

Hemangioendothelioma with a Prominent Lymphoid Infiltrate Mimicking Follicular Dendritic Cell Tumor: Report of a Case

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Abstract: Hemangioendothelioma is a vascular tumor with several different morphologic patterns that can include a component of ovoid or spindled cells, but generally lacks an inflammatory component. The combined morphologic and immunohistochemical features are generally sufficient to accurately diagnose this tumor and its many variants. We present a challenging lymphocyte-rich soft tissue lesion that was not recognized to be an unusual hemangioendothelioma until after several recurrences in the arm of a 63 year-old male, which was originally diagnosed as a follicular dendritic cell tumor instead. Local recurrence developed 3 and 11 years later with resections. The most recent tumor consisted predominantly of epithelioid spindled cells with moderate amounts of bubbly pale to eosinophilic cytoplasm with rare discrete cytoplasmic vacuoles, admixed with a prominent lymphoid infiltrate and occasional erythrocytes. The tumor cells were positive for keratin and vascular markers (CD31, CD34, and Factor VIII), but negative for follicular dendritic cell markers (CD21, CD23, CD35). Slides from the two previous excisions were re-analyzed, and showed the same morphologic and immunohistochemical features as the latest recurrence. The diagnosis was revised to recurrent lymphocyte-rich hemangioendothelioma. The patient is free of tumor at 7 years follow-up. This represents an unusual and potentially confusing pattern of hemangioendothelioma that is not previously well described in the literature. Vascular tumors should be included in the differential diagnosis of suspected dendritic cell tumors, even if a lymphocyte-rich infiltrate is present. Vascular as well as dendritic cell markers should be included in the immunohistochemical panel employed in their evaluation.

Keyword: Hemangioendothelioma, lymphocyte rich, follicular dendritic cell, tumor.

INTRODUCTION

Follicular dendritic cell (FDC) tumors are rare and under-recognized tumors of antigen processing cells that can present substantial difficulties in diagnosis. They can arise in lymph nodes as well as extranodal sites [1-3], and morphologically manifest as tumors of spindled to oval cells with a variable appearance and an often prominent intermixed lymphoid infiltrate. Hemangioendothelioma is a vascular tumor of intermediate biologic potential with several different morphologic patterns that can include a component of ovoid or spindled cells, but generally lacks an inflammatory component. The combination of morphologic and immunohistochemical features are generally sufficiently distinctive to avoid confusion of these conditions. Herein we present a case of a challenging lymphocyte-rich soft tissue lesion originally diagnosed as follicular dendritic cell tumor that was eventually recognized to be an unusual form of hemangioendothelioma with prominent lymphoid stroma following several recurrences. This represents an unusual and potentially confusing pattern of

hemangioendothelioma that is not well described in the literature.

REPORT OF CASE

The patient is a currently 63-year-old male who had a soft tissue lesion excised from his right upper arm in infancy that had locally recurred in childhood but remained stable over the ensuing years. The original pathologic material was unavailable for review, but the patient thought the lesion might have been a lymphangioma. At about 48 years of age, the patient found a continuously growing mass in the same right upper arm area following local trauma, and a 4.0 x 2.5 cm soft tissue mass was surgically excised. Microscopic study demonstrated a proliferation of oval to short spindled cells with a very prominent lymphoid stromal component (Figure 1). On immunohistochemical staining, the spindled cells were negative for actin, desmin, S-100 protein, CD68, CD3, CD21, and CD20 (L26), with equivocal staining for CD35 and patchy strong staining for cytokeratin (about 10% of cells). The lesion was deemed to be diagnostically challenging, and outside consultation was obtained with three expert pathologists. Two rendered a diagnosis of follicular dendritic cell tumor or sarcoma, and the third classified the lesion as probable dendritic cell tumor, type unspecified. The patient was

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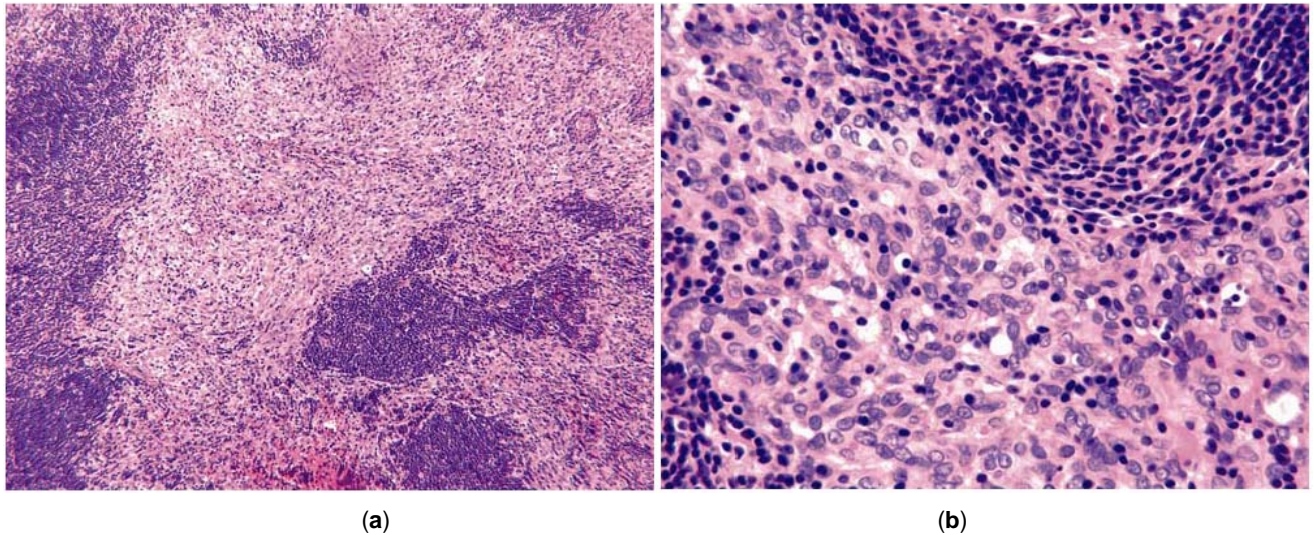


Figure 1: (a) Original tumor 8 years prior, showing a spindle cell proliferation with dense lymphoid infiltrate; (b) The spindled cells show indistinct eosinophilic cytoplasm, and bland oval nuclei with inconspicuous nucleoli, with intimate admixture of lymphocytes (Hematoxylin-eosin staining, original magnification (a) x100, (b) x400).

then treated by surgical resection and post-operative local radiation. After the initial diagnosis of the “dendritic cell tumor”, the patient underwent a local recurrence three years later, and the recurred tumor was again excised surgically but without additional local radiation. The patient continued to do well, but five years following the second local recurrence, he suffered a third local recurrence of the tumor (about 1.5 cm in size). An intra-operative frozen section diagnosis of spindled cell tumor with rich reactive lymphoid infiltrate was rendered. The tumor was again surgically excised with a wide resection margin of skin and subcutaneous tissue.

Histologically, the tumor from this last resection was again composed predominantly of spindled cells with a prominent intermixed reactive appearing lymphoid infiltrate, including an approximately equal mixture of CD3+ T-cells and CD20+ B-cell follicles (Figure 2). In some areas, erythrocytes were prominent between the stromal cells, and focally a more epithelioid appearance of the tumor cells was noted, with moderate amounts of pale to bubbly eosinophilic cytoplasm, and rare discrete cytoplasmic vacuoles. As before, nuclei lacked atypical features.

Immunoperoxidase staining of paraffin embedded sections was performed utilizing a standard multimeric

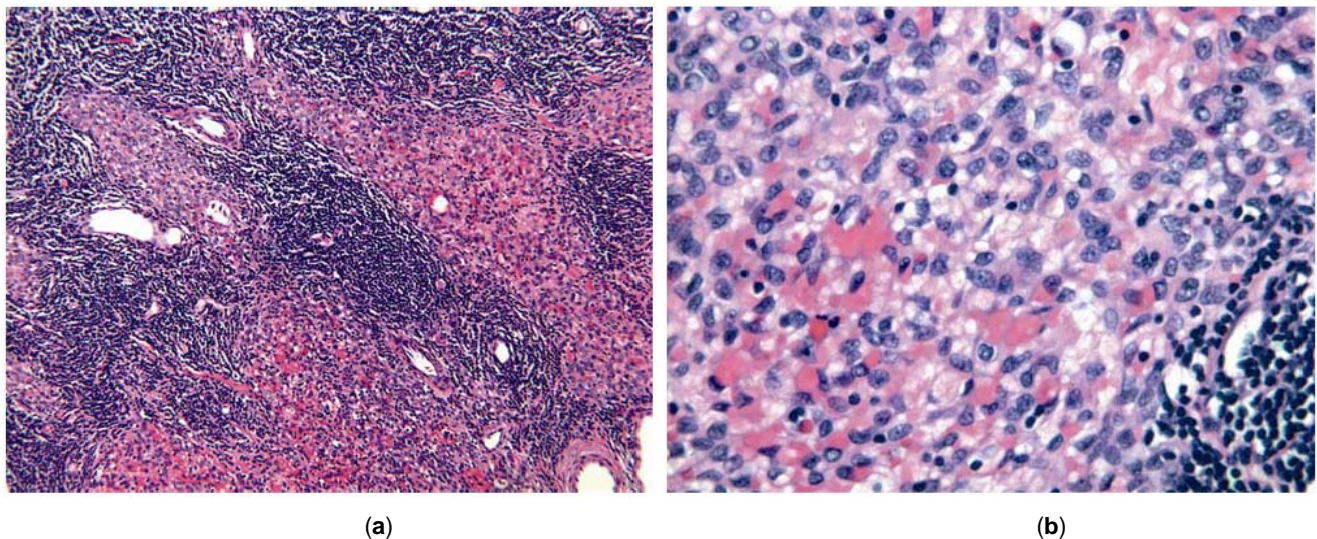


Figure 2: Most recent recurrent tumor, at low power showing a dense lymphoid infiltrate (a), and at higher magnification showing a mixture of spindled cells and epithelioid cells (b) with interspersed red blood cells and occasional distinct cytoplasmic vacuoles. (Hematoxylin-eosin staining, original magnification (a) x100, (b) x400).

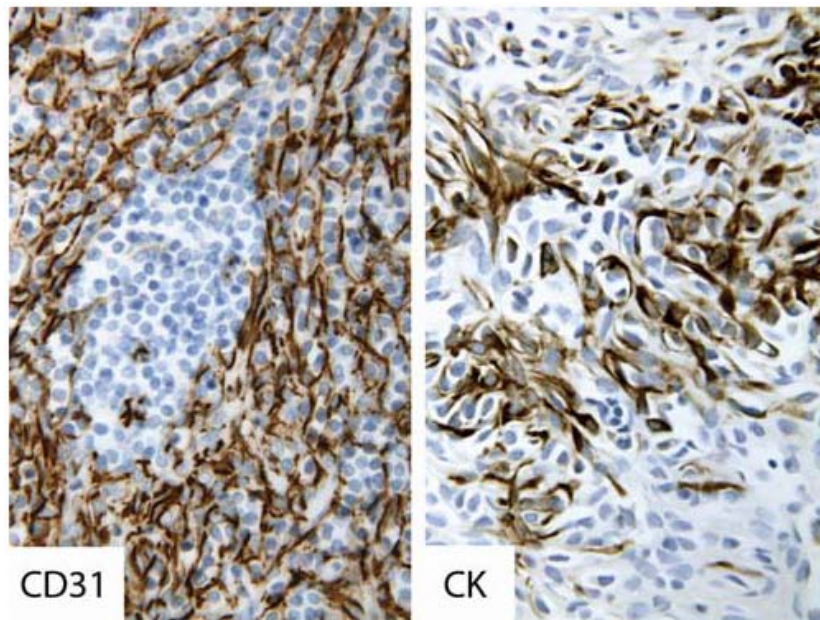


Figure 3: Immunohistochemistry: the tumor cells of the recurrent tumor showed diffuse CD31 positivity (left) and focal cytokeratin positivity (right). No staining was evident for CD21 or CD35 (not shown). (Immunoperoxidase staining, original magnification x400).

detection assay (Ultraview) on a Ventana Benchmark XT automated stainer. The spindled cells showed focal but strong staining for cytokeratin (Ventana cytokeratin cocktail) in about 10-15% of cells, strong and diffuse positivity for CD31 (Figure 3), focal moderate staining for CD34 in about 25-50% of cells, and focal weak staining for Factor VIII-related antigen in about 25% of cells. No staining of the tumor cells was observed with antibodies to CD1a, CD21, CD23, CD35, CD68, S-100 protein, HMB45, EMA, desmin, muscle-specific actin (MSA), or smooth muscle actin (SMA). Slides from the two previous excisions were obtained and re-analyzed, and these showed the same morphologic and immunohistochemical features as the latest recurrence. The diagnosis was revised to recurrent lymphocyte-rich hemangioendothelioma with a mixed spindled and epithelioid growth pattern. The patient was free of recurrence at last follow-up, about 7 years after the third local recurrence.

DISCUSSION

Follicular dendritic cell (FDC) tumors are rare neoplasms that typically occur in middle-aged adults and follow a protracted clinical course, with a recurrence rate of about 40%, metastasis in about 25% of patients, and an overall mortality of 17% [3]. Lymph nodes are the most common primary site, but skin and soft tissue sites are not uncommon. Considered to be of intermediate grade malignancy, when metastasis develops it most often involves the lung, lymph nodes,

and liver [4]. Most tumors have well-circumscribed or pushing borders and are composed of spindled, plump or ovoid cells forming fascicles, whorls, nodules, or sheets [1-3, 5-6]. The nuclei are typically bland and the spindled cells are often accompanied by a diffuse infiltrate of small lymphocytes, to the extent that they can be confused with thymoma. Occasionally, lymphocytic cuffs may be seen around blood vessels—a feature which is of diagnostic utility [7]. Immunohistochemical staining typically demonstrates positivity for CD21, CD35, and CD23, and rarely for cytokeratin. FDC tumors must be distinguished from interdigitating dendritic cell tumors, which are positive for S-100 protein, but negative for CD1a, cytokeratin and FDC tumor markers, and have a more aggressive clinical course, with about half of affected patients dying of their disease [6].

Other lesions that may be composed of spindled cells with an associated lymphocytic infiltrate, and thereby enter into the differential diagnosis of FDC tumors, include thymoma, dermatofibrosarcoma protuberans, fibrous histiocytoma, smooth muscle tumors, spindle cell melanoma, Langerhans histiocytosis, and epithelioid sarcoma. Immunohistochemistry and clinical presentation are often helpful in distinguishing these lesions.

Hemangioendothelioma (HE) is the designation currently used for vascular tumors that have a biologic behavior intermediate between that of (benign)

hemangioma and conventional (malignant) angiosarcoma. A number of different patterns of HE are recognized. Epithelioid hemangioendothelioma, first described by Enzinger and Weiss in 1982 [7], is a neoplasm of cytoplasm-rich (or epithelioid) endothelial cells in which the clusters of epithelioid cells often stream off of associated medium to large size blood vessels, particularly veins [7-9]. The tumor cells may be arranged in cords, small nests, or short trabeculae, and the stroma often has a myxoid or chondroid-like appearance. Well-formed vascular spaces are generally infrequent, but cytoplasmic vacuoles presumed to represent abortive vascular lumina may be present, sometimes containing erythrocytes, as a subtle clue to the vascular nature of the tumor [7-9]. The tumor can arise in any organ, including the liver, lung, bone [10], and soft tissues of extremities [11]. It may be multicentric, and like FDC tumors it typically arises in middle-aged adults. Metastasis occurs in up to 30% of soft tissue cases, but most commonly is only to local lymph nodes, and the overall mortality rate remains low [9-11].

Kaposiform hemangioendothelioma is another pattern of HE, characterized by nodules of spindled cells having erythrocytes interspersed in a manner reminiscent of Kaposi sarcoma, but also having capillary hemangioma-like areas. This tumor typically occurs in children rather than adults, and unlike other hemangiomas in young children, typically does not regress with age. It may be related to tufted hemangioma. Treatment is surgical, but often problematic because of the large size and infiltrative nature of these lesions [12].

Hobnail hemangioendothelioma can be of either the Dabska or retiform type, and may have a sparse associated lymphoid infiltrate. Other rare patterns of HE include epithelioid sarcoma-like hemangioendothelioma and composite hemangioendothelioma. The latter, very rare neoplasm is described as a mixture of benign, intermediate and malignant vascular elements within the same tumor [13]. Regardless of pattern, HE is generally positive for endothelial markers such as CD31 and Factor VIII-related antigen, and less commonly for CD34.

Our case presents several features of interest. First, the long clinical history, with report of what was likely some kind of benign vascular or lymphatic lesion in the same location as a child, suggests that the tumor in this patient may have arisen out of a pre-existing benign vascular proliferation or neoplasm. In addition, such a

long clinical history with multiple local recurrences of spindled cell tumor might be another valuable clue to include hemangioendothelioma in the differential diagnosis and the addition of vascular markers (CD31, Factor-VIII, and/or CD34) in the pathologic work-up would be helpful to confirm or exclude a diagnosis of hemangioendothelioma. The observation that about two-thirds of kaposiform hemangioendotheliomas appear to occur in a background of an abnormal lymphatic vessel proliferation [14] is intriguing in this regard, although no residual lymphangioma was identifiable in any of the available resection material.

Second, the exuberant lymphoid stroma is unusual for hemangioendothelioma, and has a distinctive geographic or organoid appearance, suggesting it may represent some type of homing response rather than simply inflammation, perhaps mediated by chemokines or chemokine receptors. Amongst vascular neoplasms, epithelioid hemangioma is the principal tumor associated with a prominent lymphocytic response, but even in that case the inflammation tends to be diffuse rather than as bands of dense lymphoid infiltrate surrounding geographic fields of tumor cells. Epithelioid hemangioma is also distinguished from HE by its typical component of small blood vessels formed by epithelioid cells. Eosinophils are often prominent, and subcutaneous variants of this tumor are typically associated with a muscular artery [15]. A lymphocyte-rich stroma is distinctly unusual in hemangioendothelioma, and was a misleading feature in our case that is not well documented in the literature [4].

Finally, while clearly a tumor showing vascular differentiation, the features of our patient's tumor are relatively unique, and may represent a previously undescribed pattern of hemangioendothelioma. The combination of spindled cells (in some areas partly resembling kaposiform hemangioendothelioma), epithelioid cells and dense geographic bands of lymphoid stroma, in some areas having an organoid or lymph-node like appearance, presents a fairly distinctive appearance that was present in the primary tumor and all of its recurrences. That it has behaved in a locally aggressive fashion, but not metastasized over a fairly long time frame, we believe justifies its designation as a lymphocyte-rich hemangioendothelioma.

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