

A protruding nodule on the upper lip

A 52-year-old woman presented with a 12-mm sized protruding nodule on the upper lip that had enlarged over the last 1 year and complained of occasional pain. Physical examination indicated a slightly erythematous nodule with disruption of the vermilion border of the upper lip [Figure 1]. Examination of her medical history yielded nonspecific findings, including a negative human immunodeficiency virus serostatus. A skin biopsy was performed on her upper lip.

The histopathologic examination showed that the lesion was a poorly circumscribed nodule involving the superficial and deep dermis. The nodule comprised the round or cuboidal cells with intracytoplasmic vacuolization [Figure 2a and 2b]. However, human herpesvirus

8 immunohistochemical staining yielded negative results, and hence, a second excisional biopsy was attempted to confirm the diagnosis. Spindle cells with nests and cords of epithelioid cells were noted [Figure 3a]. Immunohistochemical staining with CD31 and CD34 showed positive results, whereas immunophenotyping for human herpesvirus 8 still yielded negative results [Figure 3b-d]. Additional immunohistochemical staining for vimentin yielded positive results, and that for S-100 and CD68 yielded negative results.

Question

What is your diagnosis?



Figure 1: Solitary ill-defined erythematous to purplish nodule on the upper lip

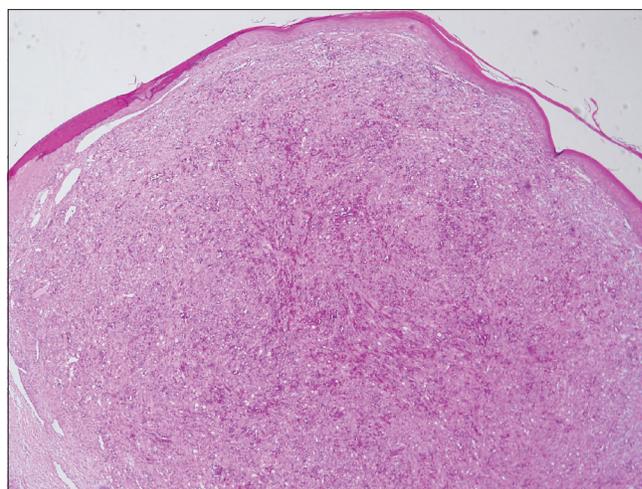


Figure 2a: Poorly circumscribed nodule involving the superficial and deep dermis (H and E, ×40)

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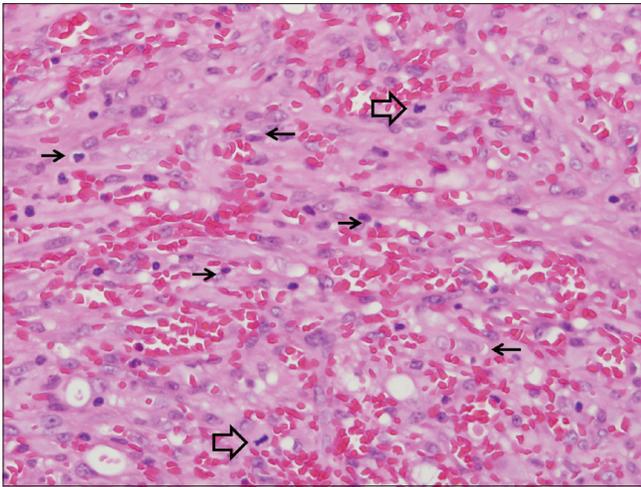


Figure 2b: The nodule is comprised of round and cuboidal cells, with intracytoplasmic vacuolization (small arrows) and many mitotic figures (big arrows) (H and E, $\times 400$)

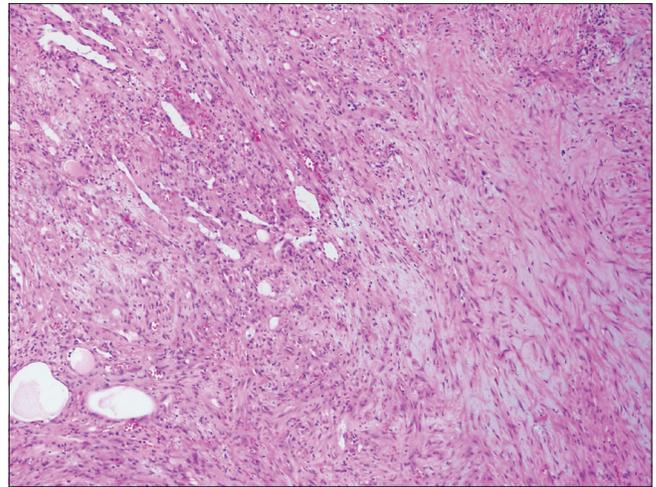


Figure 3a: Spindle cell proliferation and pleomorphic features (H and E, $\times 100$)

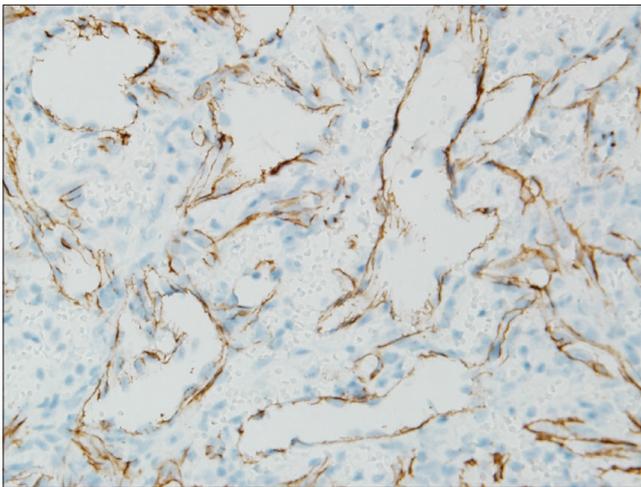


Figure 3b: Positive immunohistochemical staining with CD31 ($\times 400$)

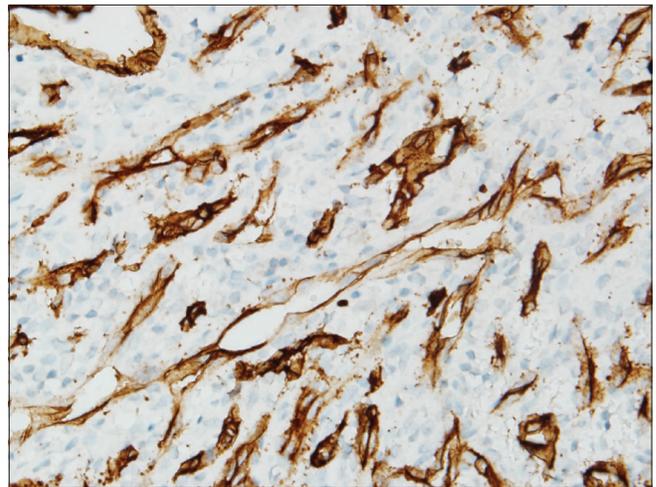


Figure 3c: Positive immunohistochemical staining with CD34 ($\times 400$)

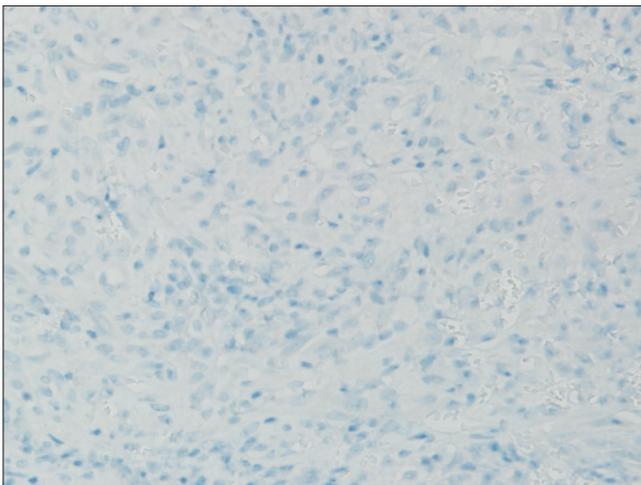


Figure 3d: Negative immunohistochemical staining with human herpesvirus 8 ($\times 400$)

Answer

Epithelioid hemangioendothelioma.

Discussion

Epithelioid hemangioendothelioma is considered as a biologically borderline neoplasm, between a hemangioma and a conventional angiosarcoma. Weiss and Enzinger first reported this unusual vascular tumor in 1982.¹ Subsequently, several reports have described biologically and pathologically similar tumors at many anatomic locations, including the lung, liver and bone. However, in rare cases, epithelioid hemangioendothelioma can also occur at the skin and soft tissue, without bone involvement. In a case series of epithelioid hemangioendothelioma of the skin, 7 (50%) cases exhibited tumors at the extremities, whereas two cases exhibited tumors at the head and neck area.² Cases of cutaneous epithelioid hemangioendothelioma on the lip are rare, and we found only a few reported cases.^{3,4}

In a previous case series of thirty patients with epithelioid hemangioendothelioma of the skin and soft tissues, cutaneous

epithelioid hemangioendothelioma usually presented as a solitary nodule and occasionally as a painful mass.⁵ This tumor is primarily observed in middle-aged adults, and no specific sexual predominance is noted. However, the affected age groups may vary, and even children can develop the tumor.⁶

Histopathologically, epithelioid hemangioendothelioma is composed of cords, strands and solid aggregates of round, oval and polygonal cells with abundant pale eosinophilic cytoplasm, vesicular nuclei and inconspicuous nucleoli, embedded in a fibromyxoid or sclerotic stroma.⁷ Nuclear pleomorphism is minimal. These cells line well-defined vascular channels in some areas, and form solid aggregates with prominent cytoplasmic vacuolization in other areas.³

In the present case, we found that the vascular tumor may have various components. An examination of the first biopsy specimen showed round or cuboidal cells, whereas that of the second biopsy specimen showed nests of spindle cells. Following repeated biopsy of the tumor, immunohistochemical staining helped

Table 1: Clinical and histopathological characteristics of differential diagnosis of epithelioid hemangioendothelioma

Disease	Clinical characteristics	Histopathological characteristics
Kaposi's sarcoma	Classic Kaposi's sarcoma: more common in men, mainly affecting patients of Eastern European, Jewish and Mediterranean origin Slow development of angiomatous nodules and plaques on the lower extremities	Slit-like vascular spaces lined by spindled endothelial cells Solid areas of spindle cells with slit-like vascular spaces in older lesions CD31 (+), CD34 (+), HHV-8 (+)
Epithelioid angiosarcoma	A rare form of angiosarcoma that usually arises in deep soft tissues of the limbs	Diffuse, sheet-like growth pattern of epithelioid tumor cells showing frequent coexpression of vascular and epithelial markers Occasional presence of intracytoplasmic vacuoles More solid areas than vascular spaces Higher cellularity, higher mitotic activity, more prominent nucleoli and areas of necrosis Solid sheets of pleomorphic neoplastic cells with high atypia and mitotic activity
Kaposiform hemangioendothelioma	A rare vascular tumor in the retroperitoneum or deep soft tissue of infants	Congested capillary spaces, similar to glomeruloid capillary proliferation Surrounded by the fascicles of spindle cells Slit-like lumen which is reminiscent of Kaposi's sarcoma
Retiform hemangioendothelioma	A slowly growing tumor noted in young adults, primarily on the lower leg Multiple recurrence, but indolent clinical behavior.	Elongated, arborizing blood vessel with hobnail endothelium Prominent lymphocytic infiltration
Composite hemangioendothelioma	Mainly observed in adults, at the extremities with a predilection for the hands and feet	Retiform hemangioendothelioma + epithelioid endothelioma + spindle cell hemangioma
Cutaneous epithelioid angiomatous nodule	Small, solitary erythematous to violaceous papules or nodules on the trunk and extremities	Benign lesion comprising epithelioid endothelial cells with frequent cytoplasmic vacuolization Producing well-formed vessels with easily discernible lumens Solid, unilobular pattern without involvement of the subcutaneous tissue
Spindle cell hemangioma	Benign lesion in older patients with a predilection for the limbs Red-blue nodules in the distal aspects of the extremities	Cavernous vascular spaces with papillary structures, and thrombi Solid area with spindle cell proliferation Focal aggregates of epithelioid cells
Epithelioid hemangioma	Solitary, slowly growing nodule at the head and neck area with accompanying blood eosinophilia (15%)	Angiolymphoid hyperplasia with eosinophilia Well-formed vascular structures lined by plump endothelial cells Prominent inflammatory process
Pyogenic granuloma	Common proliferative lesion growing rapidly for a few weeks before stabilizing as an elevated bright red papule	Polypoid mass of angiomatous tissue, constricted at its base by acanthotic epidermis

confirm the diagnosis of epithelioid hemangioendothelioma. The tumor stained positively for vascular endothelial markers, such as CD31 or CD34. Tumors exhibited positive results when staining for vimentin, and exhibited negative results when staining for epithelial membrane antigen, S-100, cytokeratins and CD68.⁸ Some authors reported positive results when staining for cytokeratins which was noted in one-fourth of the epithelioid hemangioendothelioma cases.⁹

Differential diagnosis of epithelioid hemangioendothelioma includes Kaposi's sarcoma, spindle cell hemangioma, epithelioid hemangioma and other vascular tumors such as pyogenic granuloma. The clinical and histological characteristics of each disease are listed in Table 1. Based on the currently available data, it appears that the prognosis of primary cutaneous epithelioid hemangioendothelioma is good.² The risk of local recurrence or metastasis depends on the histologic features of the tumors, including nuclear atypia, increased mitotic activity, tumor cell spindling and necrosis.¹⁰ Negative prognostic factors such as increased mitoses and nuclear atypia were associated with poor prognosis.⁵ We contend that a precise review the histopathology of a case should be undertaken to diagnose and properly treat the tumor.

In conclusion, our present case highlights the risk of misdiagnosis of epithelioid hemangioendothelioma as hemangioma or Kaposi's sarcoma, due to the various tumor components on histology examination. When a vascular tumor is suspected, a complete excision, appropriate staining and careful review is essential, particularly for large tumors.

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Conflicts of interest

There are no conflicts of interest.

**Hyun Ji Kang, Sung Eun Chang, Mi Woo Lee,
Woo Jin Lee**

Department of Dermatology, University of Ulsan College of Medicine,
Asan Medical Center, Seoul, Republic of Korea

Correspondence: Dr. Woo Jin Lee,
Department of Dermatology, University of Ulsan College of Medicine,
Asan Medical Center, 88 Olympic-ro 43 gil, Songpa-gu, Seoul 05505,
Republic of Korea.
E-mail: uucm79@hanmail.net

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