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# Epithelioid Sarcoma-Like Hemangioendothelioma

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We are reporting seven histologically identical cases of a distinctive, low-grade vascular tumor that closely mimics an epithelioid sarcoma because of growth in solid sheets and nests, the eosinophilia of the rounded to slightly spindled neoplastic cells, and the diffuse, strong cytokeratin expression. Termed epithelioid sarcoma-like hemangioendothelioma, all were diagnosed by the submitting pathologist or another expert consultant as epithelioid sarcoma. Although none displayed architectural evidence of vascular differentiation in the form of multicellular vascular channels, some displayed subtle cytologic features of vascular differentiation and all displayed immunohistochemical evidence of endothelial differentiation. The patients (four male; three female) ranged in age from 17 to 54 years (median 23 years). Ranging in size from 1 to 3.5 cm, they occurred in the extremities (n = 5), scalp (n = 1), and chest wall (n = 1), both in deep (n = 3) and superficial (n = 3) soft tissue or both (n = 1). The tumors were characterized by sheets, ill-defined nodules, or fascicles of deeply eosinophilic cells set within a desmoplastic stroma. Multicellular vascular channel formation and/or hemorrhage were absent in all cases. In four cases intracytoplasmic vacuolization suggestive of intracytoplasmic vascular lumen formation was noted. The typical neoplastic cell was large and rounded in shape but modulated in areas to a spindled or multipolar shape. Mitotic activity was low (<5 mitotic figures/50 high power fields), nuclear pleomorphism was mild to moderate, and necrosis was absent. The tumors were positive for cytokeratin (6 of 6), vimentin (6 of 6), CD31 (5 of 6), FLI-1 (6 of 6), but negative for CD34 (0 of 6). Within a follow-up period of 3–72 months (median 39 months), two patients experienced a local recurrence and one patient regional soft tissue metastases, but no distant ones. Two patients presented with multifocal lesions suggestive of regional metastases. Currently, two patients are alive with disease and five are disease free. Epithelioid sarcoma-like hemangioendothelioma appears to be a largely unrecognized epithelioid vascular tumor with an indolent course. Despite its similar clinical and histologic features, it differs from epithelioid sarcoma by the presence of endothelial markers and the absence to date of distant metastases. Its distinction from other epithelioid vascular lesions is discussed. We think this tumor fits best into the family of "hemangioendothelioma" or vascular lesions of intermediate malignancy.

**Key Words:** Hemangioendothelioma—Epithelioid sarcoma—Vascular neoplasms.

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Over the past 15 years we have recognized an unusual tumor, which was virtually always submitted in consultation with a diagnosis of epithelioid sarcoma but because of certain subtle differences was regarded by us as an unusual keratin-positive sarcoma of uncertain type. In very recent years the increase in immunohistochemical markers and enhanced antigen retrieval techniques have allowed us to characterize these distinctive lesions as endothelial tumors. Despite their epithelioid appearance, they appear sufficiently different from previously described epithelioid vascular tumors to warrant a separate designation. Given the mimicry of epithelioid sarcoma in the face of their more indolent behavior, we propose the name epithelioid sarcoma-like hemangioendothelioma (ES-H).

## MATERIALS AND METHODS

Seven histologically identical cases were retrieved from our consultation files during the period 1991–2001. The earliest cases were coded as "low grade sarcoma" with a notation that they expressed cytokeratin. The tumors were analyzed with respect to growth pattern, cellularity, nuclear atypia, mitotic figures/50 high power fields, necrosis, vasoformation, inflammation, and the characteristics of the accompanying stromal matrix. Demographic parameters were also analyzed, including referring diagnosis from the contributing pathologist and any previous consultative diagnosis. In no case did the tumor appear to arise from the overlying skin, and no patient had a history of a carcinoma. Six tumors had either blocks or slides available for immunohistochemical studies.

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**TABLE 1.** *Summary of clinical information*

| Case no. | Age (y), sex | Referring diagnosis | Location | Size (cm) | Treatment | Follow-up |
|---|---|---|---|---|---|---|
| 1 | 54/M | Epith sarc | Thigh | 2.2 | WLE | NED 61 mo |
| 2 | 23/M | Not provided | Knee | 2 | XRT | AWD 66 mo, developed multiple thigh masses |
| 3 | 45/F | Epith sarc vs. low grade vascular tumor | Scalp | <2 | WLE (2) | Rec 36 mo, NED after 2nd WLE 36 mo |
| 4 | 18/F | Epith sarc vs. epithelioid angiosarcoma | Thigh (2 separate masses) | NA | WLE, Chemo, XRT | NED 39 mo |
| 5 | 20/M | Epith sarc | Calf | 3.5 | WLE | NED 9 mo |
| 6 | 17/F | Epith sarc | Chest wall | Small | Simple exc | Probable rec 6 mo |
| 7 | 36/M | Epith sarc | Wrist and forearm | 1–3 | WLE, XRT | NED 3 mo |

Epith sarc, epithelioid sarcoma; WLE, wide local excision; Chemo, chemotherapy; EXC, excision; XRT, radiation therapy; NED, no evidence of disease; AWD, alive with disease; Rec, recurrence.

For immunohistochemistry, deparaffinized, formalin-fixed sections were immunostained with antibodies to pancytokeratin (AE1/AE3, 1:40, Dako Corporation, Carpinteria, CA, USA), vimentin (V9, 1:80, Dako Corp.), CD31 (JC70, 1:80, Dako Corporation), CD34 (QBEND 10, 1:320, Dako Corporation), and Fli-1 protein (Sc 356 polyclonal, 1:120, Santa Cruz Biotechnology, Santa Cruz, CA, USA). Negative controls consisted of substitution of normal serum for the primary antibody. Sections were subjected to heat-induced epitope retrieval, in citrate buffer using a vegetable steamer, for 15 minutes. Antigens were localized using an avidin-biotin method with 3,3′-diaminobenzidine as a chromogen. The slides were counterstained with hematoxylin.

## RESULTS

The patients (four men and three women) ranged in age from 17 to 54 years (median 23 years). The tumors occurred most commonly in the lower extremity (n = 4) followed by one each in the upper extremity, scalp, and chest wall (Table 1). The contributing pathologist's and/or other consultant's diagnosis was "epithelioid sarcoma" or "probable epithelioid sarcoma" in six cases, although in two cases alternative diagnoses of epithelioid vascular tumor (i.e., epithelioid hemangioendothelioma or angiosarcoma) were suggested. In the seventh case no diagnosis was rendered.

The tumors ranged in size from 1 to 3.5 cm. They presented as deep soft tissue masses (three cases), superficial masses (three cases), or involving both superficial and deep soft tissue (one case). One case was notable for ulceration of the overlying epidermis (Fig. 1).

Histologically, all were characterized by neoplastic cells arranged as multiple ill-defined nodules, sheets, or short fascicles (Fig. 2), which typically infiltrated soft tissue and evoked a desmoplastic response. No tumor appeared to arise from a vessel. The neoplastic cells for the most part had a rounded epithelioid shape with prominent eosinophilic cytoplasm (Figs. 3, 4) and usually indistinct cytoplasmic borders. Within nearly all tumors transitional zones were noted in which the cells acquired a spindled or a multipolar shape and lost their cellular cohesion (Figs. 5, 6). In the spindled areas the cells were usually arranged in short intersecting fascicles (Figs. 7, 8) and rarely in long fascicles similar to a well-differentiated fibrosarcoma (Fig. 9). Even in these areas, it was usually possible to appreciate the relative plumpness and eosinophilia of the spindled cells. In all areas (epithelioid, transitional, and spindled) the overall atypia

**TABLE 2.** *Differential diagnosis of epithelioid sarcoma-like hemangioendothelioma*

| Histologic feature | Epithelioid sarcoma-like hemangioendothelioma | Epithelioid sarcoma | Epithelioid hemangioendothelioma | Epithelioid angiosarcoma |
|---|---|---|---|---|
| Growth pattern | Ill-defined nodules and fascicles | Nodules often with central necrosis | Cords, often vasculocentric | Sheets |
| Vasoformation | Not evident by light microscopy except for rare cytoplasmic vacuoles | Focal intracytoplasmic vacuoles, no true lumen formation | Frequent intracytoplasmic lumens ("blister" cells) | Multicellular vascular channels, intracytoplasmic lumens |
| Nuclear atypia | Mild to moderate | Mild to moderate | Mild to moderate | Moderate to marked |
| Immunostains | CK+, CD31+, Fli-1+, Vim+, CD34– | CK+, CD31–, Fli-1–, Vim+, CD34+ (50–60%) | CK+ (25%), CD31+, Fli-1+, Vim+, CD34+ | CK+, CD31+, Fli-1+, Vim+, CD34+ |

CK, cytokeratin; Vim, vimentin.

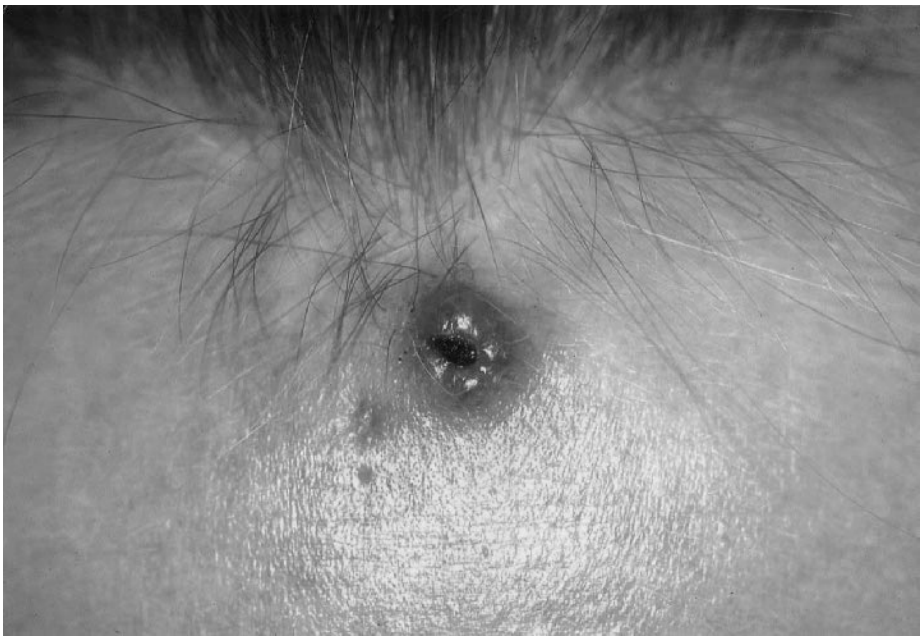

**FIG. 1.** Clinical photograph of an ulcerating ES-H of the forehead.

of the cells was minimal or modest and mitotic activity was <5 mitotic figures/50 high power fields (Figs. 10, 11). The diagnosis of vascular tumor was seldom suspected in these cases because the usual features we attribute to various vascular tumors were either absent or inconspicuous at best. For example, in no case were multicellular vascular channels, the hallmark of hemangiomas and many angiosarcomas, present. Likewise, intracytoplasmic vacuoles, which are usually interpreted as evidence of intracytoplasmic lumen formation and are commonly seen in epithelioid hemangioendothelioma, were identified in only four cases and then only in rare cells (Fig. 12). Intralesional hemorrhage, a signature of many angiosarcomas, was also totally lacking.

Six cases with available material for immunohistochemical studies were strongly positive for cytokeratin (Fig. 13) and vimentin. Five of the six cases were positive for CD31 with linear staining of the cytoplasmic

**FIG. 2.** Low power view of an ES-H involving skeletal muscle showing sheets of cells displaying a vague nodularity. The center of one coarse nodule is hyalinized in a fashion reminiscent of the hyalinizing nodules of epithelioid sarcoma.

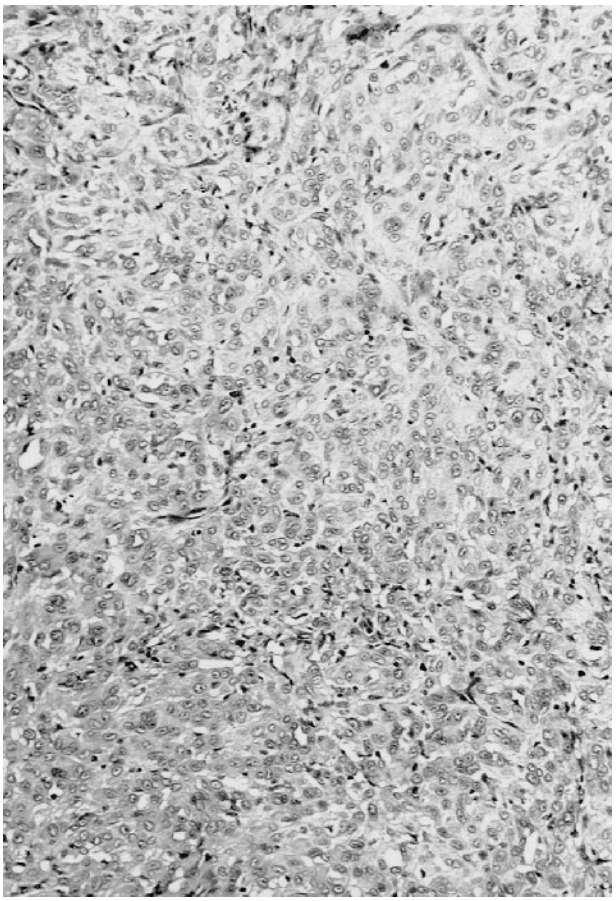

**FIG. 3.** Epithelioid areas of an ES-H.

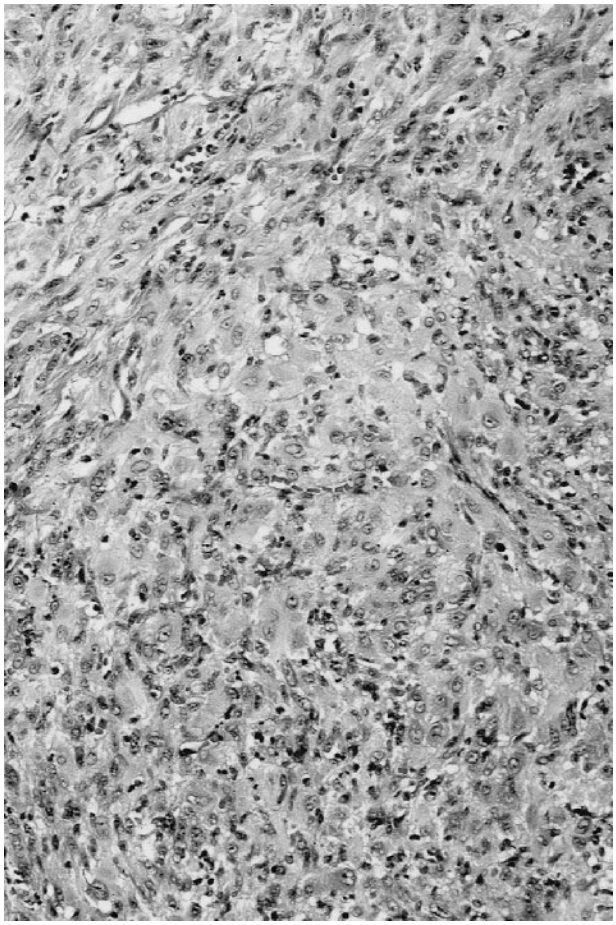

**FIG. 4.** Epithelioid areas of an ES-H. Cells have more abundant cytoplasm than those depicted in Figure 3.

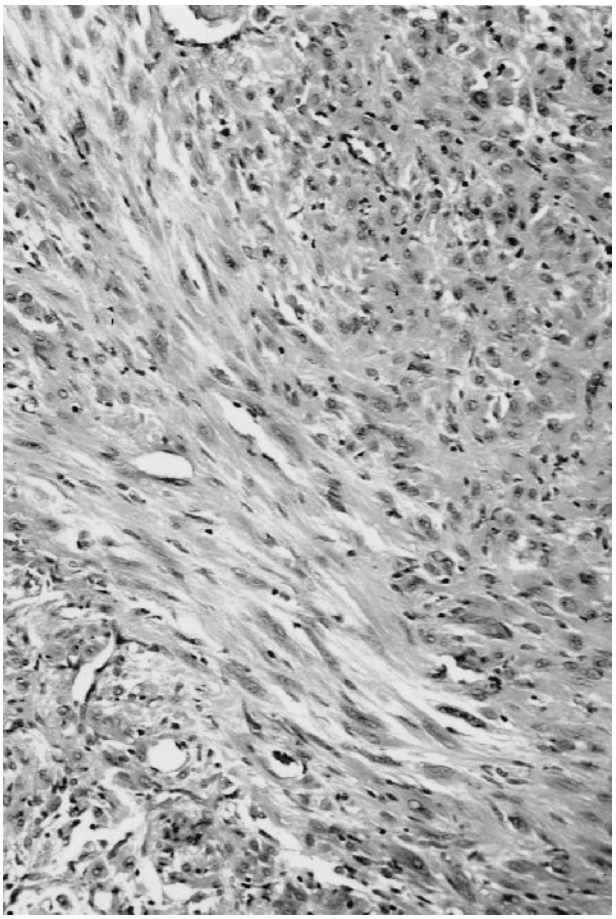

**FIG. 5.** ES-H showing transition between epithelioid and spindled areas.

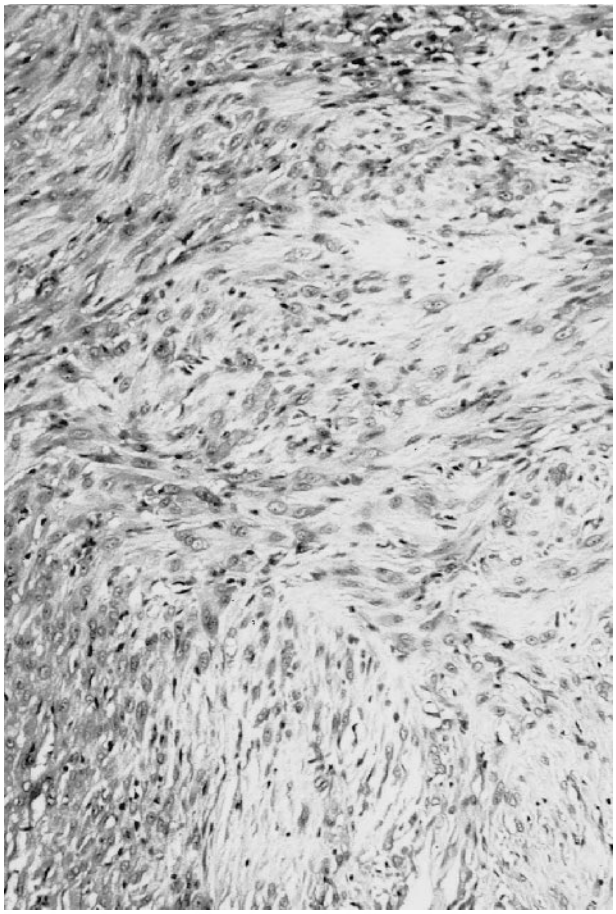

**FIG. 6.** ES-H showing transition between epithelioid and spindled areas. Striking desmoplasia is evident similar to an epithelioid sarcoma.

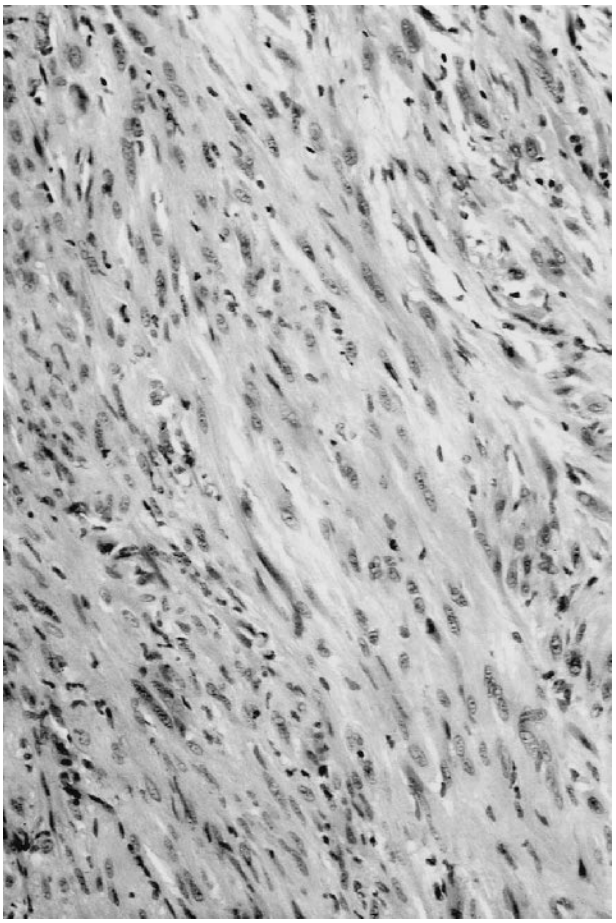

**FIG. 7.** Spindled area in ES-H. Spindled cells are plump with abundant cytoplasm.

membrane characteristic of endothelial differentiation (Fig. 14). All six were also at least focally positive for Fli-1 protein, with most cases showing moderate nuclear staining (Fig. 15). None of the six was immunoreactive for CD34. Other immunohistochemical stains, including S-100 protein (two cases), desmin (four cases), muscle specific actin (two cases), and epithelial membrane antigen (one case), were negative.

Follow-up was available on all seven cases (range 3–72 months; median 39 months). Two patients had evidence of local recurrences (case nos. 1 and 6). Case no. 1 with a scalp tumor experienced a local recurrence at 36 months. Following wide reexcision, she has remained disease free for 36 months. In case no. 6 the patient had radiologic evidence of local recurrence at 6 months but no additional biopsies or reexcision had been performed. One patient had documented regional soft tissue metastasis (case no. 2). Two cases presented with multiple masses, suggesting regional soft tissue metastasis at the time of presentation (case nos. 4 and 7). No patient has developed evidence of distant metastasis. Currently, two patients are alive with disease (case nos. 2 and 6) and five are free of disease.

## DISCUSSION

In 1988 while at the Armed Forces Institute of Pathology one of us (S.W.W.) first encountered a multifocal, epithelioid tumor from the arm of a young patient. The tumor strongly expressed cytokeratin and the referring diagnosis was "epithelioid sarcoma." All who reviewed the case, including Dr. Franz Enzinger who first described the epithelioid sarcoma,[5] doubted this diagnosis but had no firm alternative diagnosis at that time. Since then, we have seen additional examples of this tumor, but only in recent years with an expanded armamentarium of commercial antibodies have we been able to classify these tumors as endothelial.

As illustrated by our series, these lesions usually occur in young adults and most involve the distal extremities. Some may present with multifocal disease or develop

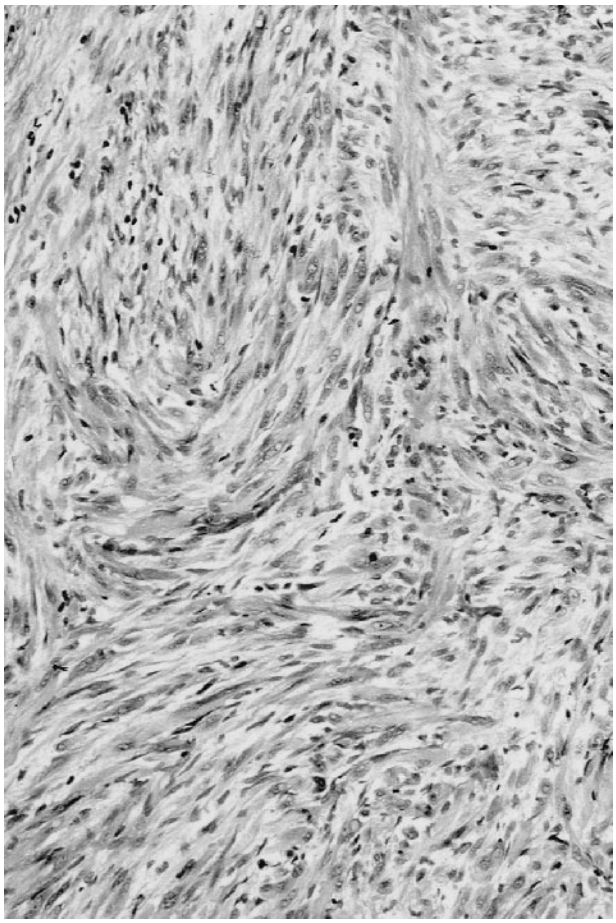

**FIG. 8.** Spindled area in ES-H in which cells are more attenuated compared with Figure 7 and are arranged in short intersecting fascicles.

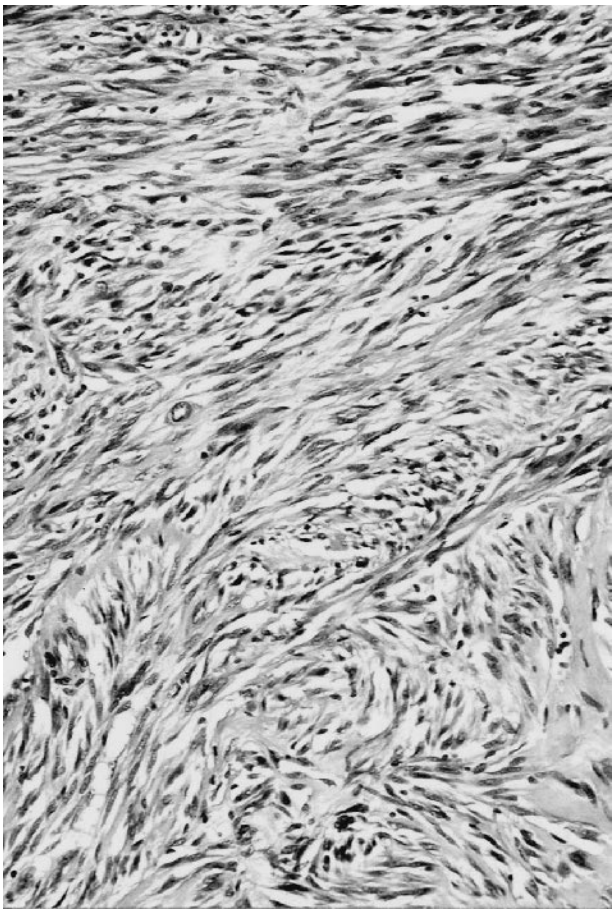

**FIG. 9.** Spindled area in ES-H in which the cells are markedly attenuated and resemble those in a well-differentiated (low-grade) fibrosarcoma. Such areas were distinctly unusual compared with areas depicted in Figures 7 and 8.

proximal lesions in the course of the disease. Thus, in many ways the clinical presentation resembles epithelioid sarcoma.[2,5,9,10] In our experience both submitting and expert pathologists rendered the diagnosis of epithelioid sarcoma or probable epithelioid sarcoma in the majority of our cases. We also suspect that most examples of this tumor have been misdiagnosed as, and included in series of, epithelioid sarcoma. This is entirely understandable because obvious features of endothelial differentiation as judged at the architectural level are virtually nonexistent. Specifically, they do not form multicellular vascular channels as are seen in both benign and malignant vascular tumors, and they do not display prominent intralesional hemorrhage as is seen in most angiosarcomas.[6,12] Cytologic evidence of endothelial differentiation, although present in some cases, is elusive. For example, intracytoplasmic vacuoles, which may signify cytologic evidence of endothelial differentiation (and are especially prominent in some vascular tumors such as epithelioid hemangioendotheliomas),[15,18] were present in about half of these tumors but were typically difficult to find. In this context the finding of strong, intense cytokeratin expression usually led to a consideration of other possibilities, such as an authentic epithelial tumor or an epithelioid sarcoma.[2,3,9,10]

Thus, the most compelling evidence of vascular differentiation is provided by immunohistochemistry. All but one case expressed CD31 in a strong, linear, membranous pattern, which is highly specific for endothelial cells.[4,14] Although a single case of epithelioid sarcoma has been reported to be CD31 positive, this case showed only cytoplasmic staining, which is considered nonspecific.[13] Membranous CD31 expression may be seen in very rare carcinomas and in macrophages/histiocytic tumors, where it has a distinctive granular pattern.[11] We are not aware of any reported cases of CD31-positive adnexal carcinomas. Furthermore, Fli-1, a DNA-binding transcription factor expressed by developing and adult endothelial cells, was expressed within the nucleus of the six cases studied. Fli-1 is expressed by >90% of vascular tumors of

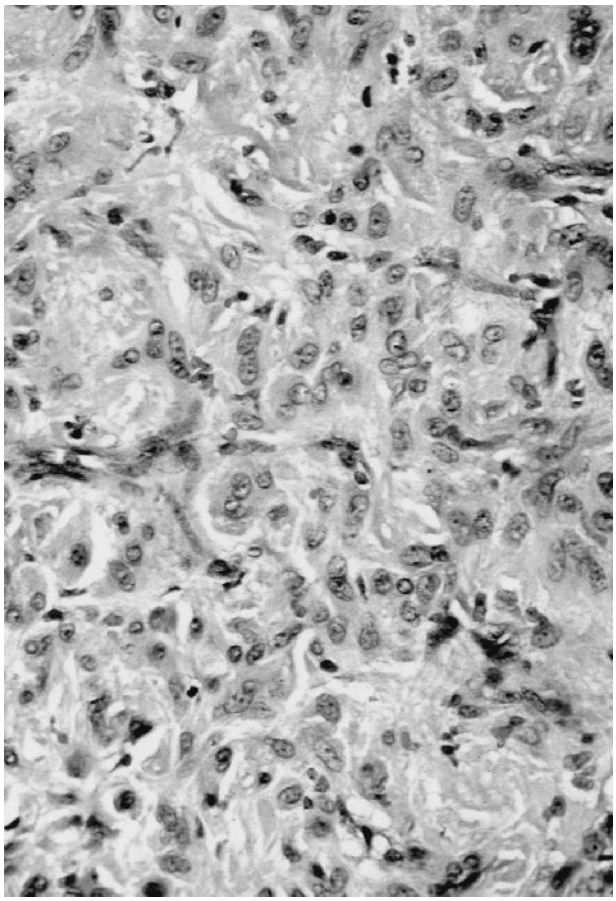

**FIG. 10.** High power view of epithelioid area in ES-H. Note the overall lack of atypia.

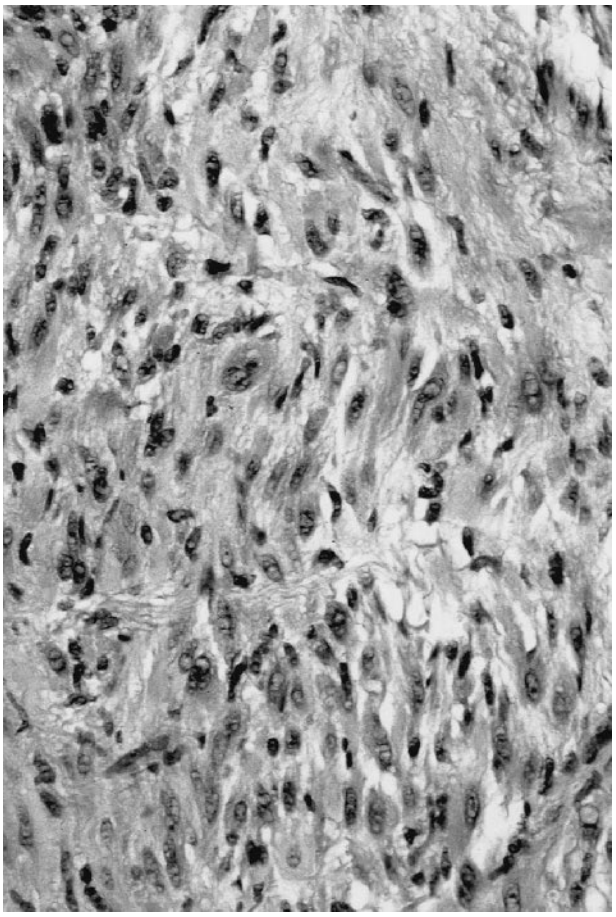

**FIG. 11.** High power view of spindled areas in ES-H. Note the overall lack of atypia and mitotic activity.

all types, but not by epithelioid sarcomas or carcinomas.[7] Interestingly, none of these cases expressed CD34, the human progenitor cell antigen, which is expressed by >90% of vascular tumors[14,17] and also 50–60% of epithelioid sarcomas.[1,13,16] Whether this absence represents a bias introduced by small sample size or signifies a distinct CD34-negative endothelial phenotype typical of this tumor is unclear. It should be emphasized, however, that many different malignant vascular tumors may on occasion be CD34 negative and that demonstration of CD34 expression is not obligatory for the diagnosis of a vascular tumor. We did not study these cases for expression of von Willebrand factor (factor VIII-related antigen) because its low sensitivity and the frequent presence of significant "background" resulting from staining of circulating antigen greatly limit the utility of this marker.

Given the myriad of vascular tumors described in recent years, one might question whether this lesion represents a variant of epithelioid hemangioendothelioma or epithelioid angiosarcoma. However, we think that there are significant and sufficient reasons for considering these lesions distinct (Table 2). Epithelioid hemangioendothelioma is typically an angiocentric lesion consisting of epithelioid endothelial cells that display frequent intracytoplasmic vacuoles/lumina occasionally containing erythrocytes.[16,18] These vacuolated endothelial cells coupled with their arrangement in short cords or strands recapitulating the primitive angiogenic cords of the yolk sac have become pathognomonic features of this lesion. The matrix is also quite distinctive and consists of a dense chondroid or hyaline material containing sulfated

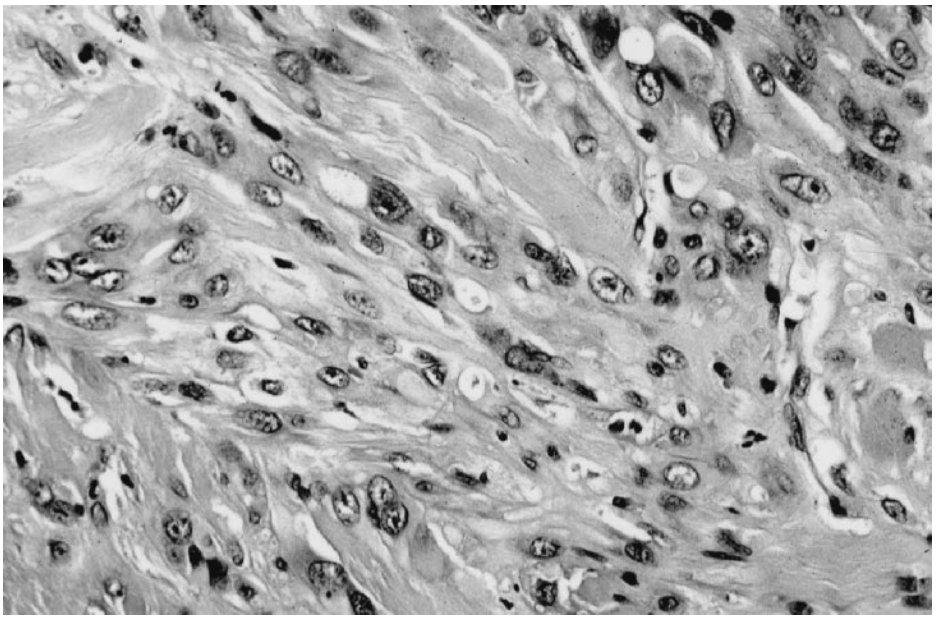

**FIG. 12.** Intracytoplasmic vacuole (a feature often associated with endothelial differentiation) within ES-H.

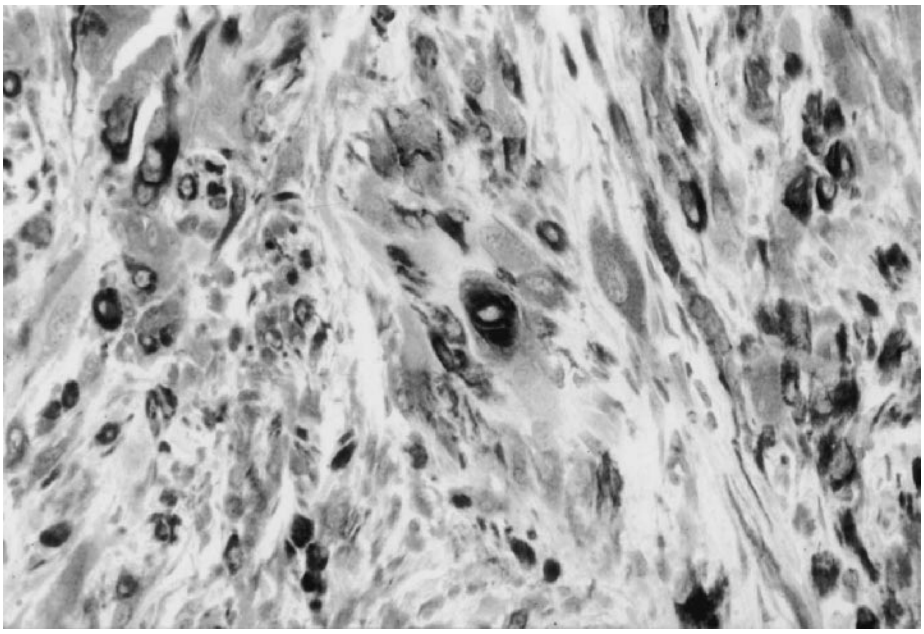

**FIG. 13.** Cytokeratin expression in ES-H.

acid mucin. All of these rather distinctive features are lacking in the ES-H. Although epithelioid hemangioendothelioma may acquire a spindled appearance similar to the ES-H, this usually occurs in more malignant forms in which there is a shift to an extremely high nuclear grade and mitotic activity. A subset of epithelioid hemangioendotheliomas expresses keratin, but expression is usually focal and rarely intense and diffuse as is seen in ES-H.[8]

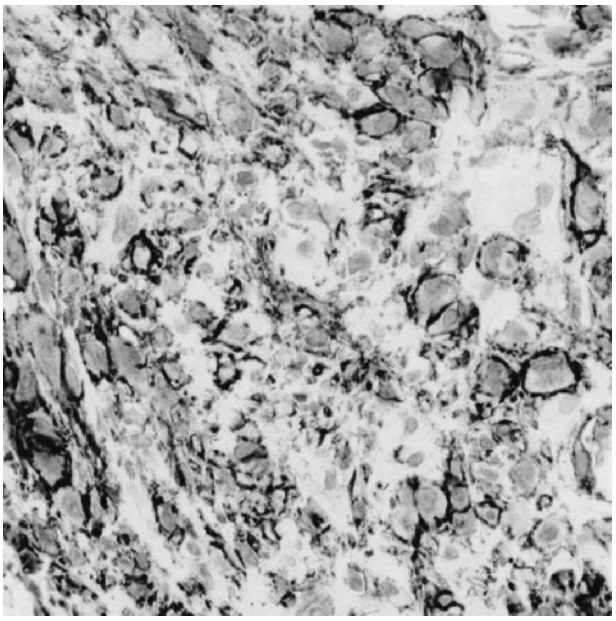

**FIG. 14.** Membranous, "linear" CD31 immunostaining in ES-H.

Epithelioid angiosarcomas tend to segregate in deep soft tissue and present as large masses composed of sheets of epithelioid endothelial cells of uniformly high nuclear grade that form distinct multicellular vascular channels within a hemorrhagic backdrop.[6,12] Some express cytokeratin, but like the epithelioid hemangioendothelioma it is usually focal. In contrast to epithelioid angiosarcoma, ES-H lacks vascular channel formation and hemorrhage and consists of endothelial cells of lower nuclear grade. The vast majority of angiosarcomas behave as high-grade sarcomas with death from tumor in over one half,[12] quite at variance with our lesions.

As implied in our choice of names, the lesion with which this tumor shares the greatest histologic and clinical overlap is the epithelioid sarcoma.[2,3,5,9,10] Clearly, the age, manner of presentation, epithelioid appearance, the curious modulation between epithelioid and spindled areas, and the strong cytokeratin expression bring this possibility to mind. We think there are some features at the light microscopic level, which allow tentative separation of the two. Epithelioid sarcoma tends to grow in distinct, cohesive nodules having central areas of hyalinization and necrosis, whereas ES-H grows in sheets and fascicles. If nodules are present, they are usually ill defined and lack cohesion. Although epithelioid sarcomas overall display more atypia than ES-H, there is considerable overlap. Epithelioid sarcomas at their initial presentation may appear surprisingly bland, and some ES-H may have significant atypia focally. Thus, it is clear that immunohistochemistry plays an important and critical role in the distinction of the two lesions. CD31 and Fli-1

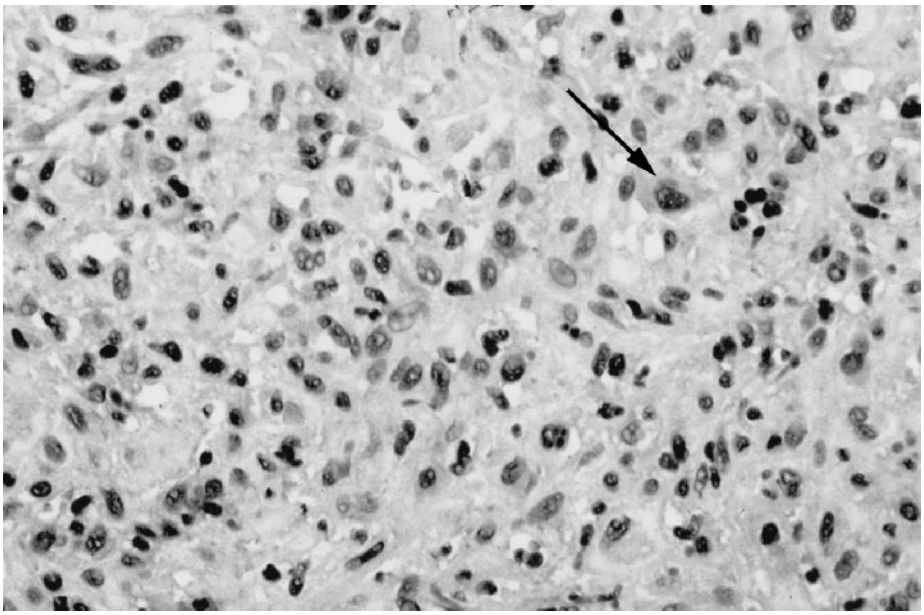

**FIG. 15.** Fli-1 expression in ES-H. A positively staining tumor cell nucleus is indicated by arrow.

are expressed by ES-H and are negative in epithelioid sarcoma, whereas many cases of epithelioid sarcoma, but not ES-H, express CD34.[7,13,16] Based on our follow-up information, which extends to 5 years in some of our cases, the behavior of ES-H and epithelioid sarcoma seems to be different. The former to date has not produced distant metastasis, although long-term follow-up is clearly needed to accurately compare the two lesions. Yet, epithelioid sarcomas generally exhibit evidence of more aggressive behavior in comparable time periods. In the series reported by Chase and Enzinger, the group of patients who had no evidence of local recurrence had an overall metastatic rate of 36% and mortality rate of 28% during a mean follow-up period of 58 months.[2] Similarly, in a series reported by Halling et al., most metastatic tumors developed within 3 years.[9] Because of the potential difference in behavior between the two lesions, we occasionally perform CD31 and/or Fli-1 immunostains on cases of epithelioid sarcoma in which the features or presentation are unusual.

In summary, we have presented an epithelioid vascular tumor that bears a striking histologic and clinical resemblance to epithelioid sarcoma but can be clearly distinguished from it immunohistochemically. Based on our follow-up, which suggests the propensity for local recurrence and regional soft tissue metastasis in the absence to date of distant metastasis, we think it should be considered a member of the family of hemangioendotheliomas or vascular tumor of intermediate malignancy, although there seem to be sufficient histologic features to distinguish it from the epithelioid hemangioendothelioma. □

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