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Bifocal Tibial Kaposiform Hemangioendothelioma Responsive to Vincristine Therapy: A Case Report

Authors' Contribution: Study Design A Data Collection B Statistical Analysis C Data Interpretation D Manuscript Preparation E Literature Search F Funds Collection G

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Patient: Female, 9-year-old
Final Diagnosis: Kaposiform hemangioendothelioma
Symptoms: Leg pain
Medication: —
Clinical Procedure: —
Specialty: Orthopedics and Traumatology

Objective: Rare co-existence of disease or pathology
Background: Kaposiform hemangioendothelioma is a rare locally aggressive vascular endothelial-derived spindle cells neoplasm. Herein, we report a rare case of bifocal tibial kaposiform hemangioendothelioma.

Case Report: A 9-year-old female presented with a 2-year history of pain and swelling in the left leg. The patient had a high plasma level of the D-dimer and fibrinogen. Radiography revealed a centric lytic lesion on the left proximal tibial metaphysis and an eccentric lateral distal tibial metaphyseal. Histopathologic examination of the sample taken from the distal tibia revealed a dense spindle cell tumor with lobular architecture composed of compact spindle cells compressing small slit-like vascular spaces, forming glomeruloid nests. No necrosis was identified. Based on these findings and the positive immunohistochemical staining for CD31, CD34, and D2-40, the patient was diagnosed with kaposiform hemangioendothelioma. Treatment was started by using vincristine chemotherapy, after which the patient developed temporary peroneal neuropathy, which improved over the next 3 months.

Conclusions: Bifocal tibial kaposiform hemangioendothelioma lesions are unique in pediatric patients and can be successfully treated with vincristine chemotherapy. In these cases, the treating physician should be aware of peroneal neuropathy as a potential complication of vincristine administration.

MeSH Keywords: Hemangioendothelioma • Peroneal Neuropathies • Vincristine

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Background

Kaposiform hemangioendothelioma (KHE), a relatively uncommon pathology, has primarily been published in the literature as case reports [1–16]. It is a rare, locally aggressive vascular endothelial-derived spindle cell neoplasm occurring most often in infants and adolescents [1]. Zukerberg et al. first described KHE and showed its association with the Kasabach-Merritt phenomenon (KMP). KMP presents with a vascular lesion, usually in the upper trunk or extremities and is associated with thrombocytopenia and consumptive coagulopathy [2,3]. KHE usually appears as an ill-defined, purplish indurated plaque in the skin or deep soft tissues. KHE has been reported to involve various sites throughout the body, but mostly present in the skin, superficial and deep soft tissues of the extremities, trunk, and to a lesser extent retroperitoneally [4–6]. Based on the International Society for the Study of Vascular Anomalies (ISSVA) classification, these tumors are considered locally aggressive or borderline vascular tumors [7]. KHE has histopathologic features intermediate between a benign well-differentiated hemangioma and anaplastic angiosarcoma [8,9] and therefore has been categorized by the World Health Organization (WHO) as a vascular neoplasm of intermediate malignancy [5,6]. Previous cases of KHE lesions have been reported to invade bones, of which none of these cases had multifocal involvement of the tibia, and these cases were treated by variable methods. Herein, we report a case of a 9-year-old female who was diagnosed with KHE with bifocal involvement of the left tibia that was successfully treated with vincristine but was complicated by the rare occurrence of vincristine-induced peroneal neuropathy.

Case Report

A 9-year-old female, a product of a full-term uncomplicated vaginal delivery, presented with a 2-year history of pain and swelling in the left leg. The swelling was diffuse along the left leg extending to the left ankle. This swelling caused a limited dorsiflexion of the ankle with continuous pressure-like pain that did not radiate elsewhere. The pain, along with difficulty in moving the patient's left ankle due to increased swelling, was disabling and prevented the patient from participating in school activities. The patient denied any history of fever, trauma, or previous fractures.

The patient's physical examination revealed diffuse swelling of the left leg that was associated with tenderness all over the leg without changes in the overlying skin color or texture, warmth, or redness. There was no documented weight loss.

Upon investigation, the patient's blood tests, including complete blood count and liver function tests, were within the normal



Figure 1. Plain x ray of the left leg revealed a centric lytic lesion of the left proximal tibial metaphysis and an eccentric lateral distal tibial metaphyseal lesion disrupting the lateral cortex of the distal tibia.

range. The platelet count on presentation was 411 000/mm³, the erythrocyte sedimentation rate was 55 mm/hour, but her plasma level of the D-dimer (0.82 ug/mL) (normal range <0.5 ug/mL) and the fibrinogen (414 mg/dL) (normal range 200–400 mg/dL) were increased.

Plain radiography (Figure 1) revealed a centric lytic lesion on the left proximal tibial metaphysis and an eccentric lateral distal tibial metaphyseal lesion disrupting the lateral cortex of the distal tibia. Magnetic resonance image (MRI) of the left leg showed a well-defined elongated lesion within the proximal left tibial metaphysis with central hyperintensity on STIR (short inversion time inversion recovery) and T2-weighted images and hypointense signal on T1. Another lesion with the



Figure 2. T2-weighted images of the distal tibial metaphysis showed the distal lesion causing a lateral cortical disruption and extension to the adjacent soft tissue component.

same characteristics was seen at the distal tibial metaphysis causing a lateral cortical disruption and extension to the adjacent soft tissue (Figure 2). The perfusion and blood pool phases of the ^{99m}Tc -MDP 3-phase bone scan of the left tibia revealed increased flow and marked hyperemia in the proximal and distal left tibia. The delayed bone phase showed only mildly increased uptake in the meta-diaphysis of the proximal and distal left tibia. The findings were suggestive of a well-perfused tumor rather than infectious process. Histopathologic examination of the sample taken from the distal tibia revealed a dense spindle cell tumor with lobular architecture composed of compact spindle cells compressing small slit-like vascular spaces, forming glomeruloid nests. The surrounding stroma was predominantly collagenous, and discrete foci of irregular dilated vascular and lymphatic channels were seen. The spindle cell areas with slit-like vascular spaces contained extravasated red blood cells in addition to hemosiderin reminiscent of Kaposi's sarcoma. Mitotic index was 1/10 HPFs (high power fields). No necrosis was identified. Immunohistochemical staining for CD31 and CD34 was positive confirming the vascular nature of the tumor (Figure 3A–3D). In addition to that, immunohistochemical for D2-40 highlights neoplastic cells at the

periphery of the nodules (Figure 3E, 3F). Based on these findings, the patient was diagnosed with KHE in the left tibia and was subsequently referred to the oncology team for further management. Treatment was started by using vincristine chemotherapy (0.05 mg/kg) for 6 cycles every 3 weeks. The movement of the patient was not restricted during therapy, and weight bearing was continued because a good bone mass was preserved on the medial side of the distal tibia. After the second cycle of chemotherapy, the patient developed weakness in the dorsiflexion of the left ankle. Nerve conduction study of the lower limb showed severe peroneal neuropathy secondary to vincristine use. This neuropathy improved over the next 3 months. The pain experienced by the patient improved gradually by the end of the chemotherapy course, accompanied by improvement of the ankle range of motion. At the most recent follow up of 30 months after the treatment, no signs of recurrence were seen.

Discussion

Kaposiform hemangioendothelioma (KHE) is a rare endothelial-derived neoplasm with a locally aggressive behavior occurring most often during childhood. KHE usually involves the soft tissues and is often associated with KMP. There are rare reports of bone involvement, such as the case report by Zhou et al. [10] with mainly unifocal involvement reported. This is the first case report of bifocal involvement of the tibia without cutaneous changes. Histopathologic and immunostaining features of the tumor are typical of those of KHE, despite the unusual site, showing the spindle cell nodules along with slit-like vascular spaces resembling Kaposi's sarcoma [1]. Ma et al. [5] and Zhou et al. [10] have previously described KHEs of the bone with similar features to our case. CD31 and CD34 positivity in the tumor cells reported herein confirm the vascular nature and exclude other soft tissue lesions. Other vascular lesions among the differential diagnoses include Kaposi's sarcoma which is usually a cutaneous or mucosal lesion. It is rarely seen in children. Histologically the tumor lacks the infiltrative pattern and the surrounding chronic inflammatory cell infiltrate rich in plasma seen in Kaposi's sarcoma. Though many experts believe that tufted angioma and KHE are part of a spectrum, the nodules of KHE are larger, less circumscribed with an infiltrative pattern and may involve deep soft tissues and bones while tufted angioma has characteristically small discrete nodules, what so called "cannonball" distribution of vascular tufts, which are not identified in our case [11]. D2-40 (i.e., podoplanin) is marker for lymphatic endothelium, which is characteristically positive in the peripheral region of the nodules composed of proliferated capillaries [12].

The perfusion and blood pool phases of the 3-phase bone scan of the left tibia showed increased perfusion to and marked

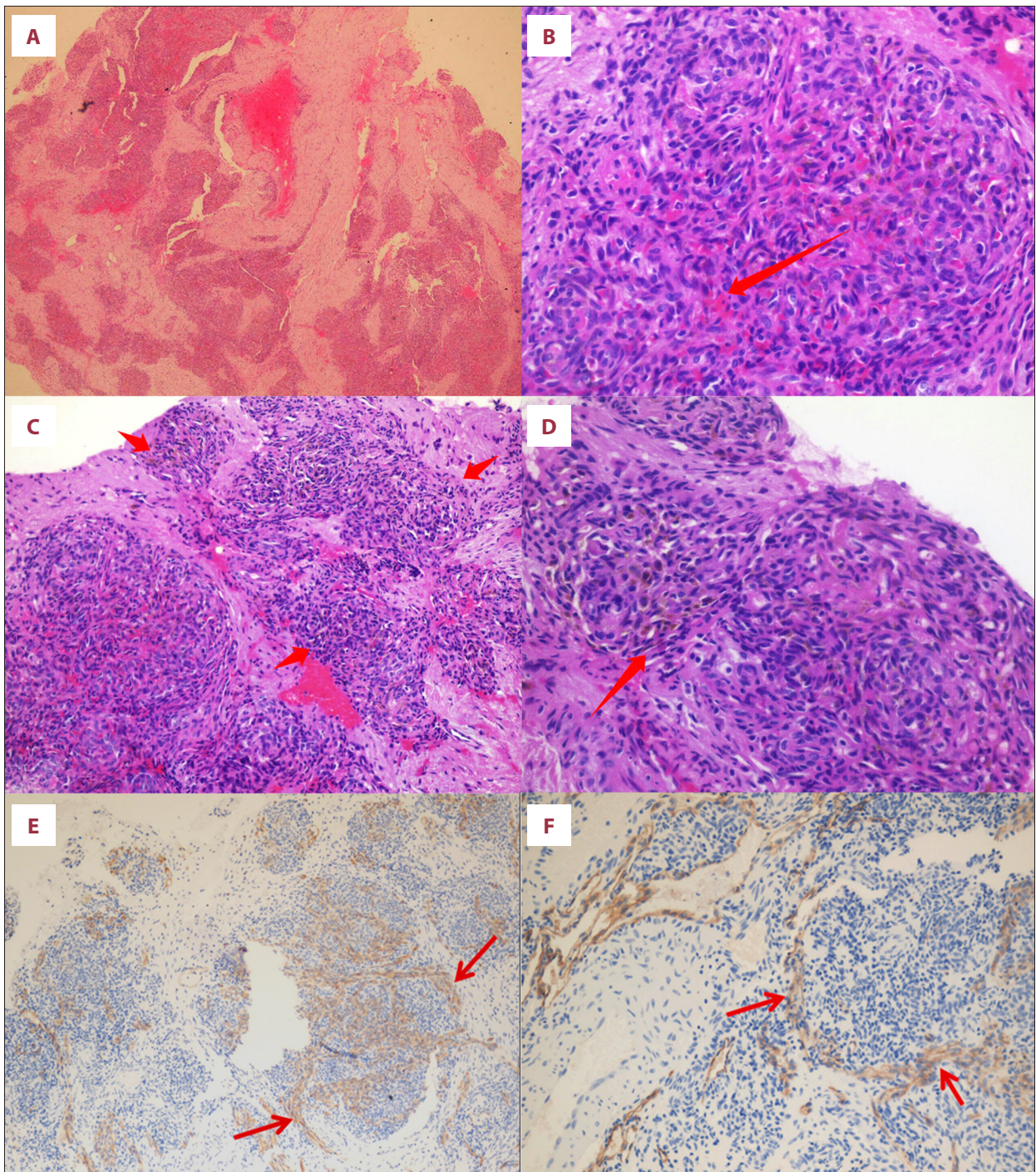


Figure 3. Microscopic low- and high-power views (A) Tumor composed of nodules separated by fibrous septa (H&E 40×). (B) Areas of spindle cell morphology with extravasated red blood cells (arrow) resembling Kaposi sarcoma (H&E 400×). (C) Characteristic glomeruloid structures formed by tumor cells (arrows) (H&E 200×) (D) Intratumoral hemorrhage forming hemosiderin (arrow) (H&E 400×). (E, F) Low power and high power views showed a D2-40 immunostaining positivity in the peripheral areas of capillary proliferation (characteristic pattern of KHE). H&E – hematoxylin and eosin; KHE – kaposiform hemangioendothelioma.



Figure 4. Plain x-ray of the same left leg showed healing of the previously described lytic lesions in the tibia.

hyperemia in the lesions in the proximal and distal left tibia. This is likely due to the fact that KHEs are by their nature well-perfused tumors with glomeruloid nests. In contrast, the delayed bone phase showed only mildly increased bone uptake in proximal and distal left tibia. This is likely related to only mild increase in uptake of the bone surrounding the KHE lesions, which might be caused by reactive changes in response to the aggressive vascular tumor and/or concomitant increase in perfusion of the bone adjacent to the well-perfused KHEs.

No consensus on an effective treatment modality for KHE was demonstrated in the literature. Surgical excision is widely used as definitive treatment for KHE when it is possible without life-threatening complications, namely coagulation disorders [13]. Ma et al. in their reported cases used wide local excision to treat patients, after a recurrence in 1 case treated with a local resection [6]. Pharmacological treatment of KHE varies depending on the location of the tumor and the involved organs, the size of the lesion and the presence of associated KMP. Aggressive treatment is preferred for symptomatic KHE, especially when it is associated with KMP and severe consumptive coagulopathy. Multiple medical therapies have been used in the reported cases to treat KHE and KMP, including systemic steroids, vincristine, low molecular weight heparin, interferon- α , and aspirin [14].

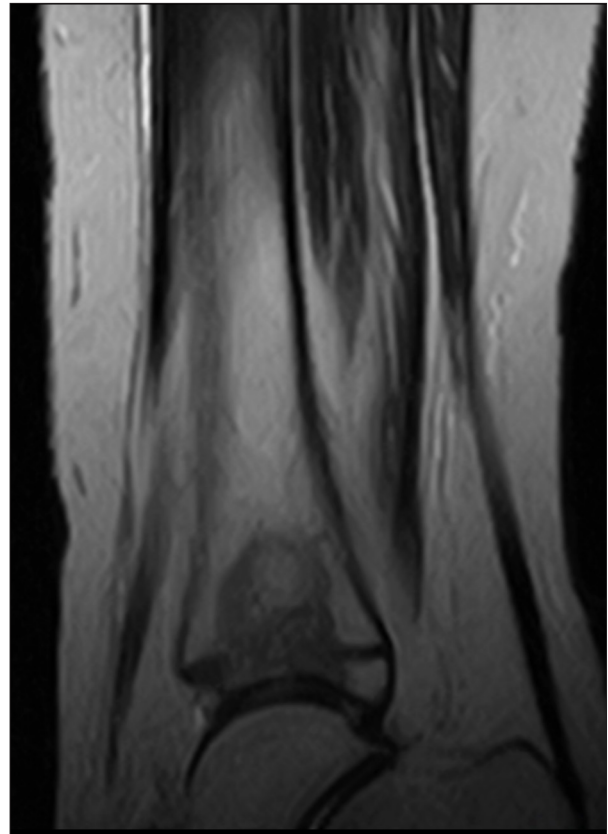


Figure 5. T2-weighted images of the distal tibial metaphysis post treatment showed healed distal lesion of the lateral cortex with disappearance of adjacent soft tissue extension.

In the present case, we have used intravenous chemotherapy with vincristine, a vinca alkaloid and an inhibitor of endothelial proliferation by destabilization of microtubules of mitotic spindles [15]. We used a regimen of 6 cycles every 3 weeks. Our patient responded well to treatment showing improved pain sensation. The range of motion of the ankle improved also following resolution of her neuropathy. Surgical excision was not included in the treatment plan of our patient as the initial response of the medical treatment was encouraging and could be considered if there is any recurrence on the long-term follow-up. Ji et al. [16] reported similar results of improvement in the range of motion of nearby joints of the periarticular KHE after vincristine monotherapy. Moreover, significant improvement of our patient's radiological findings was also seen (Figure 4), and the recent MRI image showed significant improvement of the changes that were seen initially with reconstitution of the cortices and disappearance of the soft tissue mass seen before the treatment initiation (Figure 5). The recent bone scan showed normal uptake in the meta-diaphysis of the proximal and distal left tibia, suggesting that the increased uptake in the proximal and distal left tibia in the former bone scan has apparently resolved (Figure 6). The patient did not

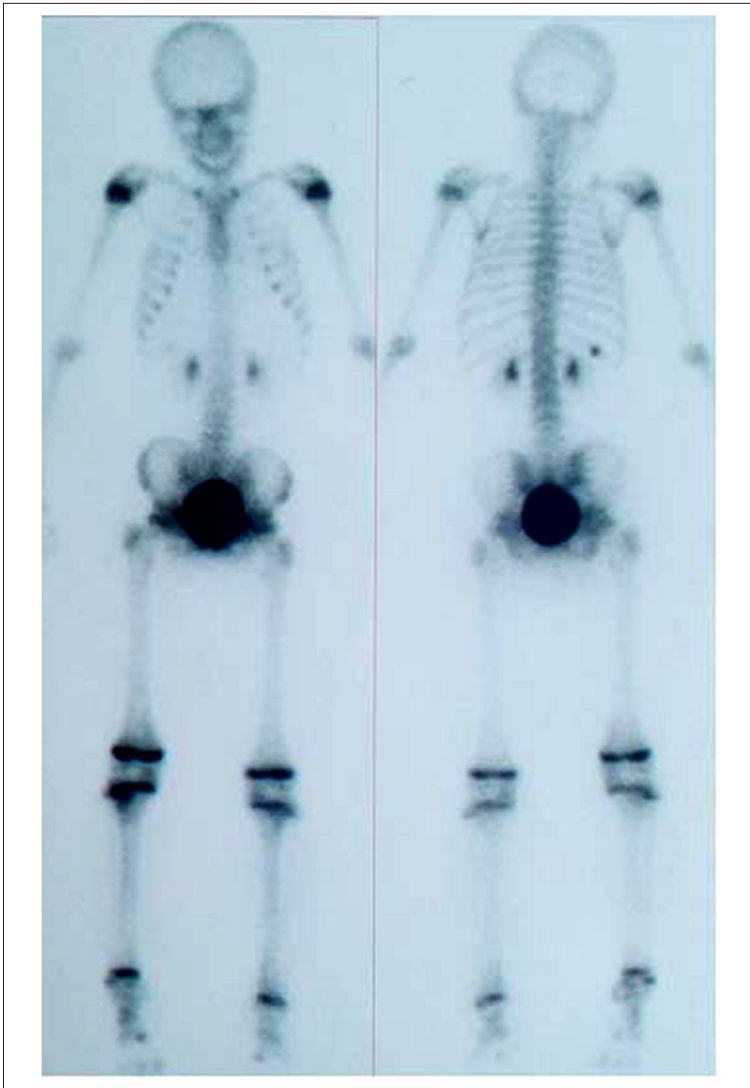


Figure 6. Anterior and posterior delayed-phase bone scan post treatment showed normal uptake in the meta-diaphysis of the proximal and distal left tibia.

show any abnormal changes in the routine blood investigations during or after the treatment. However, the patient developed weakness in the ankle dorsiflexion of the same side of the lesion that recovered over the next 3 months of treatment. Thirty months follow-up showed no recurrence of the tumor.

Vincristine has been used as a first-line treatment option for KHE associated with KMP despite its neurologic and hematologic side effects due to the excellent tumor responses and clinical improvement [17–19]. Regarding neuropathy, the motor symptoms were more frequent and severe than sensory symptoms in recent studies, presenting as slower self-selected walking velocity than in patients of the same gender and age group. The severity of these symptoms was dose-related and length dependent [20,21]. The peroneal neuropathy seen in our case was a rare complication of vincristine treatment and might, in the present case, be related to the lesion's location in the distal tibia since it occurred at the same side of the tibial lesion.

Conclusions

Bifocal tibial KHE lesions are unique in pediatrics and can be successfully treated with vincristine chemotherapy. To the best of our knowledge, this is the first case of bifocal tibial simultaneous KHE tumors in a child. In these cases, the treating physician should be aware of peroneal neuropathy as potential complication of vincristine. Further studies are needed to determine the optimal treatment for KHE with bony involvement.

Department and Institution where work was done

Orthopedic Division, Jordan University Hospital, University of Jordan, Amman, Jordan.

Conflict of interest

None.

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