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Composite Hemangioendothelioma
- A Case Report -

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Composite hemangioendothelioma (CHE) is a recently described vascular tumor of low-grade malignancy. We report a case of CHE in an 18-year-old woman who presented with a 2-month history of an enlarging palpable mass in the left axilla. Grossly, the excised tumor was relatively circumscribed, nodular, firm, and soft. It measured 6.0×4.5×4.0 cm. The cut surface revealed a whitish gray solid area and a dark red to tan cystic area containing necrotic material. Histologically, the tumor demonstrated variably intermixed benign and malignant vascular components. The benign components showed features of an arteriovenous malformation, capillary hemangioma, spindle cell hemangioma and cavernous hemangioma. The malignant components were composed of areas resembling retiform hemangioendothelioma, epithelioid hemangioendothelioma, Kaposiform hemangioendothelioma, and angiosarcoma. The angiosarcoma component showed a mixed epithelioid and spindle shaped cell morphology with moderate differentiation. A nearly imperceptible transition between the benign and malignant components was noted.

Key Words : Hemangioendothelioma; Soft tissue

Composite hemangioendothelioma (CHE) is the most recently described vascular neoplasm of low malignant potential. It is extremely rare.[1] It presents on the dorsum of the hands or feet, and on fingers and toes, as single or multiple nodules. It usually affects adults from 21 to 71 years of age (mean, 41 years). CHE has a great variety of histologic appearances that may resemble other types of HE, such as epithelioid and retiform HE, as well as areas that show strong morphologic similarity to angiosarcoma and benign vascular neoplasms, including spindle cell hemangioma. Four of the eight patients with available follow-up information developed local recurrences and one showed metastatic dissemination to a submandibular lymph node. Since the series reported by Nayler *et al*.,[1] two additional cases of CHE have been reported.[2,3] We report here a new case of composite hemangioendothelioma.

CASE REPORT

An 18 year-old woman presented with a 2-month history of an enlarging palpable mass in the left axilla. The patient was healthy without a prior history of surgery or radiotherapy. Her father and mother died of lung cancer and breast cancer, respectively. Ultrasonography revealed a relatively circumscribed cystic sold mass, measuring 6.0×5.0 cm. The patient was treated initially by marginal excision of the mass.

Grossly, the tumor was a relatively circumscribed nodular, firm and soft mass, measuring 6.0×4.5×4.0 cm. The outer surface was partly smooth, dark brown and partially covered with adipose tissue. The cut surface revealed a whitish gray, solid area and a dark reddish tan, cystic area containing necrotic material (Fig. 1).

Microscopically, the tumor was a poorly circumscribed lesion with infiltrating borders. Extensive hemorrhage and multifocal necrosis were present. The most striking features upon low power examination were the presence of a diffuse infiltrative pattern and the variability in appearance from area to area. There were benign and malignant vascular components, which were haphazardly intermixed. The benign component showed features of an arteriovenous malformation (5%), capillary hemangioma

(5%), spindle cell hemangioma (20%) and cavernous hemangioma (30%). The malignant component was composed of retiform hemangioendothelioma (25%), epithelioid hemangioendothelioma (5%), Kaposiform hemangioendothelioma (5%) and angiosarcoma (5%). The angiosarcoma (AS) portion was of high grade and showed mixed epithelioid and spindle shaped cytomorphology with moderate differentiation. Nine of 11 axillary lymph nodes showed histologic involvement by metastatic retiform hemangioendothelioma.

Areas showing histological features of cavernous hemangioma were composed of large, dilated, thin walled blood vessels (Fig. 2). Areas with capillary hemangioma features were composed of aggregates of small dilated capillaries (Fig. 2). Areas with spindle cell hemangioma features were composed of thin walled, cavernous blood vessels and more solid areas composed predominantly of spindle cells (Fig. 3). The spindle cells formed a network of slit-like spaces and short fascicles. Cytologic atypia and mitotic activity were not seen. Areas with features of arteriovenous malformation were characterized by a mixture of large, malformed, thick- or thin-walled vessels, clusters of dilated thin-walled channels and capillaries (Fig. 4). An elastic stain demonstrated arterial vessel features (Fig. 4 Inset).

Areas with a histologic pattern most in keeping with retiform HE and Kaposiform HE were intimately mixed together. Retiform HE was composed of long, arborizing, thin-walled blood vessels extending between collagen bundles in a distinctive retiform pattern. High-power examination revealed that retiform vessels were lined by a single layer of monomorphic, mitotically inactive, small cells showing a prominent apical, rounded, hyperchromatic nucleus, and scanty cytoplasm (Fig. 5). Intraluminal

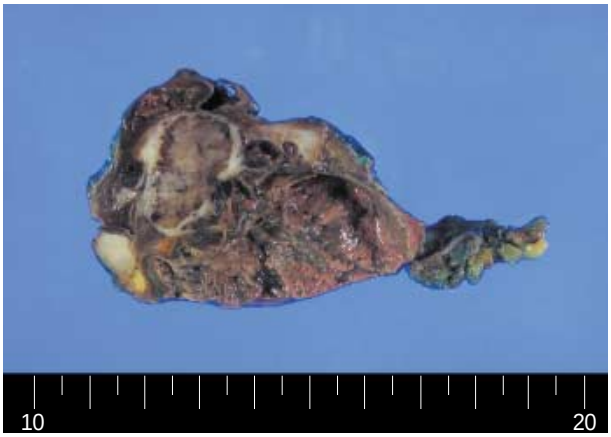

Fig. 1. The tumor is a relatively circumscribed nodular firm mass, measuring 6.0×4.5×4.0 cm. The cut surface reveals whitish-gray solid area and dark reddish-tan cystic area containing necrotic material. Extensive hemorrhage and multifocal necrosis are present.

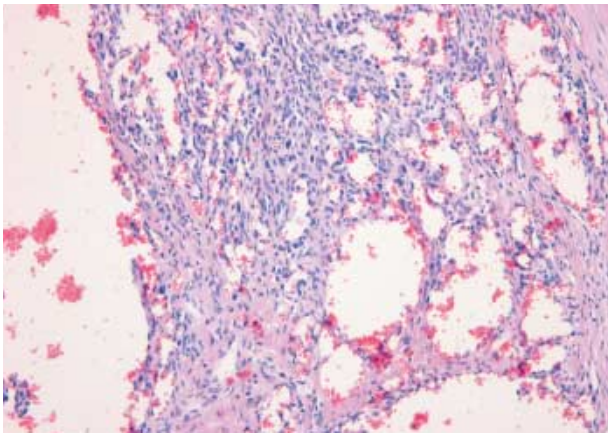

Fig. 3. Thin walled, cavernous blood vessels and more solid areas composed of predominantly spindle cells. The spindle cells form a network of slit-like spaces and short fascicles. Cytologic atypia and mitotic activity are inconspicuous.

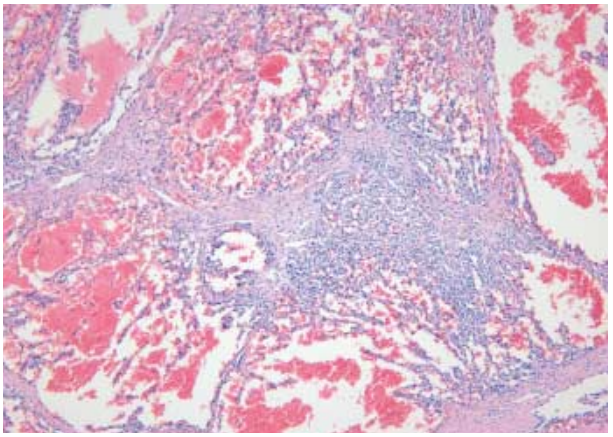

Fig. 2. Aggregates of large, dilated, thin walled blood vessels and small dilated capillaries.

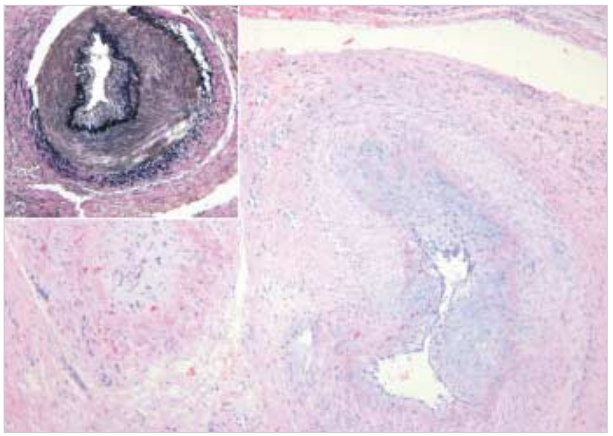

Fig. 4. Mixture of large, malformed, thick- or thin-walled vessels. Elastic stain demonstrates artery (Inset).

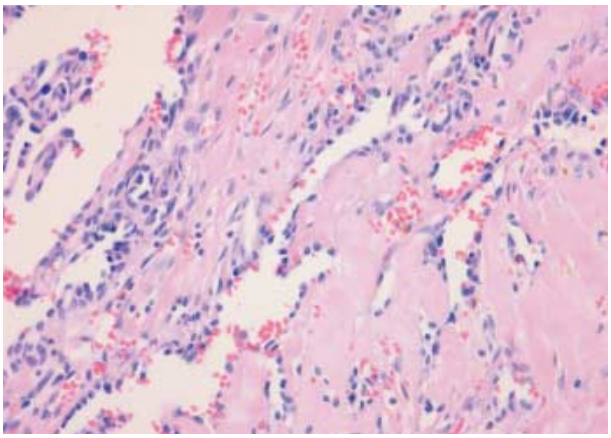

Fig. 5. Long, arborizing, thin-walled blood vessels are present in a distinctive retiform pattern. Retiform vessels are lined by a single layer of small cells with prominent apical, rounded and hyperchromatic nuclei and scanty cytoplasm.

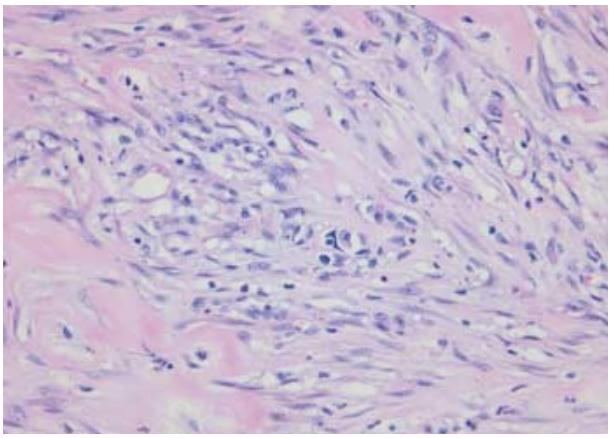

Fig. 7. Cords and strands of spindled epithelioid cells in a hyaline stroma. Small intracytoplasmic lumina are noted.

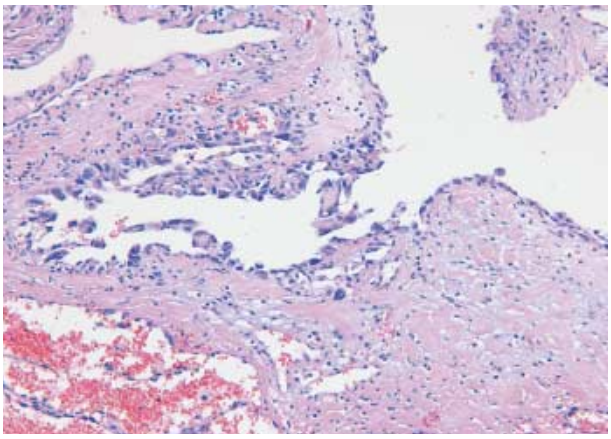

Fig. 9. The large, ectatic, thick walled vessels reveal gradual transition of lining endothelial cells from bland endothelial cells to large, pleomorphic hyperchromatic cells and multilayering of atypical cells.

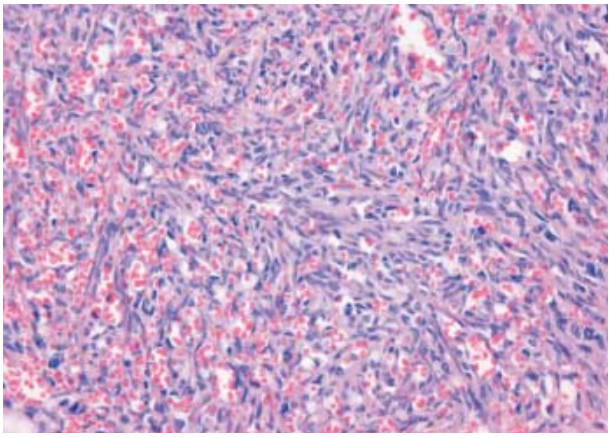

Fig. 6. Infiltrative nodules of spindle cells, along with crescent-shaped vascular spaces exhibit minimal cytologic atypia. The spindle cells are arranged in bundles or cords.

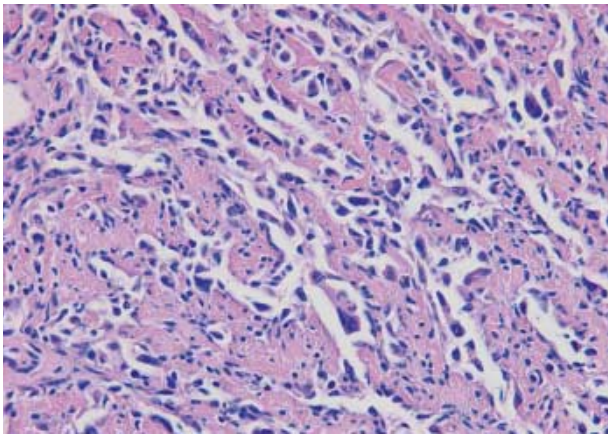

Fig. 8. Anastomosing vascular channels are lined by mitotically active, atypical nuclei with multilayering. At high power the epithelioid cells show copious, eosinophilic cytoplasms and large, pleomorphic, vesicular nuclei with prominent eosinophilic nucleoli. Tumor giant cells are admixed.

papillary tufts were also seen. Areas with Kaposiform HE features were composed of infiltrative nodules of spindle cells, along with crescent-shaped vascular spaces, and they exhibited minimal cytologic atypia (Fig. 6). The spindle cells were arranged in bundles or cords. Areas with histologic features of epithelioid HE were observed in the periphery of the tumor and were composed of cords and strands of spindled epithelioid cells in a hyaline stroma (Fig. 7). Small intracytoplasmic lumina were noted.

Areas consistent with moderately differentiated angiosarcoma were characterized by vascular channels with a complex dissecting and anastomosing growth pattern, associated with marked nuclear atypia, multilayering of atypical nuclei, and scattered papillae without hyaline cores. A few mitotic figures were identified (3 per 10 high power fields) (Fig. 8). Occasionally, tumor

giant cells were admixed. The AS was intimately admixed with angiomatous lesion, a complex aggregate of large, malformed, thick-walled blood vessels and variable HE components. The different components merged imperceptibly, making it difficult to identify the pure components. The large, ectatic, thick walled vessels revealed gradual transition of lining endothelial cells from bland endothelial cells to large, pleomorphic hyperchromatic cells and with a multilayering of atypical cells, demonstrating continuity between the benign and malignant vascular components (Fig. 9). The stroma was composed of fibrofatty tissue and moderate to prominent inflammatory infiltrates, predominantly of lymphocytes with occasional lymphoid follicles.

Endothelial cells in normal blood vessels were positive for CD31 (JC/70A, 1:20, DAKO, Glostrup, Denmark), CD34 (QBEend, 1:200, Novocastra, Newcastle, UK), factor VIII-related antigen (polyclonal, 1:400, DAKO). Neoplastic endothelial cells were also positive for CD34, CD31 and factor VIII-related antigen, but only focally and weakly. The spindle cells were also focally positive for CD31 but negative for CD34 and factor VIII-related antigen. Generally, there was greater positivity for CD31 than for factor VIII-related antigen and CD34. The tumor cells were negative for cytokeratin (MNF116, 1:500, DAKO) and EMA (E29, 1:600, DAKO). Desmin (D33, 1:300, DAKO) confirmed the presence of smooth muscle bundles around the large, thick walled vessel, but this stain was uniformly negative around HE and AS. Staining for smooth muscle actin (1A4, 1:400, DAKO) highlighted the presence of pericytes around blood vessels of hemangioma/vascular malformation (HVM) and focally in HE and AS tissues. Ki-67 (MIB-1, 1:600, DAKO) labeling index was 8% to 42% in the AS, 1% to 6% in the HE, and less than 1% in the HVM. P53 (Do-7, 1:200, DAKO) was positive in the AS area (up to 100% nuclear staining), HE area (50-80% nuclear staining) and HVM area (0-80% nuclear staining). Vascular endothelial growth factor (G153-694, 1:50, Pharmigen, CA, USA) was strongly positive in the AS, and weakly positive in HE and HVM areas.

Based upon the presence of these variable histological appearances which merged imperceptibly with one another, a final diagnosis of CHE was made.

At follow-up 4 months later, multiple metastases to bones (lumbar spine and pelvic bones) were noted. Postoperative chemotherapy and radiotherapy were administered. At follow-up two years later, there was metastatic dissemination to the lungs, bones and liver. At present, the patient is alive with tumor.

DISCUSSION

Hemangioendotheliomas (HE) are vascular neoplasms which are included in the borderline/low-grade malignancy group, on the basis of rare metastasis and infrequent mortality. HE include epithelioid HE, retiform HE, Kaposiform HE, polymorphous HE and composite HE. The most recent addition to the HE group is the composite hemangioendothelioma (CHE), which was first described by Nayler *et al*.[1] in 2000 as a low-grade malignant neoplasm.

CHE is a locally aggressive, rarely metastasizing neoplasm with vascular differentiation, containing an admixture of histologically benign, intermediate and malignant components. CHE is extremely rare, and only 10 cases have been reported in the English language literature.[1-3] The reported 10 cases usually presented as poorly circumscribed single or multinodular lesions on the hands and feet of adults (mean age 41 years; range 21-71 years), with individual nodules ranging from 0.7 to 13 cm. Histologically, the tumors were all poorly circumscribed, complex lesions with infiltrative borders, centered deep in the dermis and subcutis. The most striking feature at low power was the variability in appearance from patient to patient, and from area to area within the same patient. The different components merged imperceptibly. None of the lesions had an intravascular component. Tumors in nine patients (9/10) contained a component of epithelioid HE and retiform HE. Eight tumors (8/10) contained areas consistent with well-differentiated angiosarcoma. A single tumor also contained an area of high-grade angiosarcoma. Six of the tumors (6/10) contained areas of spindle cell hemangioma. One of the tumors was associated with an arteriovenous malformation. Another tumor contained areas of cavernous hemangioma. One tumor was associated with lymphangioma circumscriptum. Similarly, our present case was composed of cavernous hemangioma, capillary hemangioma, spindle cell hemangioma, AVM, retiform HE, Kaposiform HE, epithelioid HE and high-grade angiosarcoma.

CHE may recur locally and has the ability to metastasize. Follow-up of eight patients (8/10) identified local recurrence in four after 2 to 10 years. In one of these patients, metastasis developed in a submandibular lymph node 9 years after excision, and in the soft tissue of the thigh 2 years after nodal metastasis. The present case already had regional lymph node involvement at diagnosis. Postoperative chemotherapy and radiotherapy were performed. But multiple metastases to bones (lumbar spine and pelvic bone) were noted 4 months after excision. Metastases to both lungs and liver were present seven months later. At follow-

up two years later there was metastatic dissemination to lungs, bones and liver. Among the reported 10 cases of CHE, only a single tumor contained an area of high-grade angiosarcoma. The present case contained several areas of high-grade angiosarcoma (5%) and showed a much more aggressive clinical course than those previously reported cases.

Malignant vascular tumor spontaneously arising in a benign hemangioma is exceptionally uncommon. There are only rare case reports in the literature of angiosarcoma spontaneously arising in a hemangioma/vascular malformation.[4-7] Rossi *et al*.[8] reported four cases of angiosarcoma spontaneously arising in a hemangioma/vascular malformation (HVM). Recent experimental studies of the pathogenesis of angiosarcoma support the possibility of malignant transformation occurring in hemangiomas.[9] The involvement of p53 and vascular endothelial growth factor receptor (VEGF) in the pathogenesis of angiosarcoma has been well documented.[10] Detection of the p53 tumor suppressor gene mutation in various angiosarcomas has been reported recently.[11] Our case revealed diffuse positive p53 in both the benign and malignant vascular components. Whereas VEGF was strong positive in the angiosarcoma sections, it was weakly positive in HE and HVM. This finding suggests that over-expression of VEGF may play an important role in the progression of angiosarcoma. Our case revealed a high Ki-67 labeling index (8% to 42%) in angiosarcoma, 1-6% in HE areas and less than 1% in the HVM components. The expression pattern of Ki-67 labeling index, VEGF and p53 in our case is in accord with prior findings,[10] and provides additional evidence of the coexistence of the variable components in this case that are morphologically and biologically distinct.

The association of angiosarcoma of soft tissue and a hereditary disorder has been previously reported.[12] However, there was no family history of malignancy in the other reported cases. This patient's father and mother died of lung cancer and breast cancer, respectively. This fact suggests that this patient may have had a genetic predisposition to the development of malignancy at young age. Our case differs from the previously reported cases in both clinical and morphologic features. Our patient is young and has a family history of malignancy. There was morphologic progression from hemangioma/vascular malformation to angiosarcoma, raising the possibility of malignant transformation in a benign vascular tumor and thus a much more aggressive clinical course.

The presence of pericytes, detected immunohistochemically by smooth muscle actin, has been reported in one fourth of the cases of soft tissue angiosarcoma.[13] Our case also demonstrated the presence of pericytes around blood vessels of HVM, as well as focally in the HE and AS areas of the tissue.

The differential diagnosis in this case includes polymorphous hemangioendothelioma (PHE), angiosarcoma, metastatic carcinoma or melanoma in hemangioma, intravascular lymphoma occurring in a hemangioma, and a proximal type of epithelioid sarcoma.

PHE is a rare borderline malignant tumor of lymph nodes that is composed of varying proportions of solid, primitive vascular and ectatic angiomatous elements. On occasion, PHE may display focally a histologic appearance similar to that of retiform hemangioendothelioma, but it lacks the other components of CHE (epithelioid HE, spindle cell hemangioma, and well differentiated AS).

Haphazardly intermixed benign and malignant vascular components indicate that this case was not in keeping with "standard" angiosarcoma. The occurrence of metastatic carcinoma, or melanoma, and of intravascular lymphoma in hemangioma has been reported.[14,15] However, the presence of vasoformative areas and positive immunostaining for endothelial cell markers (CD31, CD34 and factor VIII) allow us to make this distinction.

In summary, we described here a case of CHE. A distinct and previously unreported feature in our case is the patient's young age, the presence of family history of malignancy, the morphologic progression from hemangioma/vascular malformation to angiosarcoma, and a much more aggressive clinical course.

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