Angiosarcoma, Radiation-Associated Angiosarcoma, and Atypical Vascular Lesion

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Angiosarcoma, one of the least common sarcomas, has become increasingly important because of its association with radiation therapy, especially for breast cancer. Most are sporadic, presenting as cutaneous tumors in the scalp/face of elderly patients. However, angiosarcoma has a wide anatomic distribution including soft tissue, visceral organ, and osseous locations. Predisposing conditions include environmental exposures to chemical or radioactive sources. Radiation-associated angiosarcoma typically presents as a cutaneous tumor several years posttherapy. The latency for radiation-associated mammary angiosarcoma is relatively short, sometimes less than 3 years. Atypical vascular lesion refers to a small, usually lymphatic-type vascular proliferation in radiated skin. Although most atypical vascular lesions pursue a benign course, they recur and very rarely progress to angiosarcoma. Distinguishing this lesion from well-differentiated angiosarcoma in a biopsy can be challenging, especially because areas indistinguishable from atypical vascular lesion are found adjacent to angiosarcoma. Recently, vascular-type atypical vascular lesion, which resembles hemangioma, has been described, thus expanding the definition of this entity. (Arch Pathol Lab Med. 2009;133:1804–1809)

Accounting for only 1% of soft tissue sarcomas, angiosarcoma has recently come to attention because of its association with radiation therapy, especially for breast cancer. In the early 1980s, doctors began to recognize angiosarcomas arising in mammary skin, years after a lumpectomy and radiation.1 Radiation-associated angiosarcoma is now recognized as an important, although rare complication of radiotherapy, with a cumulative incidence of 0.9 per 1000 cases during 15 years.2 The risk is not believed to outweigh the benefit, and radiation therapy continues to be a mainstay in breast cancer treatment. In 1994, Fineberg and Rosen3 reported 4 cases of an unusual vascular lesion occurring in mammary skin after radiation, which they named atypical vascular lesion (AVL). Most AVLs resemble lymphangiomas and pursue a benign course. However, they have a tendency to develop further lesions, usually more AVLs. There are also rare reports of AVL progressing to angiosarcoma, usually after multiple recurrences,4 a fact suggesting that AVL may be a precursor to or incipient angiosarcoma. Distinguishing AVL from well-differentiated angiosarcoma in a biopsy specimen can be very challenging. Recently, a vascular-type AVL resembling capillary hemangioma has been reported.4,5 This article reviews the clinical, morphologic, and immunohistochemical findings in angiosarcoma in general, with special emphasis on radiation-associated angiosarcoma. It also reviews the clinical and morphologic features of AVL, including recent developments and concepts.

OVERVIEW

The most common clinical presentation of angiosarcoma is a sporadic cutaneous tumor, typically in the scalp or face of an elderly patient. However, angiosarcoma occurs in virtually any anatomic site, including deep soft tissue, breast, visceral organs, and bone. Although most cases are sporadic, important predisposing conditions include radiation (Figure 1), chronic lymphedema (Figure 2), exposure to toxins (eg, vinyl chloride), and foreign bodies (eg, arteriovenous fistulas).

Cutaneous angiosarcoma usually appears as a bruise-like area that often ulcerates or becomes nodular. Cutaneous tumors frequently have small satellite lesions adjacent to the main tumor. Deep-seated tumors have a hemorrhagic sponglike or microcystic appearance (Figure 3), often with necrosis. Angiosarcoma of bone is peculiar in that it frequently presents as multifocal, polyostotic disease (Figure 4).

The histologic spectrum ranges from well-differentiated tumors that mimic benign vascular lesions to poorly differentiated tumors that present as undifferentiated malignant neoplasms. Well-differentiated angiosarcoma consists of irregular interanastomosing channels that infiltrate surrounding tissue (Figure 5, A). Cytologic features can be deceptively bland in some cases. However, hyperchromasia, mild pleomorphism, prominent nuclei, mitotic figures, or multilayering are usually present (Figure 5, B). Within dermis, well-differentiated angiosarcoma entraps and surrounds collagenous stroma to form intraluminal papillary structures (Figure 5, C). Atypical lymphatic and/or capillary proliferations are frequently present at the periphery of an angiosarcoma, at times making assessment of surgical margins difficult.
Moderate and poorly differentiated angiosarcomas have very heterogeneous cytoarchitectural features. The cytologic appearance can be epithelioid, spindled, or pleomorphic (Figure 6, A through C), while the architecture can be vasoformative, sievelike, kaposiform, or solid (Figure 7, A through D). Various combinations of patterns and degrees of differentiation can be present within a single tumor. Often, well-differentiated angiosarcoma is found adjacent to poorly differentiated angiosarcoma, suggesting tumor progression.

Poorly differentiated angiosarcoma often presents as an undifferentiated malignant neoplasm and immunohistochemistry is often necessary to confirm the diagnosis. CD31 is the single best marker with high sensitivity and specificity. CD31, however, is not always the cleanest marker and can show low-level staining in other tumors as well as frequent background blush. It also stains macrophages. By contrast, angiosarcoma usually has a diffuse, intense staining reaction for CD31, often with accentuation of the cytoplasmic membrane (Figure 8). CD34 and factor VIII are also expressed in most angiosarcomas, but less frequently in poorly differentiated tumors. Aberrant cytokeratin staining is an important pitfall in angiosarcoma, especially in epithelioid angiosarcoma, found in 35% of cases in 1 study. However, it is usually focal. Most carcinomas, by contrast, are CD31+. Thus, poorly differentiated angiosarcoma can be misdiagnosed as carcinoma with an overly limited panel of antibodies.

Clinically, angiosarcoma is very aggressive, and most patients die because of disseminated disease. Because it is highly infiltrative, beyond its clinically apparent extent and often multifocal, local control is fraught with a high failure rate. Although grading has been shown to have prognostic relevance in breast tumors, most angiosarcomas have a poor outcome, regardless of grade. Recently, Deyrup et al showed that prognosis in sporadic...
Well-differentiated angiosarcoma consists of irregular, interanastomosing vascular channels that infiltrate and dissect through tissue (A). Distinguishing it from a benign vascular lesion in a small biopsy can be challenging. However, some degree of nuclear atypia, mitotic activity, or multilayering is usually present (B). When well-differentiated angiosarcoma invades the dermis, it entraps collagenous stroma and forms intraluminal papillary structures (C) (hematoxylin-eosin, original magnifications ×40 [A], ×200 [B], and ×400 [C]).

Higher-grade angiosarcomas have heterogeneous cytoarchitectural features. The cytologic features range from epithelioid cells with abundant eosinophilic cytoplasm and large vesicular nuclei with prominent nucleoli (A), to spindle cells (B), and, rarely, to pleomorphic cells (C) (hematoxylin-eosin, original magnifications ×400).
cutaneous angiosarcoma correlates with high- and low-risk groups, on the basis of age, epithelioid histology, necrosis, and tumor depth.

**RADIATION-ASSOCIATED ANGIOSARCOMA**

The clinical behavior and morphologic features of radiation-associated angiosarcoma are comparable to those of sporadic angiosarcoma.\textsuperscript{11} Compared to the latency of other radiation-associated sarcomas, that for breast angiosarcoma is relatively short (5–7 years), with some patients presenting with the tumor within 3 years, thus challenging the 3-year rule.\textsuperscript{11} Compared to sporadic mammary angiosarcoma, which usually arises in the parenchyma, radiation-associated angiosarcoma is usually cutaneous. Clinically, it presents as an erythematous plaque, patch, or nodules, often with edema, and evokes a differential diagnosis that includes inflammatory carcinoma or an infectious etiology. Tumors often present with diffuse, extensive involvement of the breast (Figure 1). Median size is around 7.5 cm,\textsuperscript{9} and multifocality is common.\textsuperscript{11} Most tumors are high grade. However, low- and intermediate-grade tumors have also been described.\textsuperscript{5,11} While overall the prognosis for patients with radiation-associated angiosarcoma is bad, with high rates of local and distant recurrence, some studies have suggested a poorer prognosis,\textsuperscript{11} while others a more favorable outcome.\textsuperscript{5}

**ATYPICAL VASCULAR LESION**

Atypical vascular lesion usually presents as 1 or more small, flesh-colored papules or erythematous patches that arise in radiated skin. Microscopically, most resemble lymphangioma, comprising a relatively well-demarcated proliferation of thin-walled, often dilated, interanastomosing channels devoid of erythrocytes and lined by attenuated or hobnail endothelial cells without atypia (Figure 9, A and B). Some resemble benign lymphangiendothelioma (Figure 10, A), others lymphangioma circumscriptum (Figure 10, B), and some have features of both.\textsuperscript{12} Most AVLs are limited to superficial and mid dermis. However, examples involving deep dermis and subcutis\textsuperscript{4} have been described. Although most pursue a benign course, they tend to develop further lesions, usually more AVLs. There are rare reports of progression to angiosarcoma, usually after multiple recurrences,\textsuperscript{4,5} a fact suggesting that AVL may be a precursor to or incipient angiosarcoma. Current recommendation is that AVLs should be completely excised and the patient closely followed up for any new lesions.\textsuperscript{12}
Figure 8. CD31 is the most sensitive and specific marker for angiosarcoma. In most cases it shows diffuse, strong staining often accentuating the cytoplasmic membrane (immunoperoxidase, original magnification ×400).

Figure 9. Atypical vascular lesion comprises irregular, often dilated lymphatic channels limited to superficial and mid dermis (A) and lined by cytologically bland endothelial cells that often show hobnail features (B) (hematoxylin-eosin, original magnifications ×20 [A] and ×400 [B]).

Figure 10. Atypical vascular lesion may resemble benign lymphangioendothelioma and occasionally may infiltrate deep dermis (A) and subcutis. It may also resemble lymphangiomatosis circumscribunt (B) (hematoxylin-eosin, original magnifications ×40 [A] and ×20 [B]).

Figure 11. Vascular-type atypical vascular lesion, comprising capillary-sized blood vessels, often with a lobular configuration, has recently been recognized as a radiation-associated lesion (hematoxylin-eosin, original magnification ×400).
In 2005, Di Tommaso and Rosai\textsuperscript{6} reported 3 cases of a lobular capillary proliferation in mammary skin after radiation. All 3 patients either had or subsequently developed angiosarcoma. Thus, the spectrum of vascular lesions was expanded to include vascular-type AVL (Figure 11). Recently, Patton et al\textsuperscript{4} detailed their experience with 8 cases of vascular-type AVL, including several lesions with atypia and 1 that progressed to angiosarcoma. They suggest that vascular-type AVL is more likely to progress than the more common lymphatic-type AVL.

Distinguishing well-differentiated angiosarcoma from AVL can be very challenging in a small sample such as that obtained from a punch biopsy. Because areas within and adjacent to angiosarcoma can be indistinguishable from AVL—both lymphatic and vascular types—it is essential to correlate biopsy results with clinical findings. Size is especially important in this regard since most AVLs are small (median, 0.5 cm), while angiosarcomas are usually much larger (median, 7.5 cm).\textsuperscript{5}

References