Immunohistochemical study of epithelioid hemangioendothelioma in the leg: a case report.

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Abstract

Epithelioid hemangioendothelioma is a relatively rare lesion. Although its histogenesis has been well described, its immunohistochemical characteristics remain controversial. A case of epithelioid hemangioendothelioma of the soft tissue of the right leg in a 67-year-old Chinese woman is reported. Histologic findings of intracytoplasmic lumina in the tumor cells and positive immunostaining for vimentin, factor VIII-related antigen. CD34 and Ulex europaeus agglutinin 1 (UEA-1) were obtained, demonstrating differentiation of the tumor cells to endothelial cells, although staining for antibodies to cytokeratins AE1/AE3 and CAM5.2 was weak. CD34 as well as Factor VIII-related antigen is a useful marker of endothelial differentiation in this tumor. A review of the literature is also presented.

KEYWORDS: epithelioid hemangioendothelioma, leg, thrombophlebitis, immunohistochemistry

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Brief Note

Immunohistochemical Study of Epithelioid Hemangioendothelioma in the Leg: A Case Report

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Epithelioid hemangioendothelioma is a relatively rare lesion. Although its histogenesis has been well described, its immunohistochemical characteristics remain controversial. A case of epithelioid hemangioendothelioma of the soft tissue of the right leg in a 67-year-old Chinese woman is reported. Histologic findings of intracytoplasmic lumina in the tumor cells and positive immunostaining for vimentin, factor VIII-related antigen, CD34 and Ulex europaeus agglutinin 1 (UEA-1) were obtained, demonstrating differentiation of the tumor cells to endothelial cells, although staining for antibodies to cytokeratins AE1/AE3 and CAM5.2 was weak. CD34 as well as Factor VIII-related antigen is a useful marker of endothelial differentiation in this tumor. A review of the literature is also presented.

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Epithelioid hemangioendothelioma is a unique vascular neoplasm of the soft tissues characterized by epithelioid tumor cells and borderline malignancy, as described by Weiss and Enzinger (1). Differential diagnosis from other lesions is often necessary, although the immunohistochemical characteristics of this lesion have not yet been clearly established. It has also been reported that this lesion can occur not only in soft tissues but in many other sites including the liver (2, 3), lung (4-7), bone (8), anterior mediastinum (9, 10), lymph nodes (11), brain (12), and heart (13). Unfortunately, it is difficult to predict accurately the behavior of this tumor on the basis of its histologic features (1).

We report a case of epithelioid hemangioendothelioma of the soft tissue of the right leg and thrombophlebitis of the left leg, and present the results of immunohistochemical study and a review of the literature.

A 67-year-old Chinese woman was hospitalized in October of 1994 for edema of the left leg for a week with the clinical diagnosis of thrombophlebitis. She also complained of a mass in the soft tissue of the right leg that developed 2 years ago and had become painful 1 year ago. At operation, the mass was found in the lumen of a vein with no adhesion to the surrounding tissue. After ligating the vein at both ends, the mass was extirpated with a part of the vein. On follow-up examination 14 months later, no evidence of recurrence or metastasis was found.

The specimen was fixed in 10% formalin solution and embedded in paraffin using routine procedures. Deparaffinized sections were stained with hematoxylin and eosin, and by silver impregnation. In addition, the deparaffinized sections were studied with the labelled streptavidin biotin (LSAB) peroxidase complex kit (DAKO) using monoclonal antibodies against vimentin (DAKO/1:400), factor VIII-related antigen (DAKO/1:400), CD34 (Becton-Dickinson/1:10), AE1/AE3 (Boehringer-Mannheim/1:400), CAM5.2 (Becton Dickinson/1:20) and 35βH11 (ENZO/1:5000), and also Ulex europaeus agglutinin-1 (UEA-1) lectin (Vector Laboratories/1:200). To enhance reactivity, the sections stained for cytokeratins (AE1/AE3, CAM5.2 and 35βH11) were preincubated with 0.1% Pronase E (Sigma, St. Louis, MO, USA) in phosphate-buffered saline for 20 min, and the sections stained for vimentin were pretreated with microwave irradiation (H2500

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The tumor located in the vascular lumen and extending into the intermuscular space of the vascular wall. [Hematoxylin and eosin; magnification × 100].

The tumor is composed of solid nests of cells and shows prominent cytoplasmic vacuolization representing intracytoplasmic lumina. [Hematoxylin and eosin; magnification × 320].

Immunohistochemical reactivity for CD34 is present in cytoplasm of most tumor cells, especially around the cytoplasmic lumina. [labelled streptavidin biotin (LSAB); magnification × 320].

Microwave Processor, Energy Beam Sciences, USA).

The resected mass was a 1.5 × 1 × 1 cm lesion, and its external surface was partially covered by yellow adipose tissue. The cut surfaces exhibited a white and homogeneous appearance.

At low magnification, there was a mass filling the
vascular lumen and extending centrifugally to the intermuscular space of the vascular wall (Fig. 1). The mass was mainly composed of small nests or short cords of rounded to short, spindled tumor cells that contained large vesicular nuclei with prominent nucleoli (Fig. 2). In some areas, the tumor was composed entirely of solid nests of tumor cells. Although the formation of vascular channels was rarely seen, vascular differentiation was less developed and intracytoplasmic lumina due to cytoplasmic vacuolization were apparent at the cellular level (Fig. 2). Almost all the tumor cells exhibited intensely positive immunoreactivity to the antibody against vimentin. Most tumor cells were also positive to the antibodies against factor VIII-related antigen and CD34 (Fig. 3), which also stained the surfaces of intracytoplasmic lumina. In some locations on the vascular wall, most tumor cells stained strongly positive for the antibody against UEA-1. A few tumor cells exhibited scattered weakly positive staining to the antibodies to AE1/AE3 (Fig. 4) and CAM5.2. No 35βH11-positive cells were found.

On the basis of the histologic and immunohistochemical findings, a final diagnosis of epithelioid hemangioendothelioma was made.

Epithelioid hemangioendothelioma is a relatively rare lesion. It was first reported in 1982 by Weiss and Enzinger to describe a distinctive morphologic variant of vascular endothelial neoplasms of soft tissue exhibiting histology and clinical features intermediate between benign hemangioma and angiosarcoma (1). Reports since then have verified that the tumor can occur not only in soft tissue but also in other sites, including the liver (2, 3), lung (4-7), bone (8), anterior mediastinum (9, 10), lymph nodes (11), brain (12) and heart (13). Although some investigators have suggested that oral contraceptives (14) and vinyl chloride may be involved in the pathogenesis of these lesions, there is no evidence confirming these hypotheses.

The most characteristic histological appearance of epithelioid hemangioendothelioma is prominent cytoplasmic vacuolization, which represents primitive intracytoplasmic lumen formation by a single cell (1). In lesions arising from vessels, as in our case, there is another characteristic appearance that they expand the vessel, usually preserving its architecture as they extend centrifugally from the lumen to the surrounding tissue (15). In diagnostically ambiguous cases, both immunohistochemistry and electron microscopy may provide the most reliable clues of differentiation. The antibody against factor VIII-related antigen has been considered as the optimal marker for neoplasms of vascular origin, but recently it has been suggested that CD34 is even more sensitive (16). However, the results of another study indicate that, although CD34 shows a high sensitivity for the staining of normal vascular endothelium, its specificity may be restricted to mature, well-formed vessels, thus limiting its discriminatory value for the identification of poorly
differentiated vascular endothelial neoplasms (17). In fact, all the 12 reported cases of epithelioid hemangioendothelioma were negative to the antibody against CD34 (9). On the other hand, there are other reports describing the positive reaction with CD34 in the same disease manifesting some obvious malignant features (18, 19). Further studies are needed to resolve whether or not these differences may reflect different pathogenic mechanisms or different experimental conditions, such as the dilution of the antibody staining procedure and the fixation method used. UEA-1 is also useful for making a differential diagnosis (17, 18), but the findings in our case suggest that it may be less sensitive than factor VIII-related antigen and CD34.

Negative staining for cytokeratin is considered one of the characteristics of this tumor (9), but our patient exhibited weakly positive staining for AE1/AE3 and CAM5.2. It has been suggested that a phylogenic degree of expression of keratin by endothelial cells may exist whereby the ability of endothelium to synthesize keratin observed in lower vertebrates is lost in higher vertebrates. Furthermore, dual expression may to some extent reflect this degree in human carcinogenesis (20). On electron microscopy, the tumor cells have characteristic endothelial features, including a well-developed basal lamina, pinocytotic vesicles, occasional Weibel-Palade bodies and a super-abundance of intermediate filaments crowded in the cytoplasm (1).

Like most soft tissue lesions, the tumor in our patient developed as a solitary, slightly painful mass. However, some lesions in other sites may exhibit an indolent course (21). Despite the very favorable overall prognosis of this tumor, some patients have developed local recurrence and even metastasis (1, 22), and a small percentage of benign-appearing epithelioid hemangioendotheliomas do metastasize and cause death (19), and rarely can involve several organs (23). For these reasons, careful examination and diligent follow-up examinations are necessary.

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References


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