Musculoskeletal complication in kaposiform hemangioendothelioma without Kasabach–Merritt phenomenon: clinical characteristics and management

Yi Ji, Kaiying Yang, Siyuan Chen, Guoyan Lu, Xingtao Liu

Introduction
Kaposiform hemangioendothelioma (KHE) is a rare, locally aggressive, and nonmetastatic vascular tumor of intermediate malignancy. The annual incidence of KHE has been estimated at 0.071 per 100,000 children. In contrast to infantile hemangiomas, which have a tendency to spontaneously regress, KHE shows a highly invasive behavior with a very low tendency to resolve spontaneously. Clinically, KHE has high mortality and morbidity rates, primarily due to local invasion characteristics, compressive effects, or the life-threatening complication known as Kasabach–Merritt phenomenon (KMP). KMP is profound thrombocytopenia with hypofibrinogenemia resulting from intralesional platelet activation, trapping, and consumption.
The outcome of KHE is strongly influenced by tumor characteristics, timing of diagnosis, and initiation of appropriate treatment. The infiltrative nature of the tumor, risk of bleeding, and anatomic site of the lesion can make complete surgical removal difficult or impossible. Clinically, the management of high-risk patients is very challenging. Several different approaches, including various medical therapy regimens, have been described, but they have shown variable degrees of success. The destructive growth patterns of the tumor and the development of muscular and periarticular fibrosis can cause pain and functional limitations, all of which may affect patients’ abilities to perform routine daily activities, potentially leading to a substantial decrease in quality of life.

Musculoskeletal complications in KHE without KMP have received less attention in clinical research than the life-threatening complications associated with KMP (eg, thrombocytopenia, acquired hypofibrinogenemia, and severe anemia), and the decreased range of motion (ROM) is likely underappreciated in clinical practice. Currently, there is a paucity of literature specifically addressing musculoskeletal complications in patients with KHE. Therefore, the purpose of this study was to investigate the features of musculoskeletal complication in KHE without KMP to improve our understanding of this rare disease.

Patients and methods

From January 2006 to February 2017, a descriptive study was conducted across three tertiary medical centers in China. The study was approved by the Ethics Committee of the West China Hospital of Sichuan University, the study site of the principal investigator, and by the local institutional review boards at each participating site. Patients were included if they 1) had verified KHE by pathological examination; 2) showed decreased ROM; 3) had no history of KMP; 4) had given written informed consent or patients’ parents had given the consent for their clinical records to be used in this study; and 5) had a minimum of 6 months of follow-up.

Clinical data including demographics, clinical presentation, anatomic location, laboratory results, imaging results, pathology reports, follow-up examinations, and outcome were obtained. Diagnosis of KHE was based on clinical presentation, imaging, and histopathologic examination. All patients underwent incisional biopsy or punch biopsy during diagnostic workup. Thrombocytopenia is the most definitive and distinguishing factor associated with KMP symptoms. We defined KMP as a platelet count of <100×10⁹/L. In addition to the ultrasound results, the available radiology database was queried for magnetic resonance imaging data. Based on our previous studies, KHE was typed according to the depth of infiltration as determined by radiographic findings and designated as superficial, mixed, or deep.

Decreased ROM was defined as ≥10° of extension loss, flexion <120°, or both. Associated chronic pain was defined as daily pain for at least 3 months. ROM measurements were performed using standard goniometers. To determine intra-rater reliability, goniometer measurements were performed twice for each joint. A targeted history was obtained by trained study coordinators, with questions addressing signs and symptoms related to musculoskeletal complication. Based on previous studies, the severity of musculoskeletal complication was scored by using a 4-point scale: 1, asymptomatic or mild symptoms, clinical or diagnostic observations only; 2, moderate symptoms, limiting age-appropriate instrumental activities of daily living; 3, severe or medically significant symptoms, disabling or limiting self-care activities of daily living; and 4, life-threatening consequences, with urgent intervention indicated. Higher values represent more profound functional disability or symptoms.

Treatment responses were evaluated at the initiation of each treatment regimen, at 1, 2, 3, and 6 months after treatment, at each scheduled visit, and at the last available visit. Successful treatment responses were defined as an improvement in the patient’s signs and/or symptoms. According to previous studies, improvement in signs and/or symptoms was defined as a decrease in the severity score of ≥1.

Results

Twenty-nine patients were considered to have decreased ROM related to KHE. None of these patients had a history of KMP. Nearly all were referred because of KHE complex and/or musculoskeletal complication. The demographic and clinical characteristics of these patients are presented in Table 1. The sex distribution was 16 males and 13 females. The age at diagnosis of KHE ranged from 3.5 months to 50 years, with a mean age at diagnosis of 4.5 years.

Twenty-six lesions (90.0%) involved the extremities. Three patients had multiple locations where the KHE lesions extended into more than one anatomic region: one patient had lesion involving both neck and trunk and two patients had lesions involving both trunk and extremity. The maximum diameter of the lesions ranged from 2.5 to 11.0 cm (mean, 5.3 cm). Ten patients (34.5%) had mixed-type KHE. These cutaneous lesions infiltrated deeply into muscles, bones, and joints. Two patients had superficial lesions on the knee involving the dermis, subcutaneous tissue, and deep fascia.
remaining 17 patients had lesions confined to the involved muscle–bone–joint regions. The most commonly involved joints were the knees, followed in order of decreasing frequency by the shoulders and hip joints. Bone–joint changes, including bone–joint erosion or destruction, were noted in 22 cases (75.9%; Figure 1).

Eight patients (27.6%) did not have decreased ROM at the initial evaluation, but developed ROM decreases thereafter. In the remaining patients (72.4%), decreased ROM was identified within 2 years of KHE onset. Only 2 (2/29, 6.9%) patients reported decreased ROM before the age of 12 months. Associated chronic pain was reported in 12 patients, including 4 of 5 patients with lesions involving the spine. Over the study period’s mean follow-up time of 4.1 years (range 0.5–9.0 years), the highest severity scores in each patient ranged from 1 to 4, with a mean highest score of 2.8.

All patients received at least one medical therapy. In eight cases, multiple agents were given in sequence: these patients received at least two different medical therapies. Corticosteroids were used in eight patients, six of whom did not show an improvement in associated musculoskeletal complications, requiring a switch to partial resection and orthopedic physical therapy (three) or sirolimus (three). Vincristine monotherapy was used in seven patients, with three showing definite improvement of ROM. The four patients who did not respond to vincristine underwent treatment including surgical excision (two), partial resection and orthopedic physical therapy (one), and sirolimus (one). Propranolol was used in three patients, all of whom suffered from progressive enlargement of their tumors and ongoing decreased ROM (Table 2).

Oral sirolimus was used in 19 patients, including 7 patients who had been treated with drugs described above: corticosteroids (3), vincristine (1), and propranolol (3). All but one of the patients showed improvement (Figure 2). The size of the lesions was significantly reduced, with rapid improvements in ROM (Figure 3). In eight patients with chronic pain, significant pain relief was obtained within 3 months of sirolimus treatment. At the last follow-up, eleven patients had been successfully tapered off sirolimus treatment. The mean duration of sirolimus therapy in these patients was 26.0 months (range, 17–36 months). One patient who was tapered and discontinued from sirolimus after 18 months of treatment showed newly diagnosed decrease in ROM. Additional courses of sirolimus were administered with subsequent improvement.

**Discussion**

Previous studies have demonstrated that decreased ROM is a complication of KHE.12–15 We present the clinical features of decreased ROM in a sample of 29 KHE without KMP,

![Figure 1](https://www.dovepress.com/)

**Table 1** Demographics and clinical characteristics of KHE with decreased ROM without KMP

<table>
<thead>
<tr>
<th>Variables</th>
<th>N=29</th>
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<tbody>
<tr>
<td>Patients</td>
<td></td>
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<tr>
<td>Sexa</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (55.2)</td>
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<tr>
<td>Female</td>
<td>13 (44.8)</td>
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<tr>
<td>Age at diagnosis of KHE (years)b</td>
<td>4.5 (0.3–50.0)</td>
</tr>
<tr>
<td>Duration of follow-up (years)b</td>
<td>4.1 (0.5–9.0)</td>
</tr>
<tr>
<td>KHE</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Head, face, and neck</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Extremity</td>
<td>26 (90.0)</td>
</tr>
<tr>
<td>Trunk</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Multiple locations</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Mixed</td>
<td>10 (34.5)</td>
</tr>
<tr>
<td>Deep</td>
<td>17 (58.6)</td>
</tr>
<tr>
<td>Maximum diameter (cm)b</td>
<td>5.3 (2.5–11.0)</td>
</tr>
</tbody>
</table>

**Notes:** Values are presented as the number (%). bValues are presented as the mean (range).

**Abbreviations:** KHE, kaposiform hemangioendothelioma; KMP, Kasabach–Merritt phenomenon; ROM, range of motion.

**Table 2** Management of KHE with decreased ROM without KMP

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>No. (%)</th>
<th>Response</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>Better</td>
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<tr>
<td>Corticosteroids</td>
<td>8 (27.6)</td>
<td>2</td>
</tr>
<tr>
<td>Vincristine</td>
<td>7 (24.1)</td>
<td>3</td>
</tr>
<tr>
<td>Propranolol</td>
<td>3 (10.3)</td>
<td>0</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>19 (65.5)</td>
<td>18</td>
</tr>
</tbody>
</table>

**Note:** Eight patients received at least two different medical therapies, which were given in sequence.

**Abbreviations:** KHE, kaposiform hemangioendothelioma; KMP, Kasabach–Merritt phenomenon; ROM, range of motion.
which has rarely, if ever, been previously reported. Using this well-characterized cohort of KHE patients, we show that decreased ROM and associated chronic pain may be common in KHE without KMP. To the best of our knowledge, this is the largest study that assesses the clinical feature and treatment of musculoskeletal complication in KHE. In addition, this is the first study that assesses the efficacy of different treatment regimens in KHE. We hope that the information gained in this study will help improve the diagnosis and treatment of KHE and associated musculoskeletal complications to ultimately improve patients’ quality of life.

The majority of KHEs with decreased ROM but without KMP were mixed and deep lesions, but a significant minority of KHEs consisted of superficial lesions. Decreased ROM was commonly seen in patients with KHE involving the extremities, with a majority of these lesions located on or adjacent to large joints. Patients may become debilitated over time by decreases in ROM at the involved site. We also
found that decreased ROM occurred most commonly in older children and adults, with only 6.9% of the patients showing decreased ROM before 12 months of age. Interestingly, the lesions involving spine did seem to result in significant pain and disability. This is important. Perhaps these patients should be treated more aggressively at the outset even in the absence of KMP.

We demonstrated that decreased ROM did occur in several patients who attained partial tumor involution. We suspect that decreased ROM may be an independent complication of therapy, which is consistent with the results of previous studies. In addition, decreased ROM can occur early in the disease course. Our study provides novel data showing that decreased ROM typically presented within 2 years of KHE onset. The precise etiology of KHE-associated decreases in ROM remains uncertain. Tumor infiltration of the muscles, connective tissues, and joint structures can alter the structural matrix and mechanical properties of these tissues, leading to diffuse muscle fibrosis and joint contracture. Clinical manifestations include joint pain and disability. This is important. Perhaps these patients should be treated more aggressively at the outset even in the absence of KMP.

Currently, there is no definite treatment guideline for the long-term observation of patients with KHE. In the present study, we found that more than one-fourth of patients did not experience musculoskeletal complication at the initial assessment. We advocate for at least annual visits to monitor for musculoskeletal complications. For lesions at high risk of causing mid-or long-term functional complications, patients and their families should be educated about potential symptoms and the need for observation. Further study is needed to evaluate the precise duration of treatment required to avoid long-term complications. For certain cases, maintenance treatment with sirolimus monotherapy should be evaluated. In this regard, various studies have demonstrated that a relatively low dose of sirolimus can markedly ameliorate the development of inflammation and fibrogenesis.

**Conclusion**

This is the largest study assessing the clinical characteristics and treatment of musculoskeletal complication in KHE patients. We demonstrate that musculoskeletal complications may be common in patients with KHE without KMP. In addition, our data demonstrate that sirolimus therapy can improve outcomes in patients with musculoskeletal complication. Nonetheless, better treatments are needed to improve the life expectancy of KHE and associated musculoskeletal complication. Surveillance for musculoskeletal complications should be added as a recommendation to the routine care and follow-up schedule of patients with KHE. Given the rarity of KHE, an international collaborative effort may be able to shed new insights regarding the demographics, etiology, management, and prognosis of patients with KHE.

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Disclosure
The authors report no conflicts of interest in this work.

References