Cutaneous Epithelioid Sarcomalike (Pseudomyogenic) Hemangioendothelioma

A Little-Known Low-Grade Cutaneous Vascular Neoplasm

Luis Requena, MD; Carlos Santonja, MD; Jose Luis Martinez-Amo, MD; Carlos Saus, MD; Heinz Kutzner, MD

Importance: Epithelioid sarcomalike (pseudomyogenic) hemangioendothelioma (ES-H) is a recently described and little-known vascular neoplasm that frequently presents with dermatologic lesions. Histopathologic characterization includes sheets or fascicles of plump, spindled and epithelioid, rhabdomyoblast-like neoplastic cells involving the dermis and often extending to subcutaneous tissue. Immunohistochemical analysis reveals neoplastic cells that show a constant immunophenotype characterized by immunoreactivity for cytokeratins and endothelial markers.

Observations: We described the clinical, histopathologic, and immunohistochemical features of 2 cases of cutaneous ES-H. Clinical examination revealed multifocal lesions that consisted of erythematous nodules on the leg and foot in case 1 and small perioral papules in case 2. Neoplastic cells had a rhabdomyoblastic appearance, with large nuclei and ample eosinophilic cytoplasm. Immunohistochemical analysis revealed expression of cytokeratin AE1/AE3, CD31, ERG, and FLI-1, with focal and weak positivity for CAM 5.2 and smooth muscle actin. The nuclei of neoplastic cells showed intact expression of INI-1. This immunoprofile, especially the ERG positivity, demonstrated the endothelial nature of proliferating cells.

Conclusions: We recommend adding the low-grade neoplasm ES-H to the large list of cutaneous vascular proliferations. Dermatologists should be aware of this low-grade cutaneous vascular tumor.


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IN 2003, BILLINGS ET AL.1 DESCRIBED 7 CASES OF A DISTINCTIVE, LOW-GRADE VASCULAR NEOPLASM WITH A CLOSE HISTOPATHOLOGIC RESEMBLANCE TO AN EPITHELIOID SARCOMA BECAUSE OF ITS GROWTH IN SOLID SHEETS AND NESTS, THE CYTOLAPMIC EOSINOPHILIA OF THE ROUNDED TO SLIGHTLY SPINDLED NEOPLASTIC CELLS, AND THE DIFFUSE, STRONG CYTOKERATIN EXPRESSION. FOR THESE REASONS, THEY NAMED THE NEOPLASM EPITHELIOID SARCOMALIKE HEMANGIOENDOTHELIOMA (ES-H).2 ALL THOSE CASES CONSISTED OF DEEPLY SITUATED SOFT-TISSUE TUMORS, AND IN NO CASE DID THE NEOPLASM APPEAR TO ARISE FROM OVERLYING SKIN. MORE RECENTLY, A NEW HISTOPATHOLOGIC VARIANT OF HEMANGIOENDOTHELIOMA HAS BEEN REPORTED UNDER THE NAME PSEUDOMYOGENIC HEMANGIOENDOTHELIOMA.2 AFTER CONSIDERABLE CONTROVERSY IN THE LITERATURE ABOUT WHICH AUTHOR FIRST DESCRIBED THIS NEOPLASM,3 THE GENERAL CONSENSUS IS THAT ES-H AND PSEUDOMYOGENIC HEMANGIOENDOTHELIOMA ARE THE SAME ENTITY. PROBABLE EXAMPLES OF THE SAME NEOPLASM WERE INCLUDED IN PUBLISHED SERIES OF EPITHELIOID SARCOMA4 OR DESCRIBED UNDER DIFFERENT NAMES, INCLUDING FIBROMALIKE VARIANT OF EPITHELIOID SARCOMA5 OR SPINDLE-CELL VARIANT OF EPITHELIOID SARCOMA.6

This neoplasm seems to be more common in male than in female patients, has a predilection for developing during the second through fifth decades of life, and shows an indolent biological behavior. Clinically, the neoplasm most commonly presents as multiple nodules involving the lower extremities and, in most cases, multiple lesions grouped in an anatomical region. The neoplasm has no distinctive clinical feature, and the most frequent clinical diagnoses include cutaneous cyst, nodular fasciitis, or benign subcutaneous tumor.7,8 The clinical, histopathologic, and immunohistochemical characteristics of 2 entirely cutaneous examples of this neoplasm are the basis of this report. Because ES-H may present as a cu-
taneous lesion, it should be added to the list of cutaneous vascular neoplasms, and dermatologists should be aware of this low-grade cutaneous vascular tumor.

REPORT OF CASES

CASE 1

A 20-year-old woman with a history of endometriosis presented in October of 2008 with an asymptomatic erythematous nodule on the left calf that had been present for 1 year. After this original lesion, the patient progressively developed painful erythematous nodules on the left calf, left heel, left sole, and pad of the third left toe (Figure 1). A cutaneous biopsy of the first lesion on the left calf was performed and a diagnosis of ES-H was established. Subsequently, all cutaneous nodules were surgically excised, and histopathologic findings demonstrated clusters of neoplastic cells close to the margins of excision in some. Since then, the patient has been followed up with periodic reviews, which included clinical examination, computed tomographic scans of the chest and abdomen, and magnetic resonance imaging of the left lower extremity, with no evidence of recurrence or metastatic disease. In November of 2011, the patient presented again because of pain on the external aspect of the left calf. Magnetic resonance imaging of the left lower extremity demonstrated a nodular lesion of the left outer gastrocnemius muscle 1 cm in diameter that was surgically excised and showed histopathologic features identical to the previously excised nodules. On follow-up in July of 2012, she showed no evidence of recurrence or metastatic disease. The last computed tomographic scan of the chest, however, demonstrated multiple small nodules approximately 3 mm in diameter in both lungs, which are presently being followed up with computed tomographic scans for comparison.

All excised lesions showed identical histopathologic and immunohistochemical features. On low power, the lesions showed normal epidermis and diffuse involvement of the middle and deep reticular dermis, extending to the subcutaneous tissue, mostly throughout the connective tissue septa of the subcutis (Figure 2). The neoplasm had infiltrative margins with a somewhat plexiform configuration. In some areas, the lesion exhibited a focal storiform pattern, and small lymphoid aggregates were scattered within the tumor. The neoplasm was composed of well-defined fascicles of plump spindled cells with vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. In some areas, clusters of larger cells with a more epithelioid or rhabdomyoblastic appearance, round morphology, slightly atypical vesicular nuclei, and ample eosinophilic homogeneous cytoplasm were seen. In one area of the deep connective
tissue septa of the subcutis, neoplastic cells involved the lumen of a thick vein. Mitotic figures were scarce, with only 2 to 3 per 10 high-power fields.

Immunohistochemical analysis revealed neoplastic cells that expressed strong and diffuse reactivity for vimentin and cytokeratin AE1/AE3, FLI-1, CD31, and ERG and focal and weak positivity for CAM 5.2 and smooth muscle actin. Findings for CD34, factor XIIIa, podoplanin, human herpesvirus 8, epithelial membrane antigen, S-100 protein, pancytokeratin MNF-116, desmin, myogenin, MyoD1, CD99, and CD10 were negative. The nuclei of neoplastic cells showed intact expression of INI-1.

CASE 2

A 27-year-old man had a 4-year history of dysphonia, dysphagia, and muscular cramps in the upper and lower extremities. A diagnosis of amyotrophic lateral sclerosis was considered, and a skeletal muscle biopsy showed muscular atrophy secondary to motor neuron disease, although a definitive diagnosis of the neurologic disorder has not been established yet, and the patient is still undergoing evaluation by the Department of Neurology, Fundación Jiménez Díaz. He presented in the Department of Dermatology with a 5-month history of asymptomatic papulonodular lesions involving the perioral skin of the face and the mucous membrane of the upper lip (Figure 3). Some of the lesions progressed to ulcerate the epidermis and appeared to be covered by a necrotic crust, with a molluscum contagiosum–like appearance. Laboratory investigations, including complete blood cell count, biochemistry, proteinogram, urinalysis, and autoantibodies and serology for human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and syphilis yielded normal or negative results. A papule on the upper lip was excised (Figure 4), and, after a diagnosis of ES-H was established, all lesions were surgically excised with clear margins. The patient has been now followed up for 1 year, and in the last review in July of 2012, no evidence of recurrence or metastatic disease was seen.

All excised lesions showed similar histopathologic findings. The epidermis was unremarkable, except in ulcerated lesions. The neoplasm involved the upper half thickness of the dermis with no extension to subcutaneous tissue and was composed of sheets of plump, spindled, rounded, andHistopathologic features of a biopsy from the lesions on the left calf in case 1. A, Scanning power showing a lesion involving the middle and deep dermis and extending to the subcutaneous tissue throughout the connective tissue septa of the subcutis (hematoxylin-eosin, original magnification ×10). B, Fascicles of plump and spindled cells with eosinophilic cytoplasm (hematoxylin-eosin, original magnification ×400). C, Cluster of rhabdomyoblastic cells with large eosinophilic cytoplasm (hematoxylin-eosin, original magnification ×400). D, Intravascular involvement of a vein of the connective tissue septa of the subcutis (hematoxylin-eosin, original magnification ×200).
Epithelioid sarcoma-like hemangioendothelioma usually occurs in young adults; although the distal extremities seem to be the most common location, lesions may also develop on the face, trunk, abdominal wall, and upper extremities.1-3,7,8 Usually, the neoplasm presents with multifocal lesions and, in most cases, multiple papules or nodules grouped in an anatomical region. In most cases, the neoplasm involved the dermis and subcutis, with intramuscular and intraosseous lesions in a few cases; thus, the lesion may require dermatologic consultation. The clinical appearance, however, is nonspecific, and only rarely is a vascular lesion suspected. In case 1, the clinical appearance of the lesions raised a diagnosis of pos-

pleomorphic atypical vesicular nuclei and ample eosinophilic cytoplasm (Figure 4). Very few cells exhibited cytoplasmic vacuolization. In the spindled areas, the cells were arranged in short intersecting fascicles. Scattered among these fascicles were elongated cells with eccentric nuclei and large eosinophilic cytoplasm with a comma-like tail shape, giving them a rhabdomyoblastic appearance. Some of these cells were multinucleated. An inflammatory infiltrate of small lymphocytes intermingled with neoplastic cells. Immunohistochemical analysis of the excised lesions was performed with the same panel of antibodies as in case 1. Neoplastic cells expressed strong immunoreactivity for vimentin, cytokeratin AE1/AE3, CD31, FLI-1, ERG, and INI-1, whereas the rest of the markers yielded negative results (Figure 5).
sible vascular neoplasm; in case 2, the lesions were clinically interpreted as molluscum contagiosum or multiple juvenile xanthogranulomas, demonstrating that ES-H has nonspecific clinical characteristics.

At scanning magnification, ES-H appears to be a poorly circumscribed lesion with architectural features of a malignant neoplasm. The neoplasm shows infiltrative borders involving the adjacent soft tissues and may be entirely dermal or may extend to the subcutaneous fat and underlying skeletal muscle. Dermal lesions may show a variable degree of epidermal hyperplasia similar to dermatofibroma. Most lesions exhibit a fascicular pattern and areas of myxoid stroma; neutrophils scattered over the neoplastic fascicles also have been described. The most characteristic neoplastic cells exhibit a round or an oval shape with vesicular nuclei and prominent nucleoli, but they show striking ample homogeneous eosinophilic cytoplasm. In many areas, these ample cytoplasms result in a rhabdomyoblastic appearance of neoplastic cells. Mitotic figures are sparse. In some cases, intravascular invasion by neoplastic fascicles within entrapped blood vessels may be seen, as in our case 1. This histopathologic finding, however, does not seem to confer a worse prognosis.

Immunohistochemical analysis demonstrates expression of cytokeratin AE1/AE3, CD31, ERG, and FLI-1 by most neoplastic cells, with variable focal and weaker immunoreactivity for CAM 5.2, smooth muscle actin, epithelial membrane antigen, and pancytokeratin MNF-116 and no expression of CD34, desmin, and S-100 protein. In contrast to neoplastic cells of epithelioid sarcoma, the plump spindled and rhabdomyoblastic cells of ES-H keep intact their expression of INI-1. The immunoreactivity for CD31, FLI-1, and in particular ERG suggests an endothelial nature of the neoplastic cells. As an ETS family transcription factor, ERG recently has been found to be expressed in endothelial cells, and oncogenic ERG gene fusions occur in subsets of prostatic carcinoma, acute myeloid leukemia, and Ewing sarcoma. Immunohistochemical studies have demonstrated that nuclear ERG expression is highly specific for detecting ERG protein in normal endothelia (internal control) and in the endothelial cells of hemangiomas, lymphangiomas, angiosarcomas, epithelioid hemangioendotheliomas, and Kaposi sarcomas. Among nonvascular mesenchymal tumors, only blastic extramedullary myeloid tumors and rare Ewing sarcomas were positive for ERG.

Figure 5. Immunophenotype of neoplastic cells with immunoperoxidase technique in case 2 (original magnification ×400). A, Strong expression of cytokeratin AE1/AE3. B, Positivity for CD31. C, Immunoreactivity for FLI-1. D, Strong nuclear expression for ERG in neoplastic cells. E, Nuclei of proliferating cells kept intact the expression of INI-1. F, Neoplastic cells did not express CD34. Positive endothelial cells of preexisting capillaries served as an internal control. G, Neoplastic cells were negative for podoplanin. Positive preexisting lymphatic capillaries served as an internal control. H, Only scattered single cells expressed the pancytokeratin MNF-116. I, Neoplastic cells were negative for cytokeratin CAM 5.2.
Among epithelial tumors, only 50% of prostatic adenocarcinomas showed focal to extensive ERG positivity, with no immunoreactivity in the normal prostate. A large series of other carcinomas and epithelial tumors were negative for ERG. On the basis of these observations, ERG may be considered the most specific new marker for normal endothelial cells and proliferating endothelial cells of benign and malignant vascular tumors. Our study is the first to demonstrate strong immunoreactivity for ERG in the nuclei of neoplastic cells of ES-H, further supporting the endothelial nature of the proliferating cells.

Cytogenetic studies have recently identified the balanced translocation t(7;19)(q22;q13) as the sole anomaly in 3 lesions from the same patient and the unbalanced der(7)t(7;19) translocation in another case. This translocation between chromosomes 7 and 19 seems to be a recurrent phenomenon and is likely to be of pathogenetic significance in at least a subset of ES-H.

The histopathologic differential diagnosis of ES-H includes epithelioid sarcoma, epithelioid hemangioendothelioma, and epithelioid angiosarcoma. Epithelioid sarcoma tends to grow in cohesive nodules of epithelioid cells, which often have central areas of necrosis and display more atypia than those of ES-H. Their immunophenotype is quite different because they express CD34 and epithelial membrane antigen, whereas the endothelial markers CD31, FLI-1, and ERG are not expressed. Furthermore, neoplastic cells of epithelioid sarcoma show loss of INI-1 expression, which is retained intact by neoplastic cells of ES-H, making this marker the most helpful immunohistochemical tool for histopathologic differential diagnosis between these 2 neoplasms. The biological behavior is also quite different because epithelioid sarcoma metastasizes to the lymph nodes and lung in 40% to 50% of the cases, whereas ES-H shows a significant risk for locoregional recurrence but low potential for distant metastasis. Epithelioid hemangioendothelioma is an angiocentric neoplasm composed of cords of epithelioid cells, with prominent cytoplasmic vacuolization, embedded in a myxohyaline stroma. A subset of epithelioid hemangioendotheliomas expresses cytokeratins, but expression is usually focal and rarely strong and diffuse as in ES-H. Immunohistochemical findings of neoplastic cells of epithelioid hemangioendothelioma include expression of CD34, which is characteristically absent in ES-H. Recently, a translocation t(1;3)(p36.3;q25), which fuses the CAMTA1 gene on 1p36.26 to the WWTR1 gene on 3q25.1, has been identified in 17 cases of epithelioid hemangioendothelioma but none of the other vascular neoplasms composed of epithelioid cells. Therefore, this cytogenetic aberration seems to be specific for epithelioid hemangioendothelioma. Epithelioid angiosarcoma is usually a deep soft-tissue neoplasm composed of large masses of epithelioid endothelial cells with prominent atypia, high nuclear grade, and frequent mitotic figures, which form irregular vascular channels within a hemorrhagic background. Some epithelioid angiosarcomas express cytokeratin but, as in epithelioid hemangioendothelioma, this expression is only focal. Epithelioid angiosarcoma is a high-grade sarcoma resulting in death in approximately one-half of patients. The Table summarizes the differential diagnosis of ES-H.

Most patients with ES-H have been treated with simple excision, and few received postsurgical radiotherapy. On follow-up, more than half the patients showed local re-

### Table. Differential Diagnosis of ES-H

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ES-H</th>
<th>Sarcoma</th>
<th>Hemangioendothelioma</th>
<th>Angiosarcoma</th>
</tr>
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<tbody>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
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<tr>
<td>Neoplasm type</td>
<td>Dermal or soft tissue</td>
<td>Dermal or soft tissue</td>
<td>Dermal or soft tissue</td>
<td>Dermal or soft tissue</td>
</tr>
<tr>
<td>Most common age</td>
<td>Young adult</td>
<td>Adolescent and young adult</td>
<td>Any age, but rare in childhood</td>
<td>Elderly persons</td>
</tr>
<tr>
<td>Most common location</td>
<td>Distal extremities</td>
<td>Distal extremities</td>
<td>Any location in soft tissues, but also visceral lesions</td>
<td>Lower extremities</td>
</tr>
<tr>
<td>Most common sex</td>
<td>Male outnumber female patients by about 4:1</td>
<td>Male outnumber female patients by about 2:1</td>
<td>Both sexes affected equally</td>
<td>Both sexes affected equally</td>
</tr>
<tr>
<td>Growth pattern</td>
<td>Poorly demarcated nodules and fascicles</td>
<td>Nodules often with central necrosis</td>
<td>Vasculo-centric cords in myxohyaline stroma</td>
<td>Sheets</td>
</tr>
<tr>
<td>Cytologic atypia</td>
<td>Mild</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Marked</td>
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<tr>
<td>Vasoformation</td>
<td>Not evident</td>
<td>No true lumen formation</td>
<td>Intracytoplasmic vacuoles</td>
<td>Irregular vascular channels, intracytoplasmic vacuoles</td>
</tr>
<tr>
<td>Immunostains</td>
<td>Positive for cytokeratin AE1/AE3, CD31, FLI-1, ERG, and INI-1; negative for EMA and CD34</td>
<td>Positive for cytokeratin AE1/AE3, FLI-1, EMA, and CD34; negative for CD34, ERG, and INI-1</td>
<td>Positive for cytokeratin AE1/AE3 (focal), CD31, FLI-1, ERG, INI-1, and CD34; negative for EMA</td>
<td>None known</td>
</tr>
<tr>
<td>Cyto genetics</td>
<td>t(7;19)(q22;q13)</td>
<td>None known</td>
<td>t(1;3)(p36.3;q25); AMT1/WWTR1 gene fusion</td>
<td></td>
</tr>
<tr>
<td>Treatment and follow-up</td>
<td>Surgery, frequent recurrences, low-grade malignancy (&lt;7% of patients with metastases)</td>
<td>Surgery, high-grade malignancy, overall 5-y survival, 50%-85%</td>
<td>Surgery, frequent recurrences, intermediate-grade malignancy with 31% of patients developing metastases</td>
<td>Surgery, high-grade malignancy, overall 5-y survival, 10%-30%</td>
</tr>
</tbody>
</table>

Abbreviations: EMA, epithelial membrane antigen; ES-H, epithelioid sarcomalike hemangioendothelioma.
currence of the tumor or new nodules appearing in adjacent soft tissues. A review of all previously published cases demonstrated that, from the approximately 70 reported cases,1-8,12 3 patients developed metastases to the regional lymph nodes or distant metastases, and 2 of them died as a consequence of widespread metastatic disease.2,5 Therefore, ES-H seems to behave with an indolent clinical course, with frequent recurrences but with small risk of distant metastases.

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