Chapter 68
Vascular Tumors: Hemangioma, Epithelioid Hemangioendothelioma, and Angiosarcoma

Marco Gambarotti

Definition: Hemangiomas are benign tumors that closely resemble normal vessels. It is difficult to distinguish clearly among neoplasm, hamartoma, and malformations. Epithelioid hemangioma is a benign vascular tumor with well-formed but often immature vessels, lined by plump, epithelioid/histiocytoid endothelial cells. Epithelioid hemangioendothelioma is an angiocentric low-grade malignant vascular tumor, composed of epithelioid endothelial cells arranged in short cords and nests set in a distinctive myxohyaline stroma. Angiosarcoma is a malignant tumor composed of cells that variably recapitulate the morphologic features of normal endothelium.

In the previous 2002 WHO classification, hemangioendothelioma and angiosarcoma represent a spectrum of malignant vascular neoplasm. In the 2013 WHO classification, they are listed as separate entities reflecting their different genetic abnormalities.

Epidemiology: Benign hemangiomas represent 7 % of all benign soft tissue tumors, the most frequent in infancy and childhood. In this age group, they are generally cutaneous or subcutaneous capillary hemangiomas. They grow until body growth has ended. Intramuscular hemangioma, although relatively uncommon, is one of the most frequent deep-seated soft tissue tumors. Adolescents and young adults are most commonly affected, with an equal sex incidence. Hemangiomas can also arise in a synovium-lined surface, particularly in the knee (synovial hemangiomas), or can affect a large segment of the body (angiomatosis) in a contiguous fashion, either by vertical extension to involve multiple tissue planes or by crossing muscle compartments to involve similar tissue types.

Epithelioid hemangioma affects a wide age range, peaking in the 3rd through 5th decades. Females appear to be more commonly affected than males. Epithelioid

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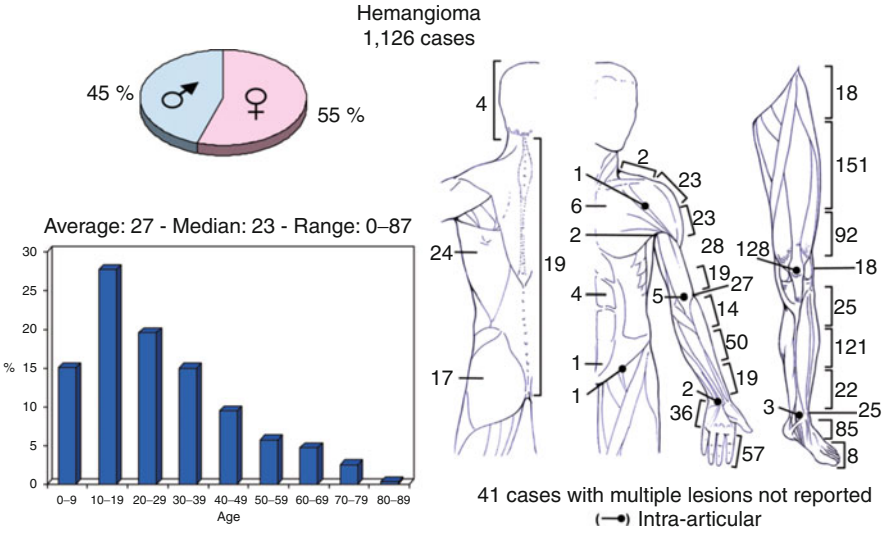
hemangioendothelioma is a rare vascular tumor occurring in nearly all age groups with the exception of early childhood; both sexes are equally affected.

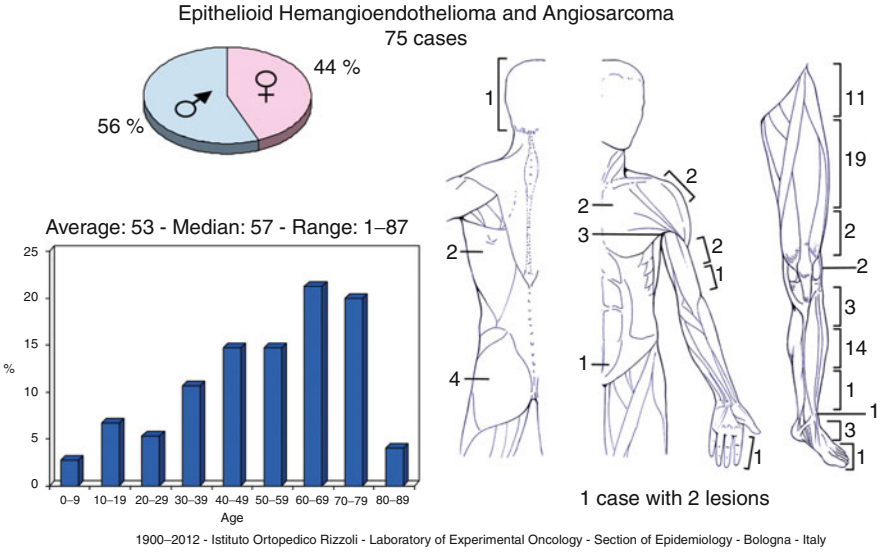
Angiosarcomas are rare tumors; the majority develops as cutaneous lesions, particularly in patients suffering from lymph edema or after radiation for a previous malignancy. Less than 25 % are deep-seated soft tissue neoplasms evenly distributed throughout the decades with a peak incidence in the 7th decade. Angiosarcomas are very rare in children.

Location: Intramuscular hemangioma most commonly affects the lower limb, particularly the thigh.

Epithelioid hemangioma most commonly affects the head, especially the forehead, preauricular area, and scalp, and distal portions of the extremities, especially digits. Epithelioid hemangioendothelioma develops as a solitary tumor in either superficial or deep soft tissue of the extremities. Nearly 50–60 % originate from a vessel, usually a small vein.

Most soft tissue angiosarcomas occur in deep muscles of the lower extremities, followed by the arm, trunk, head and neck, and the abdominal cavity. Rarely lesions are multifocal.





Clinical: Superficial (cutaneous/subcutaneous) hemangiomas are reddish-wine-colored painless lesions, generally present at birth. Intramuscular hemangioma arises within the belly of a single muscle; only in the hand and foot it may expand between the fascia, muscles, and tendons. It is possible to observe pain and swelling associated with venous stasis. Pain is sharp and becomes more intense with tension of the muscle. Shortening of muscles causes first joint dysfunction and then joint deformity. In the hand and foot, an increase of skin temperature, of the superficial venous reticulum, telangiectasia, cyanosis, and hyperhidrosis are observed.

The majority of epithelioid hemangioma presents as subcutaneous masses of a year or less in duration. The process is usually uninodular, but multinodularity, generally in contiguous areas, can be present. Dermal examples are less frequent, and deep-seated cases are rare. Epithelioid hemangioendothelioma develops often as a painful nodule in either superficial or deep soft tissue. Deeply situated tumors may be associated with focal ossification that can be detected on plain films.

Soft tissue angiosarcoma develops as enlarging mass, in 1/3 of patients associated with other symptoms such as coagulopathy, anemia, persistent hematoma, or bruisability.

Imaging: X-rays are usually negative although small round granular calcifications with a smooth surface and concentric stratifications (phleboliths) can be seen. Vascular tumors present an inhomogeneous pattern on MRI. The lesion often appears as a "bunch of grapes," occasionally with a serpentine or tubular pattern. On T1, angiomatous tissue has an intermediate intensity between that of muscle and fat, but areas of stagnant blood and hemorrhage can cause high signal intensity. On T2, vascular spaces seen are hyperintense, but fibrous septa and calcified foci are hypointense. Fluid-fluid levels can be appreciated. Malignant vascular lesions often show nonspecific characteristics. The presence of intratumoral necrosis may be demonstrated by the use of contrast agents.

Histopathology: Benign hemangiomas can be cavernous, capillary, or pseudovenous. Cavernous hemangiomas are the most frequent. Grossly they are made of a bunch of scattered nodules, from dull red to bluish, with internal cloistering. Histologically, they are composed of extremely dilated vessels with a very thin wall of flattened endothelium and collagen membrane, filled with blood. Capillary hemangiomas are more compact and pinkish. They are composed of many small vessels regularly coated with endothelium spreading into collagen stroma. Pseudovenous hemangiomas appear spongelike with fibrous cloisters and intercommunicating lacunae only partially filled with blood, thrombi, and phleboliths. They are composed of craggy, ramified, labyrinthic cavities with very irregular, thick walls with a pseudovenous fibromuscular structure. Intramuscular hemangiomas have been traditionally classified according to vessel size in small (capillary), large (cavernous), and mixed.

Epithelioid hemangioma is usually 0.5–2.0 cm in size, generally with a rather nonspecific nodular appearance. Subcutaneous examples of epithelioid hemangioma are histologically characterized by a prominent proliferation of small, capillary-sized vessels lined by plump, epithelioid endothelial cells, with a typical immature appearance, sometimes lacking a well-defined lumen. These vessels are rimed by a single cell endothelium layer with an intact myopericytic/smooth muscle layer. The process is usually well demarcated from the surrounding soft tissue, and commonly, it is associated with or centered around a larger vessel, usually a muscular artery. An inflammatory milieu rich in eosinophils and lymphocytes is generally present. Dermal examples of epithelioid hemangioma generally show a more mature appearance with a well-canalized lumen, and endothelial cells are somewhat less plump, frequently more cobblestone, or hobnail-like in appearance. In addition, dermal examples are less circumscribed and are not usually associated with a larger central vein or muscular artery. Epithelioid hemangioendothelioma generally arises as a fusiform intravascular mass that may resemble an organizing thrombus. Histologically, they are composed of short strands, cords, or solid nests of epithelioid eosinophilic endothelial cells, sometimes with intracytoplasmic lumina (vacuoles) containing erythrocytes. Cells appear quite bland with little or no mitotic activity and are embedded in a distinctive matrix that varies from light blue (chondroid-like) to deep pink (hyaline) in color.

Angiosarcomas are high-grade tumors composed of highly malignant cells displaying mitotic activity. These cells may vary in appearance from spindle (resembling a fibrosarcoma) to epithelioid (resembling an undifferentiated carcinoma) and are arranged in sheets, small nests, cords, or rudimentary vascular channels irregular in shape; freely intercommunicate with one another in a sinusoidal fashion; and infiltrate surrounding tissues in a destructive fashion. Malignant endothelial cells can be also arranged in intraluminal buds, projections, or papillae. Extensive hemorrhage is a characteristic feature of most angiosarcomas.

Course and Treatment: Complete local excision and eventually follow-up are the optimal management for symptomatic benign hemangiomas (including epithelioid hemangioma). Local recurrence is reported to occur in 1/3 of epithelioid hemangiomas. Metastases do not occur. Behavior of epithelioid hemangioendothelioma is

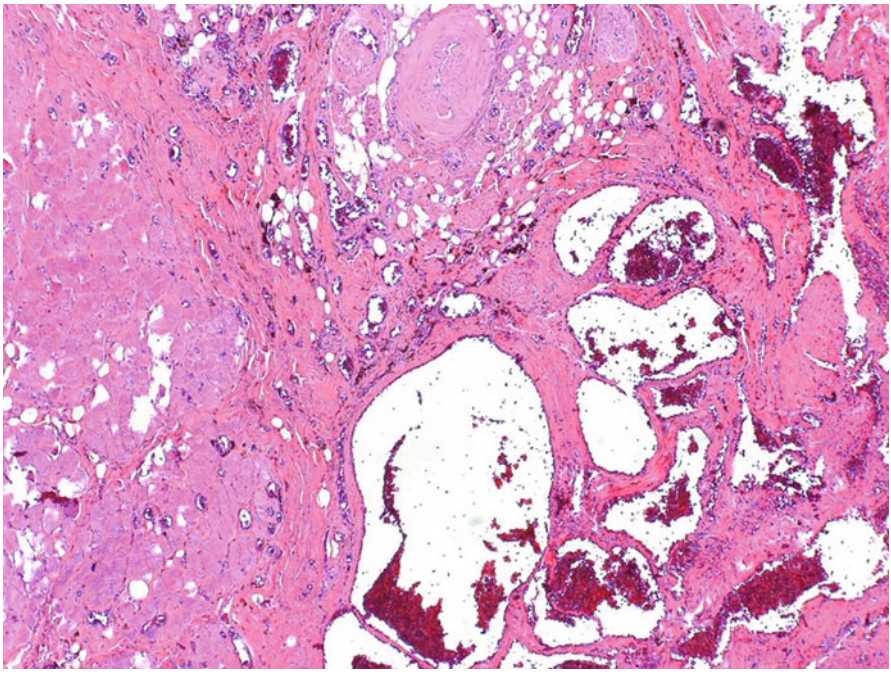
intermediate between hemangiomas and angiosarcomas, with a metastatic rate of 17 % and mortality of 3 %. Soft tissue angiosarcomas are highly aggressive tumors. Local recurrences develop in about 20 % of patients, and 50 % of these may be expected to die within the first year from diagnosis with metastatic disease in the lung, lymph nodes, bone, and soft tissues.

Immunohistochemical Panel

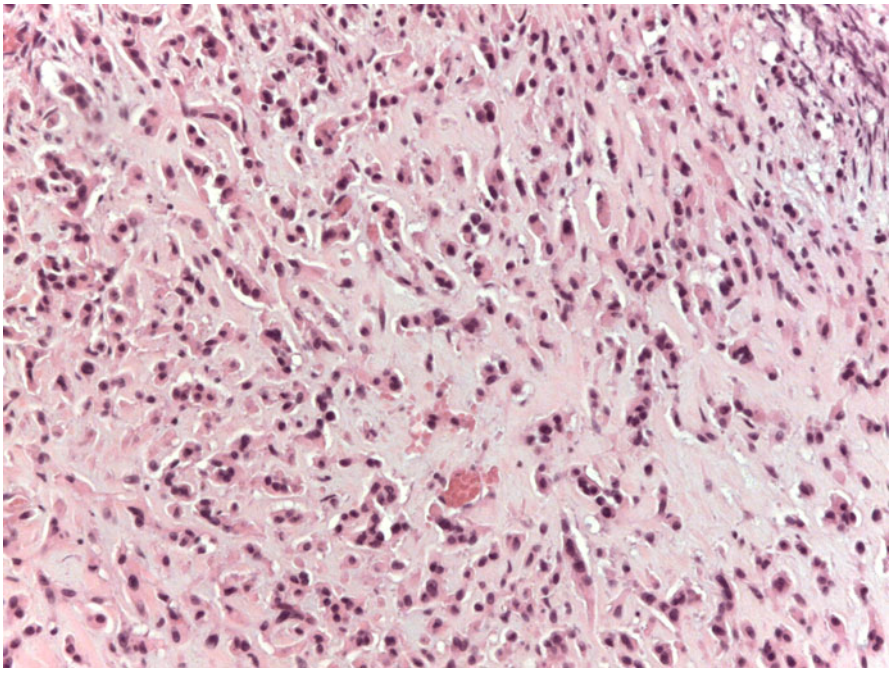
VIM	+
CD31	+
CD34	±
Fli-1	+
CK	±
ERG	+ (Am J Surg Pathol 35(3):432–441)

Chromosomal Translocations

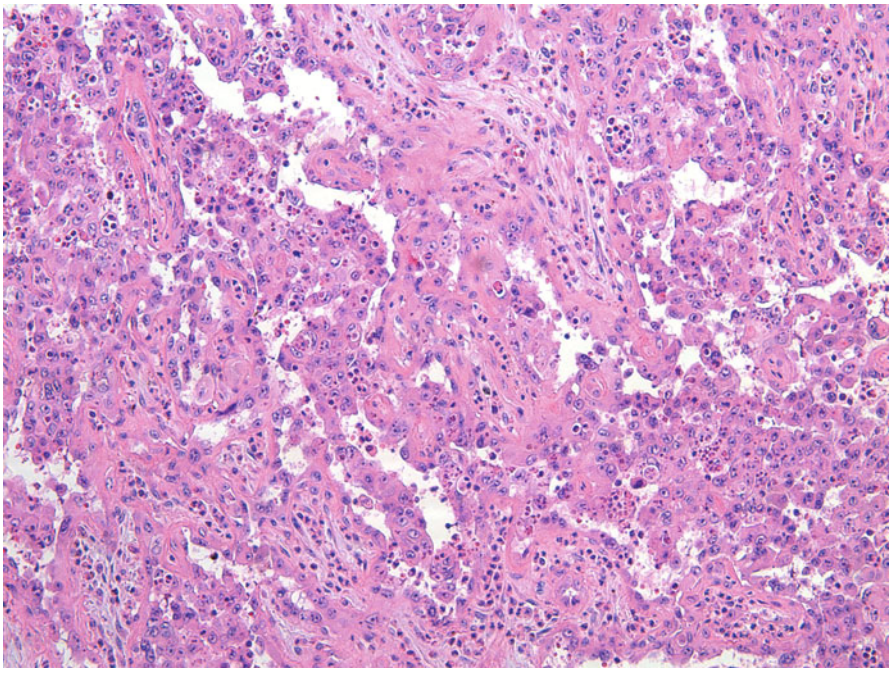
Epithelioid hemangioendothelioma		
t(1;3)(p36.3;q25)	WWTR1-CAMTA1	100 %



Hemangioma. Blood-filled cavities rimmed by flat endothelium in variable-sized vessels (capillary, cavernous, mixed)



Epithelioid hemangioendothelioma. Short strands and cords of epithelioid cells in a chondroid-like matrix



Angiosarcoma. Irregular and haphazard blood-filled cavities rimmed with highly malignant and atypical cells

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