessels and liver sinusoidal endothelium. FVIII-RA is a commonly used immunohistochemical marker of vascular endothelial cells, expressing on the surface of macrophages, platelets, mast cells as well as glomerular interstitial area. The positive rate of FVIII-RA in angiosarcoma cells reached 40–100% as reported by Poblet et al. (1996). In particular, its positive rate in vascular area was significantly higher than that in nonvascular or pancivascular area.

Both Ulex Europaeus Agglutinin 1 (UEA-1) and FVIII-RA are standard endothelial cell markers. UEA-1 is a specific lectin for a-L-fucose-containing glycocompounds, and a marker for human vascular endothelium. Among 98 cases of angiosarcoma, the UEA-1positive rate was up to 70% in angiogenesis region whereas 46% in nonvascular or pancivascular area, which was less sensitive than FVIII-RA or CD31 (Ohsawa et al. 1995).

CD31 is an adherent molecule present in the endothelial cells, monocytes, and platelet surface, also known as endothelial/platelet adhesion molecule. CD31 is positively expressed in the junction between adjacent endothelial cells. The positive rate of CD31 was reported to be higher than that of FVIII-RA in malignant vascular endothelial cells. A study (Ohsawa et al. 1995) involving 98 cases of angiosarcoma found that the positive rate of CD 31 in vascular area was 80%, lower than that of FVIII-RA (84%) but higher than that of UEA-1 (70%). Miettinen (2006) reported that 18/23 (78%) cases of angiosarcoma were positive for CD31.

Cytokeratin is a maker of epithelial origin. Al-Abbadi et al. (2007) found that cytokeratin was positive in the vascular endothelial cells. Notably, cytokeratin positive angiosarcoma is easily misdiagnosed as cancer. In another study, the positive rate was 11% in vascular area whereas 21% in non-vascular area. EMA (epithelial membrane antigen) and cytokeratin have similar positive rate and significance. Angiosarcoma with positive expression of EMA and cytokeratin is easily misdiagnosed as cancer, especially for a tumor originated in non-vascular or pancivascular area.

VEGF is a mitogen secreted by vascular endothelial cells, and plays an important role in the development of angiosarcoma. Ohsawa et al. (1995) reported that VEGF was positive in only 36% of the biopsies and 14% of cadavers. Fujimoto et al. (1998) measured VEGF concentration using ELISA assay, and found VEGF varied with tumor load. However, VEGF concentration was not deviated from the normal range (cut-off value of 18 pg/ml) throughout the clinical process. The average concentration of VEGF in angiosarcoma tissue was 108.3 pg/ml, comparable to hypervascular malignancies (such as RCC and glioblastoma multiforme) or benign angiomas. Increased mRNA level of VEGF and/or its receptor (VEGFR) was reported in angiosarcoma (Park et al. 2010; Hoshina et al. 2013). VEGF was proposed to play an important role in the pathogenesis of angiosarcoma and may serve as a vital therapeutic target (Hoshina et al.). The autocrine or paracrine mechanisms of VEGF and its receptor may contribute to the development of angiosarcoma.

Tumor suppressor gene p53 is critically involved in a variety of tumors. In murine models, loss of p53 promotes spontaneous hepatic angiosarcoma. Trivers et al. (1995) analyzed 148 serum samples from 72 patients (including 15 cases of hepatic angiosarcoma) who had been exposed to PVC, and found that loss of p53 predicted the onset of hepatic angiosarcoma. If 20% of nuclear staining positive rate serves as a cut-off value, p53 protein is positive in 20% of these cases. Mutations of p53 gene have been detected in angiosarcoma. The p53 protein plays an important role in DNA damage repair machinery.

4 Clinical Manifestation

Angiosarcoma may occur anywhere in the body, most commonly (more than 50%) in the head and facial skin and soft tissue. Angiosarcoma is roughly divided into nodular, diffuse, and ulcerated types. Among various clinical manifestations, the early appearance is a superficial lesion like bruising, petechiae, or ecchymosis, similar to bumping. The lesion is ill-defined, with slightly hard margin. The lesion grows more quickly in the advanced stage, and may bulge from the surface of the skin. It is purple in color, occasionally accompanied by ulceration. Sometimes the lesion is surrounded by small satellite nodules. Poorly differentiated type is manifested as multifocal and extensively local invasion. The focal lesions are red in color, deeply located, and locally bulged, at a rapid growth speed, vulnerable to bleeding, and in mold-like appearance with deep ulcers.

Retroperitoneal angiosarcoma is extremely rare, and its clinical manifestations are similar to other retroperitoneal tumors, such as pain and compression of local organs. The tumor size can be more than 20 cm. It mainly metastasizes through blood, and is most likely to spread to the lung, thus causing symptoms such as pleural disease, bloody pleural effusion, or pneumothorax. Other common metastatic sites include the liver, bone, soft tissue, and lymph nodes. Retroperitoneal angiosarcoma has a poor prognosis.

5 Detection and Staging

Clinically, the UICC/AJCC TNM system applies to the staging of soft tissue sarcoma. As angiosarcoma is a poorly differentiated tumor, histological classification is not considered for clinical staging.

6 Treatment

Surgery is the mainstay for treatment of angiosarcoma. Surgical procedure is the first choice. The resection margin should be 3 cm laterally from the visible basal part of the tumor, and then extend outwards 4 cm subcutaneously. Alternatively, resection margin should be determined by the pathologic findings of intraoperative frozen section. Preoperative or postoperative radiotherapy and/or chemotherapy are expected to reduce local recurrence or distant metastasis. As retroperitoneal angiosarcoma is adjacent to vital organs and blood vessels, surgical resection becomes one of the most challenging tasks and results in the worst prognosis. For giant retroperitoneal angiosarcoma, preoperative embolization of the primary feeding vessels to the tumor can reduce bleeding and surgical risk. Since patients with retroperitoneal sarcoma exhibit a high rate of postoperative relapse, Colombo et al. (2012) proposed that the scope of removal should be extended and if necessary, combined resection of multiple organs should be performed in order to reduce the recurrence rate.

Local radiotherapy can effectively control the multicentric and invasive angiosarcoma. For multicentric or ill-defined angiosarcoma, radiation of >50 Gy within a few centimeters circled the margin of gross target volume can generally achieve good results. Postoperative radiotherapy may improve local control of angiosarcoma that is multicentric and deeply infiltrated with positive margin. Preoperative radiotherapy also plays a role in inhibiting tumor growth, reducing bleeding, preventing intraoperative implantation, and increasing the resection rate.

Chemotherapy is a necessary palliative treatment for patients who have advanced non-

resectable angiosarcoma, experience a relapse, or develop a distant metastasis. Commonly used chemotherapy regimens include doxorubicin (Adriamycin/ADM)-, paclitaxel-, or gemcitabine-based protocols, of which doxorubicin-based regimen is most commonly used. Meta-analysis of randomized clinical trials found that postoperative chemotherapy with ADM-based regimen had notable efficacy in the treatment of soft tissue sarcoma (including angiosarcoma). ADM-based chemotherapy is recommended as the first-line regimen. As a new therapy for angiosarcoma, paclitaxel with anti-angiogenic effect has aroused great interest clinically. FNCLCC (French Federation of Cancer Centers Sarcoma Group) reported that 78% of patients with angiosarcoma who received two cycles of weekly paclitaxel regimen achieved tumor progression-free survival, and 3/30 achieved complete response (Penel and Lansiaux 2007). A 2-year progression-free survival was achieved in patients with primary or metastatic sarcoma after receiving docetaxel plus gemcitabine regimen (Hensley 2010).

Although the underlying molecular mechanism of angiosarcoma is yet to be elucidated, the role of anti-angiogenic molecules in the treatment of angiosarcoma has attracted great attention worldwide. Encouragingly, patients with head and facial angiosarcoma who received VEGF monoclonal antibody (bevacizumab) in combination with radiation had achieved pathologically complete response (Koontz et al. 2008). Two of three cases of progressive and recurrent angiosarcoma had complete response after receiving bevacizumab combined with docetaxel and gemcitabine (Hingorani et al. 2012). Broad-spectrum tyrosine kinase inhibitors targeting a variety of VEGF receptors have been used. In a cohort of patients who received sorafenib of 800 mg/d, 13% had response, 65% had a three-months' progression-free survival, and 31% had six-months' progression-free survival. Yoo et al. (2009) proposed that Sunitinib could effectively fight against retroperitoneal angiosarcoma that is resistant to paclitaxel and doxorubicin. Rosen et al. (2010) reported that 3 out of 26 patients who received monotherapy of bevacizumab (15 mg/kg) once every 3 weeks for 3–16 cycles had achieved partial response; and 13 out of 26 patients who received the above regimen for 3–22 cycles had achieved progression-free survival.

Biotherapy against angiosarcoma has been rarely reported. Interferon is an immune molecule with anti-angiogenic activity, which can be used as neoadjuvant therapy before surgery. Among 24 cases of soft tissue sarcomas (including angiosarcoma) who were treated with isolated limb perfusion obtained an effective rate of 84% (CR 18%; PR 64%) (Lejeune et al. 2000). In 2009, Asano et al. (2009) found that interleukin-2 alone or in combination with chemotherapy was effective in the treatment of angiosarcoma.

7 Efficacy and Prognostic Factors

Angiosarcoma denotes a higher degree of malignancy and poorer prognosis compared to other types of sarcoma. Regardless of therapeutic regimen, the risk of local recurrence and distant metastasis remains high. Local recurrence can be as high as 75%, and approximately one-third of patients may experience metastases. Most distant metastases occur within 24 months after treatment, commonly in lymph nodes, lungs, liver, bone, kidney, and suprarenal gland. Angiosarcoma has the poorest prognosis among soft tissue sarcomas. Most patients die 2–3 years after diagnosis, with a median survival time of 15–24 months and an average 5-year survival rate of about 20%. Retroperitoneal angiosarcoma is located adjacent to vital organs and blood vessels, resulting in worse prognosis than the tumor occurring in other parts of the body.

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