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CASE REPORT

Kaposiform hemangioendothelioma involving the neck

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Summary Kaposiform hemangioendothelioma is a rare locally aggressive vascular neoplasm of infancy and childhood. An 18-month-old Chinese infant with a rapidly enlarging mass in the neck was presented here. Physical examination revealed a dark-red, firm mass measuring 7.0×4.5 cm in the anterior neck. No associated with KMS was observed despite its size. Morphologically, the tumor consisted of dense spindle cells with a nodular growth pattern, with hypocellular areas of hyalinized fibrous stroma. Immunohistochemically, both spindle and epithelioid were immunoreactive to CD34, CD31 and UEA-1, while negative to GLUT1, EMA, cytokeratin or S-100 protein. The well-formed capillaries and mature vessels but not spindle tumor cell showed reactivity for FVIII-Rag. α-SMA were detected in pericysts surrounding spindle cells. Large vessels in the tumor were positive for VEGFR3. Recurrence occurred 6 month after first operation. Wide resection was performed a second time, the patient was still alive during the 7-year follow-up period.

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Introduction

Kaposiform hemangioendothelioma (KHE), a rare vascular neoplasm of infancy and childhood, was first described in 1993 by Zukerberg.[1,2] The name was coined for its distinctive morphology, characterized by a Kaposi sarcoma-like spindle cell growth pattern.[1,2] Clinically, the tumor shows the predilection for involving the retroperitoneum, mediastinum, and deeper soft tissues of the trunk and extremities.[1–4] KHE is commonly associated with the Kasabach–Merritt syndrome (KMS), related to its unique vascular architecture associated with turbulent blood flow and platelet trapping.[1,4,6] Of 60 cases reported in the English literature[2–14] and three cases in Chinese publication,[15] lesions involving the neck were rarely described.[6,8–14] We report here a case of KHE involving the anterior neck, not associated with KMS despite its size, with special reference to immunohistochemical study.

Case report

An 18-month-old Chinese infant presented with a rapidly enlarging mass in his anterior neck at the midline, which was first noticed 3 month previously. The patient was referred to the Department of Oral and Maxillofacial Surgery, School and Hospital of Stomatology of the Wuhan University, on October 25th, 1998. At that time, the anterior neck mass was dark-red, firm, and measured 7.0×4.5 cm. The submandibular region in both sides was diffuse expanded, and the mandible margin was blurred. There were no signs of tracheal compression, such as choking or stridor elicited, and no lymphadenopathy in the head and neck region. The mass did not appear to invade the hypoglottic area and floor of mouth in the intra-oral examination. The neck radiograph demonstrated the soft tissue tumor in the anterior region, and an intact hyoid bone (Fig. 1). General evaluation including a chest X-ray and abdominal sonography showed no evidence of distant metastasis. Laboratory findings, including complete blood count, blood biochemistry, fibrinogen and fibrin-split products and urine analysis were all within normal limits. The patient was seronegative for HIV and HHV8. At surgery, a horn-shape, firm, hemangioma-like tumor was identified, which measured $4.0 \times 2.5 \times 2.0$ cm and focally infiltrated the strap muscles. While the hyoid bone was easily separated from the tumor, the invaded thyroid gland was partially resected with sharp dissection. The pathology

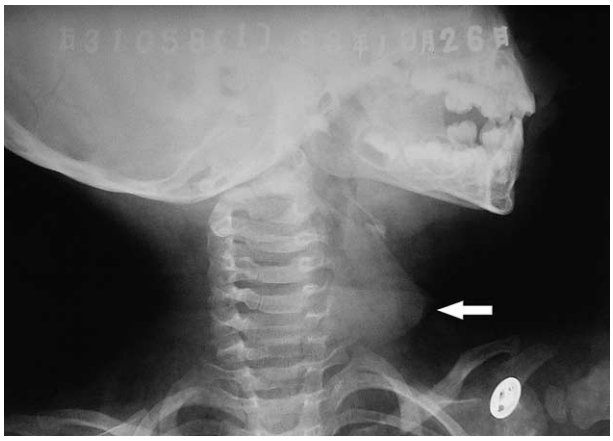

Figure 1 A lateral neck radiograph showing the soft tissue mass in anterior neck region.

reported the diagnosis of KHE. Six months postoperatively, however, a 5 cm recurrent lesion was detected at the surgical site, associated with pain and similar clinical appearance as the primary tumor. Corticosteroid therapy was ineffective in controlling the tumor growth and pain. This time, the recurrence was widely excised, and confirmed on pathology. Seven years after the initial examination, the boy was alive and well.

Morphologically, the tumor consisted of dense spindle cells with a nodular growth pattern, with hypocellular areas of hyalinized fibrous stroma (Fig. 2(A) and (B)). The spindled tumor cells showed no cytological atypia, and focally exhibit slit-like and gaped lumen, but most often did not show a luminal formation. The spindle tumor cells may appear epithelioid with glomeruloid capillary proliferation and formation of microthrombi (Fig. 2(C)). In areas, lymphocytes but not plasma cells were seen. There was no encapsulation, and the tumor infiltrated the peripheral skeleton muscles as well as the thyroid gland. Large feeding vessels were present at the periphery of the tumor. The solid spindle cells areas associated with slit-like lumen containing red blood cells were reminiscent of Kaposi's sarcoma (Fig. 2(D)). The gaped lumen, nodular growth pattern, and broad hyalinized fibrous septa permitted differentiation with Kaposi's sarcoma.

The tumor cells, whether epithelioid or spindled were immunoreactive to CD31 (1:200, DAKO, Fig. 3(A)) and CD34 (Q Bend-10, 1:500, DAKO, Fig. 3(B)), but not to factor VIII-related antigen (FVIIIRAg, 1:200, DAKO, Fig. 3(C)), in contrast to well-formed capillaries and mature vessels. Lectin Ulex Europaeus Agglutinin I (UEA-1,1:100, DAKO) was expressed on the endothelial cells lining

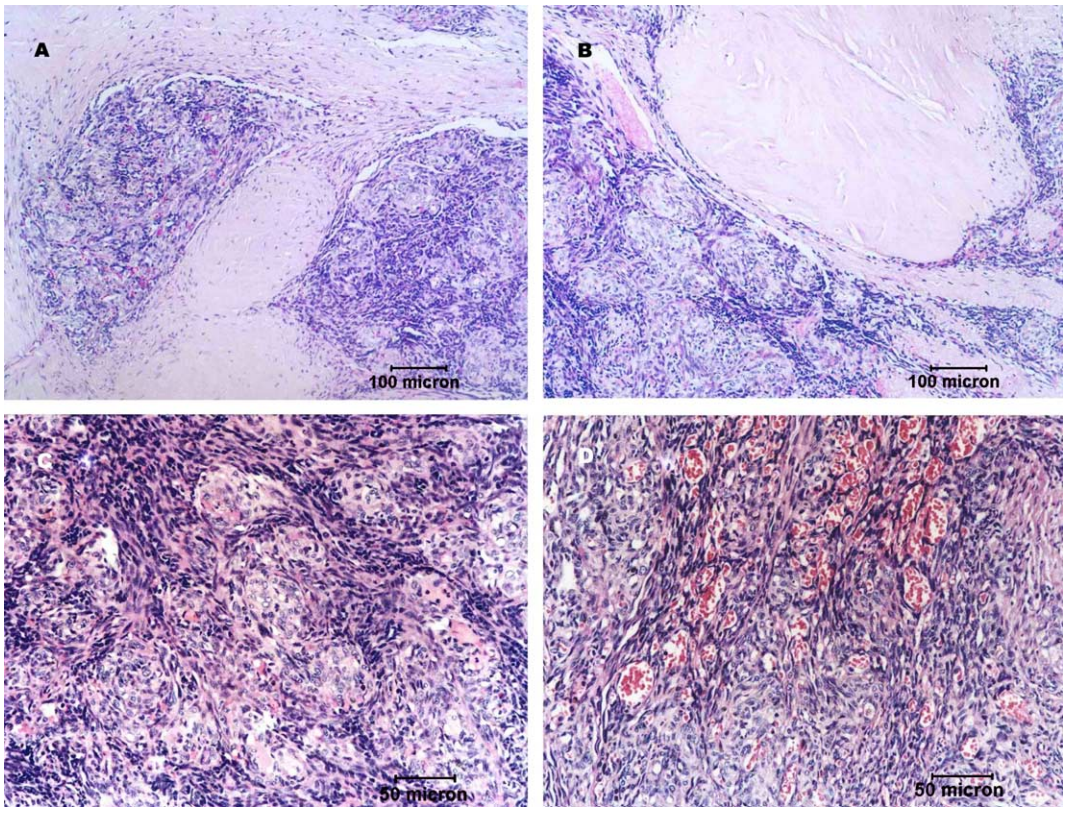

Figure 2 (A) Low power view of KHE showing irregular nodules growing pattern separated by fibrous septa. (B) Dense hyaline sclerosis surrounding infiltrating tumor nodules. (C) Irregularly dilated capillaries or slit-like lumen containing erythrocytes and lined by flat endothelia interrupted the spindle area, reminiscent of Kaposi's sarcoma. (D) Lobules composed of glomeruloid nests of epithelioid cells and densely packed plump spindle cells.

slit-like spaces and capillaries. Spindle cells surrounding endothelial lining and epithelioid cells were immunoreactive to alpha-smooth muscle actin (α-SMA, 1A4, 1:400, DAKO, Fig. 3(D)). Peripheral thick walls bleeding vessels were also positive for α-SMA. Large vessels in the tumor were positive for VEGFR3 (Flt-4, 1:400, DAKO, Fig. 3(E)). The spindle and epithelioid cells were not immunoreactive to human erythrocyte-type glucose transporter (GLUT1, MYM, 1:500, DAKO, Fig. 3(F)), neither to epithelial membrane antigen (EMA 1:200, DAKO), cytokeratins (AE1/AE3, 1:50, DAKO) or S-100 protein (1:100, DAKO).

Discussion

KHE, also known as Kaposi-like infantile hemangioendothelioma, Kaposi sarcoma-like hemangioma, but not related to HIV infection, is defined as a locally aggressive vascular tumor, of intermediate malignant potential in the latest WHO classification of soft tissue tumor.[1,2] KHE typically occurs in infancy and childhood, but lesions in adult have also been reported.[9] KHE involving the neck is very rare, presenting as single or multiple ecchymotic masses, which may involve deeper soft tissue and bone, to include structures such as thyroid, trachea, parapharynx, mandible, cheek, parotid gland, temporomandibular joint and external auditory canal.[5–14] The infiltrative tumor may cause upper airway obstruction by obstruction and compression. Eighteen of the 21 neck lesions, like most reported cases from other sites, were associated with KMS, but for patients without this syndrome and cutaneous manifestations, it would be difficult to consider the diagnosis of KHE prior to surgery.[5,6] While the possibility of KHE may be considered on clinical and radiological grounds, tissue diagnosis is required.

Despite its unusual site, the tumor in our patient showed rather typical morphology of KHE, with a deeply infiltrative nodular growth, dense fibrous septa, spindle cells with slit-like vascular lumen and unmistakable resemblance to Kaposi's sarcoma.[1–3,7] The differential diagnosis of KHE may include monophasic synovial sarcoma,[16] juvenile hemangioma,[6] Kaposi sarcoma,[1,2] tufted

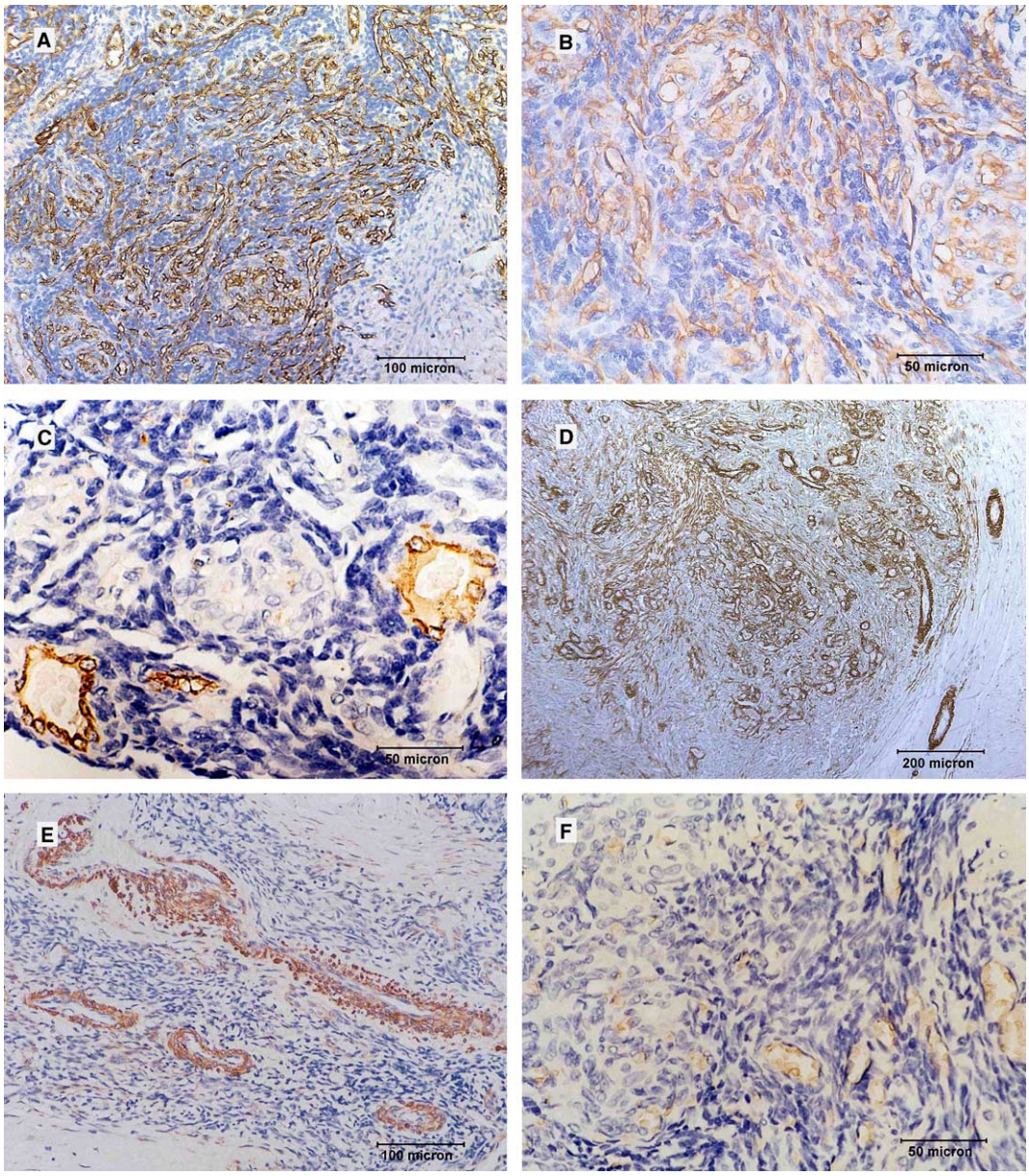

Figure 3 (A) The spindle cell show diffuse reactivity for CD31. (B) The spindle cells and epithelioid cells show strong reactivity with CD34. (C) The well-formed capillaries and mature vessels but not spindle tumor cell showed reactivity for FVIII-RAg. (D) α-SMA highlights variable member of spindle cells by immunoreactive to pericytes. (E) Large vessels in KHE are immunoreactive for VEGFR3. (F) GLUT1 is negative detected in spindle cell and epithelioid cells, but positive in erythrocytes.

angioma,[4,6] spindle cell hemangioma (hemangioendothelioma),[17] and epithelioid hemangioendothelioma.[18] The monophasic synovial sarcoma was excluded, because our patient's tumor lacked the fibrosarcoma-like fascicular growth, and the immunoreactive EMA or cytokeratins of a synovial sarcoma.[16] Juvenile hemangioma shows a more distinct lobular growth, a diffusely well-formed gaped vascular lumen, but absence of spindle cell without canalization.[8] Kaposi's sarcoma and KHE share in common uncanalized spindle cells or tumor cells forming slit-like spaces, but Kaposi's sarcoma shows no gaped vascular lumen, and presence of inflammatory and plasma cells. Moreover, Kaposi's sarcoma is often associated with HIV infection, characterized by multifocal, superficial cutaneous or mucosal lesions, and is rarely seen in children, apart from the lymphadenopathic form seen in African children.[1,2,6] The superficial lesions of acquired tufted angioma, or angioblastoma of Nakagawa

may be undistinguishable from KHE, and hence regarded by many as a limited form of KHE, with its distinctive ''cannonball'' pattern of the vascular lobules, but differs from KHE by the absence of the deep and irregular infiltrative tumor sheets.[4,6,19] Spindle cell hemangioma shows focal areas of solid spindle cells with slit-like vascular lumen, but is distinctive for the presence of cavernous vascular space, organized thrombosis and calcified phleboliths.[17] Epithelioid hemangioendothelioma is distinctive for its small solid nests and short strands of endothelial cells, set in a pale myxoid or hyaline stroma. The epithelioid endothelial cells may demonstrate intracytoplasmic lumen, while Kaposi sarcoma-like and ''glomeruloid'' area are scare.[18]

In our patient, both epithelioid and spindle tumor cells expressed endothelial markers CD31, and CD34, but not FVIII-RAg and UEA-1, results consistent with the reported observations.[1,6] Mature capillaries and vessels in this patient were positive for FVIII-RAg and UEA-1. α-SMA was expressed by pericytes that outlines tumor spindle cells, but not by these spindle cells. GLUT1 has recently been recognized as a specific marker for infantile hemangioma, and useful in assessing the differential diagnosis, since it is not expressed in KHE.[6] Our results confirmed VEGFR3 as a marker of lymphatics and large vessels in KHE, but we did not examined D2-40, found to be a more specific marker for lymphatic vessels, and not detected in KHE.[20,21]

The precise biologic potential and pathogenesis of KHE remains uncertain. It was classified as borderline malignant because of its locally aggressive behavior, causing significant morbidity and mortality as a result of the compression and invasion of surrounding structures. Prognosis in this tumor was mainly related to the size, anatomic site, and extent of the neoplasm.[2–4,6] So far only two cases develop local metastasis and no distant metastasis has been reported.[6] Three of 21 cases with neck involvement died, with death related to disease complications rather than to the tumor recurrence.[5–14] Clearly in the head and neck region, upper airways obstruction and non resectable tumor constitute the biggest threat of KHE.[5–14] In the present case, limited excision was not effective, resulted in recurrence which required wide excision for cure.

The most effective therapy of KHE is complete excision, but for not respectable and extensive lesion with KMS, there is no established protocol for systemic treatment.[4–6] Treatment with corticosteroids, alpha-interferon, embolization, ticlopidine plus aspirin, chemotherapy, and radiation therapy have all been reported, with varying success.[8–15] Systemic steroids are usually the first line of treatment in patients with KMS, but the results were of questionable benefit. The use of interferon alfa-2a has shown great promise. Multimodal intervention may be required to manage fastidious hemangioendothelioma of childhood, achieve clinical improvement, and prevent further morbidity.[1,4,5]

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