



# Kaposiform Hemangioendothelioma Presenting as a Paraspinal Mass. Case Report and Review of the Literature

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## Abstract

Kaposiform hemangioendothelioma (KHE) is a rare, locally invasive vascular tumor with intermediate malignancy situated somewhere between the spectrum of hemangioma and angiosarcoma. It is known to be locally aggressive, infiltrating the surrounding tissue, but with no firm evidence of metastatic potential. KHE can be diagnostically challenging due to the known histomorphologic overlap among different endothelial lesions with varying malignant potential. Although the infiltrating pattern of KHE is well documented, it rarely infiltrates the adjacent bone. Treatment approach for these tumors is not consistent, largely because cases are rare and managed by various specialists in different fields. We report a case of paraspinal KHE, an unusual location for this tumor, and discuss the benefit for rehabilitation for all patients with KHE, especially patients with musculoskeletal complications caused by the tumor.

**Keywords:** Hemangioendothelioma; Kaposi; Malignancy; Infiltrating; Rehabilitation; Bone

## ABBREVIATIONS

**KHE:** Kaposiform hemangioendothelioma, **KMP:** Kasabach-Merritt phenomenon, **IH:** infantile hemangioma, **CH:** congenital hemangioma, **VM:** venous malformation, **TA:** tufted angioma, **SCH:** spindle cell hemangioendothelioma, **KLA:** kaposiform lymphangiomatosis and **KS:** Kaposi sarcoma

## INTRODUCTION

Kaposiform hemangioendothelioma (KHE), first described by Zuckerberg et al. in 1993 (25), is an aggressive, rare, locally invasive vascular tumor (1). KHE presents as violaceous subcutaneous masses with ill-defined borders and a purpuric, bruised appearance (2). The term "Kaposiform" conveys to its resemblance to Kaposi's sarcoma, with compact spindled tumor cells and displaying slit like vessels. The term "hemangioendothelioma" refers to its biologic behavior, a tumor with intermediate malignancy situated somewhere between the spectrum of hemangioma and angiosarcoma (3). KHE develops in infancy in 93% of cases, with 60% as neonates (4), with a median

age at diagnosis of 6.5 months (range 0.3–14.0 months) (3), and slightly more common among male than female patients (5). KHE has an incidence of less than 1 per million (3), and prevalence is 0.91 cases per 100,000 (6). This tumor is most commonly located in the dermal and subcutaneous tissue of the overlying joints on the extremities but may also involve the torso (including retroperitoneum and intrathoracic cavity) and cervicofacial region in decreasing order of frequency (7). Other rare sites of involvement are bones, mediastinum, and gastrointestinal tract (8). KHE extends to more than one region in 7 - 26 % of cases, in extracutaneous sites in 11 - 17 % of patients, and 3 - 10 % are found in the intrathoracic location (7). Here, we report a case of paraspinal KHE, an unusual location for this tumor, and discuss the benefit for rehabilitation for all patients with KHE, especially patients with musculoskeletal complications caused by the tumor.

## CASE PRESENTATION

A 3-years-old boy presented with 4.5 cm ill-defined hemorrhagic para-spinal swelling with purpuric, bruised appearance. There was no evidence of thrombocytopenia and consumptive coagulopathy, and the life threatening Kasabach-Merritt phenomenon (KMP) was excluded. In addition, there was no evidence of multifocality. MRI studies showed a 4.5 cm irregular mass with no defined margins. The mass showed intense heterogeneous enhancement, and multicompartiment involvement and appeared to infiltrate the adjacent rib bone and fibrocartilaginous tissue (**Figure 1A**). In a multidisciplinary meeting, it was decided to surgically remove the entire mass for pathological examination.

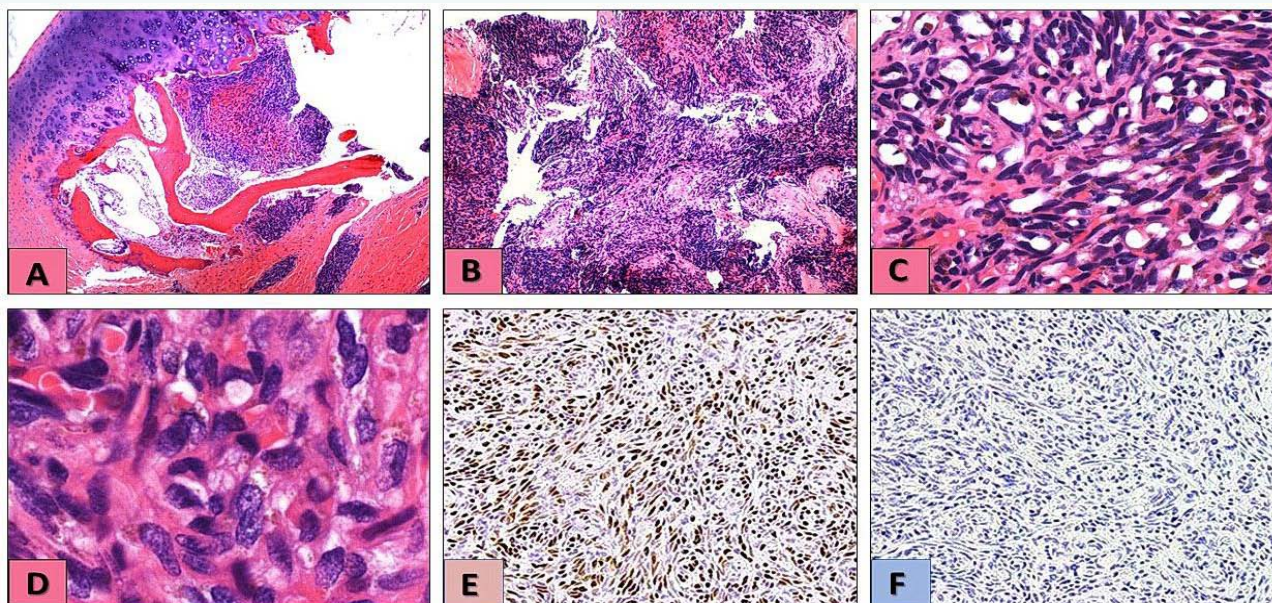
The excised mass showed a lobulated white tan tumor with rich vascularity infiltrating the rib bone. Microscopic examination showed a mixed pattern of cellular spindle cells and areas of lymphangiomatosis at the peripheries (**Figure 1B**).

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**Figure 1** Microscopic examination of the tumor mass.

A: Multicompartiment involvement and infiltration into the adjacent rib bone and fibrocartilaginous tissue (H&E stain X20).

B: Mixed pattern of cellular spindle cells and areas of lymphangiomatosis at the peripheries (H&E stain X20).

C: Slit-like vascular channels, extravasated red blood cells and spindle cells with intracytoplasmic hemosiderin and microthrombi (H&E stain X40).

D: Tumor cells showing absence of significant nuclear atypia, necrosis, or mitosis (H&E stain X60).

E: Tumor cells positive for endothelial marker ERG.

F: Tumor cells negative for Kaposi sarcoma marker HHV-8.

Slit-like vascular channels, extravasated red blood cells, and cells with intracytoplasmic hemosiderin and microthrombi were also noted (**Figure 1C**). There was absence of significant nuclear atypia, necrosis, or mitosis (**Figure 1D**). A dense hyaline stromal response was seen secondary to the spindle cells nodules. Immunohistochemistry studies showed the tumor cells positive for endothelial markers CD31, CD34, and ERG (**Figure 1E**). The tumor cells were negative for HHV-8 (**Figure 1F**) excluding Kaposi Sarcoma. All soft tissue and bone surgical margins were free of tumor. The histomorphology with the immunohistochemistry profiles were diagnostic of Kaposiform hemangioendothelioma.

The patient did not receive any post-operative treatment and was followed up for three years with no evidence of recurrence, after which he was lost to follow up.

## DISCUSSION

KHE is of intermediate malignancy due to the absence of firm evidence of its metastatic potential, while being locally aggressive (3). Unlike the more common infantile hemangioma, KHE shows no tendency toward spontaneous regression (7). Due to associated complications, KHE has high morbidity rates. Just over two-thirds of patients with KHE develop Kasabach-Merritt phenomenon (KMP), which is a life-threatening thrombocytopenia and consumptive coagulopathy (5) which can result in life-threatening bleeding and compression of vital structures (7). KMP is typically associated with more aggressive lesions and poorer outcomes, with a mortality rate estimated at 10–30%

often due to intralesional hemorrhages (5). The identified risk factors for KMP include larger tumor size, multifocality, depth of tumor infiltration, and intrathoracic, intra- and retroperitoneal locations (7). Musculoskeletal complications are also common in KHE and have received less attention in clinical research than the life-threatening complications associated with KMP. These complications, however, still have serious consequences, and often lead to disability and influence the patients' quality of life (QoL) (9). Currently, there is very little literature specifically addressing musculoskeletal complications in patients with KHE. As a result, these complications are often missed and not properly managed (10).

Vascular tumors with a predominantly spindle-cell component represent a diagnostic challenge for a histopathologist because of the morphologic overlap between different entities with varying malignant potential (7). KHE shares overlapping patterns of age of presentation, clinical symptoms, and anatomical location with other vascular anomalies and tumors such as: infantile hemangioma (IH), congenital hemangioma (CH), venous malformation (VM), tufted angioma (TA), spindle cell hemangioendothelioma (SCH), kaposiform lymphangiomatosis (KLA) and Kaposi sarcoma (KS) (8). One of the most important diseases to rule out in the differential diagnosis of KHE is IH, the most common tumor of childhood. IH shares the same age of presentation as KHE but can be differentiated on microscopy and immunochemistry. IH lacks platelet-rich thrombi and spindled endothelial cells on microscopy and the endothelial cells in IH





lesions are positive for Glut-1, which are absent in KHE and other vascular tumors (11). CH is biologically and behaviorally distinct from KHE. They are benign vascular tumors of infancy that arise in utero and are present and fully formed at birth and typically have an accelerated regression within the first year of life (11). VM can be distinguished histologically. On microscopy, they appear large and have irregular venous channels lined by flattened endothelial cells. (8) TA are considered a milder and more localized form of KHE, but the individual nodules of TA resemble a lobular capillary hemangioma, comprised of pericytes and endothelial cells with the absence of deep infiltration, spindling and fibrin microthrombi (8). KMP can also occur in TA, but only in about 10% of cases. Whereas KMP occurs in up to 70% of cases in KHE (6). SCH has a biphasic composition with cavernous vascular spaces and more solid spindle-cell areas containing cytoplasmic vacuoles (7). KLA shares overlapping patterns of clinical symptoms (including KMP), anatomical location, imaging features and complications with KHE, but can be distinguished histologically by the presence of poorly marginated clusters and sheets of kaposiform spindled cells oriented in parallel fashion amidst abnormal, dilated lymphatic channels (7). KS is very rare in children but if present, usually involves only lymph nodes. Histopathologically, KS has immature endothelial cells, is actin negative, HHV-8 positive, lacks a prominent lobular pattern, and has an absence of perivascular dense hyaline fibrosis and microthrombi (8).

The diagnosis of KHE is made based on clinical presentation, imaging, histopathologic examination, and immunohistochemistry (3). Just like for other superficial soft tissue masses in children, ultrasound (US) is often used as the initial diagnostic imaging modality. However, US fails to clearly demonstrate the infiltrative portions of KHE. Which is why magnetic resonance imaging (MRI) is the imaging modality of choice. KHE on MRI will show a mass exhibiting ill-defined margins, intense heterogeneous enhancement, multicompartiment involvement, adjacent fat stranding, destructive changes of adjacent bone, swelling/edema of soft tissue, with or without KMP (9).

Histopathology of the excised tumor is the gold standard for establishing a diagnosis of KHE (8). Microscopic features of KHE includes a biphasic tumor composed of infiltrating isolated and fusional poorly circumscribed nodules of spindle cells and areas of lymphangiomatosis at the peripheries. Within each nodule there is glomeruloid pattern of small capillaries and lobules of endothelial cells (12). Also seen are slit-like vascular channels, extravasated red blood cells, cells with intracytoplasmic lumina, edema, hemosiderin deposition and microthrombi. There is an absence of significant nuclear atypia, necrosis, and mitosis. A dense hyaline stromal response may be seen secondary to the nodules of spindle cells (8).

Immunohistochemistry can also be helpful in the diagnosis of KHE. Since KHE lesions are vascular, they are immunoreactive to non-specific endothelial markers, including CD31, CD34 and ERG, and smooth muscle actin (SMA) marker indicating the presence of pericytes (8). Since KHE also have a lymphatic component, immunoreactivity with either Prox-1 or D2-40 within the

neoplastic spindled endothelial cells also supports the diagnosis (2). To differentiate KHE from other vascular tumors, immunonegativity for glucose transporter-1 and human herpesvirus-8 can be helpful (1). KHE has also been shown to be immunonegative for factor VIII-AG and surrounded by a population of factor XIIIa-positive cells (3).

The strategies used in the treatment of KHE can be divided into three groups: resection, interventional procedures including vascular embolization (13), ligation, and percutaneous sclerotherapy (2); irradiation, and pharmacological agents (7). The gold-standard for treatment remains complete surgical removal with wide margins but may not be possible in some cases where the lesions are not well-circumscribed, are infiltrating and bleeding profusely, or have systemic bleeding due to platelet consumption often due to KMP (4). For non-resectable lesions, pharmacological management is desirable to shrink tumor size. Treatment approach for these tumors is not consistent, largely because cases are rare and managed by various specialists in different fields (6).

In 2013, Drolet et al. presented consensus guidelines based on limited clinical literature that suggested managing KHE based on whether KMP was present. For cases of KHE associated with KMP, first-line therapy with intravenous vincristine 0.05 mg/kg once weekly and oral prednisolone 2 mg/kg/d or intravenous methylprednisolone 1.6 mg/kg/d was recommended. For cases of KHE that require intervention because of growth or symptoms but do not have KMP, oral prednisolone 2 mg/kg/d was recommended as the first-line therapy. Treatment with aspirin at an antiplatelet dose of 2–5 mg/kg/d could be considered as adjunctive therapy (14). More recently, many studies have demonstrated a very effective response to sirolimus treatment, so is now considered the first-line therapy for KHE and KMP (4,15,16). In some patients, sirolimus 0.1 mg/kg/day resulted in rapid and dramatic response (4,17) even when other therapies have been ineffective. Sirolimus was also found to be effective for complications from KHE such as decreased range of motion and chronic pain (10). Other pharmacological treatments used in the literature include: propranolol (18), IFN-alpha (19), VAT (vincristine-aspirin-ticlopidine) (20), and combination therapy utilizing cyclophosphamide, methotrexate, vincristine and actinomycin-D in severe cases (21).

Since musculoskeletal disorders are frequently seen in KHE patients with or without KMP, they must be considered when constructing a management plan. The destructive growth patterns of the tumor, with a majority located on or adjacent to joints, and the development of muscular and periarticular fibrosis can alter the structural matrix and mechanical properties of the muscle and connective tissue, leading to chronic degenerative changes and fibrosis. The diffuse intraarticular and periarticular fibrosis can lead to muscular atrophy, subluxations, fixed contractures, recalcitrant pain, and functional limitations of the involved joints (22), which will affect patients' abilities to perform routine daily activities, potentially leading to a substantial decrease in QoL (10). In some cases, residual KHEs will continue to infiltrate surrounding tissues, long after the initial diagnosis, eroding bone



and destroying joints. A study by Ji et al., found that one-fourth of patients did not experience musculoskeletal complication at the initial assessment, but developed them many years later (10).

Rehabilitation has enjoyed tremendous success in relieving pain and improving the function and Quality of life (QoL) of cancer survivors (23). Physiatrists have extensive training in neuromuscular and musculoskeletal medicine and in the principles of functional restoration. With this knowledge, they are uniquely positioned to help direct efforts to improve QoL for cancer survivors. The main goal of rehabilitation in chronic conditions is improvement of the affected body function and an increase in daily activities. This treatment is a complex process consisting of education, physical therapy, occupational therapy, orthotics, procedures, and medications (24). It has been well documented the improvements patients have made with rehabilitation from fibrotic syndromes, such as radiation fibrosis syndrome (RFS), caused by cancer treatment (23), but there is little to no literature on the benefits of early and routine rehabilitation for KHE patients, with or without KMP, to improve pain and functional limitations caused by the tumor. There is also no definite treatment guideline for the long-term observation of patients with KHE (10). Along with the recommendation for routine surveillance for musculoskeletal complications suggested by Ji et al., the sequelae of fibrosis from KHE with or without KMP can be improved with early detection and management by tumor rehabilitation physiatrists and should be added to the routine care and follow-up schedule of patients with KHE.

We report this case with the hope that continued investigation drives further development of efficacious diagnosis and safe treatments including rehabilitation measures for improving patient outcomes.

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