

Rare adult Kaposiform hemangioendothelioma with multiple-bone invasion – clinical experience and literature review

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Abstract. – BACKGROUND: Kaposiform hemangioendothelioma (KHE) is a borderline vascular tumor between hemangioma and malignant angiosarcoma. While KHE has strong local invasion with rare spontaneous regression, it is not observed with distant metastasis. Even if KHE is asymptomatic or without the Kasabach-Merritt phenomenon (KMP), bone or joint invasion should clearly receive proactive treatment. KHE commonly affects infants/children but is rarely seen in adults.

CASE REPORT: We reported a rare adult KHE case with an invasion of >10 separate forearm/hand bones, who underwent multiple-lesion resection and finger amputation after tumor recurrence. Tumor recurrence and KMP were not observed during the 6-month follow-up after the final operation. During the hospitalization and follow-up period, the patient only received medications for infection prevention and pain relief.

CONCLUSIONS: Multiple resectable lesions were found in the distal limb, for which complete resection might not present typical features (high-intensity T2-weighted MRI), which might fail to detect all KHE lesions. Therefore, complete excision is not optimal for multiple resectable KHE lesions.

Key Words:

Kaposiform hemangioendothelioma, Multiple bony lesions, Tumor recurrence, Excision.

to important deep organs². However, the single giant tissue mass is the main feature in most patients, which can attack the skin³, bone and musculature⁴, deep organs⁵, and other systems¹. Reports of KHE with multiorgan involvement are rare^{5,6}. Therefore, it is difficult to diagnose KHE by its varying clinical manifestations. KHE pathological characteristics include infiltrating nodules composed of spindle-cell sheets, tissue positivity for *CD31* and *CD34* (vascular endothelial markers), *VEGFR-3* and *D2-40* (lymphatic endothelial markers), *lymphatic endothelial hyaluronan receptor-1 (LYVE-1)*, and *Prox-1*, and tissue negativity for *glucose transporter-1 (Glut-1)* and *human herpes virus-8 (HHV-8)*. KHE clinical diagnosis mainly depended on the immunohistochemical assay and histological staining by biopsy. Nonetheless, it is difficult to identify rare KHE, particularly in adults without highly recognizable KMP⁷. Due to its rarity, KHE studies were mainly case reports or small case series^{3,8}. Here we reported an adult KHE case involving >10 forearm bones on one side; also, we reviewed previous literature on KHE.

Case Presentation

A 42-year-old man found a painless mass in his left wrist joint on January 2021, which had not significantly affected his health. The patient was referred to our hospital six months later as the mass grew fast and showed tenderness.

On physical examination, a protuberant large mass with a 3 cm diameter showed a clear boundary, a rubbery/hard consistency, and tenderness in the volar side of the wrist joint (Figure 1). Few soy bean-like satellite masses were palpable

Introduction

Kaposiform hemangioendothelioma (KHE) is a locally aggressive vascular tumor of intermediate malignancy, which commonly affects infants but is seldom seen in adults¹. KHE shows various clinical manifestations, including the presence/absence of the Kasabach-Merritt phenomenon (KMP) and various tissue appearances, ranging from cutaneous signs

around the protuberant large mass. Skin color and temperature around the mass were normal. KMP was not observed. While the ranges of initiative and passive motions of the left wrist were normal, it could not confront external force to motion due to unbearable pain.

In imaging examination, left forearm X-ray and computed tomography (CT) showed osteolytic destructions in the distal radius, scaphoid bone, capitate bone, trapezium, trapezoid, first metacarpal base, second and third metacarpal heads, a distal phalanx of the thumb, and nail root. In magnetic resonance imaging (MRI), all lesions detected by CT and X-ray were nearly isointense to muscles in the T1-weighted image (T1WI) and hyperintense to muscles in the T2-weighted image (T2WI). The large mass wrapped around the radial artery (Figure 2). CT and MRI showed no abnormal signs in the abdomen and chest regions.

No abnormality was observed in routine blood tests, clinical chemistry examination, and coagulation profile at admission.

To ascertain the diagnosis, we performed a percutaneous bone biopsy in the left wrist joint under general anesthesia, which showed tissue positivity for *CD31*, *CD34*, *vimentin*, *friend leukemia integration-1 (Fli-1)*, *neuron-specific enolase (NSE)*, *S-100 protein (S-100)*, *CD57*, *smooth muscle actin (SMA)*, *erythroblast transformation-specific family of transcriptions factors (ERG)*, and tissue

negativity for *D2-40*, *epithelial membrane antigen (EMA)*, *desmin*, and *HHV-8* (Figure 3). *IDH1/IDH2 mutations* were not tested by Sanger sequencing. By biopsy, the patient was diagnosed with KHE and treated by complete lesion resection.

Volar skin and subcutaneous tissue of the wrist joint were sectioned intraoperatively. After incising for approximately 6 cm, it was clear that the tumor wrapped around the radial artery and concomitant veins and corroded the supporting flexor muscle of the wrist and pronator quadratus. We then ligated the radial artery and veins in the proximal and distal sides separately, bluntly separated and removed the masses completely, and scraped tumor in the distal radius until normal bone tissue was visible. The subchondral bone of the distal radius was aggressed. To completely excise the tumor, we had to remove the subchondral bone and cartilage located on its surface. The incision was extended to the distal side, the lunate bone, scaphoid bone, trapezium bones, and the first metacarpal bone with complete cortex exposure. We then punctured the fragile cortex and scraped the tumor until normal bone tissue was observed. Tumors in the second and third metacarpal heads were scraped through a 2 cm dorsal incision. To resect the tumor in the phalanx of the distal thumb, the nail was removed. We observed that the nail bed's root

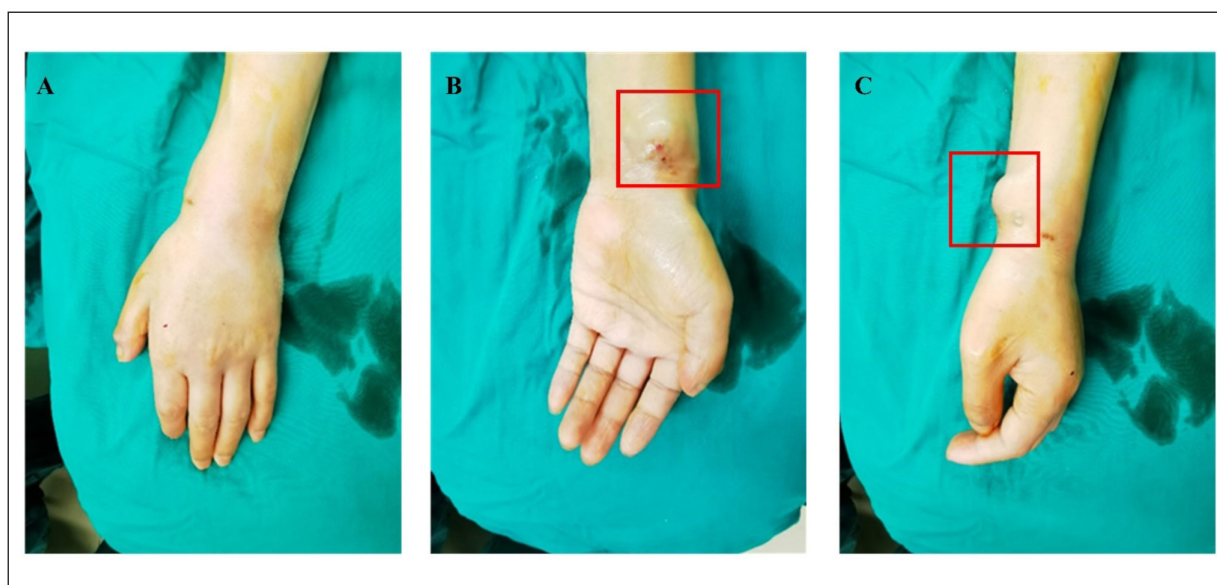


Figure 1. Gross view of the patient's left forearm. A, Posterior view. B, Anterior view. C, Lateral view. The tumor was highlighted by the red square.

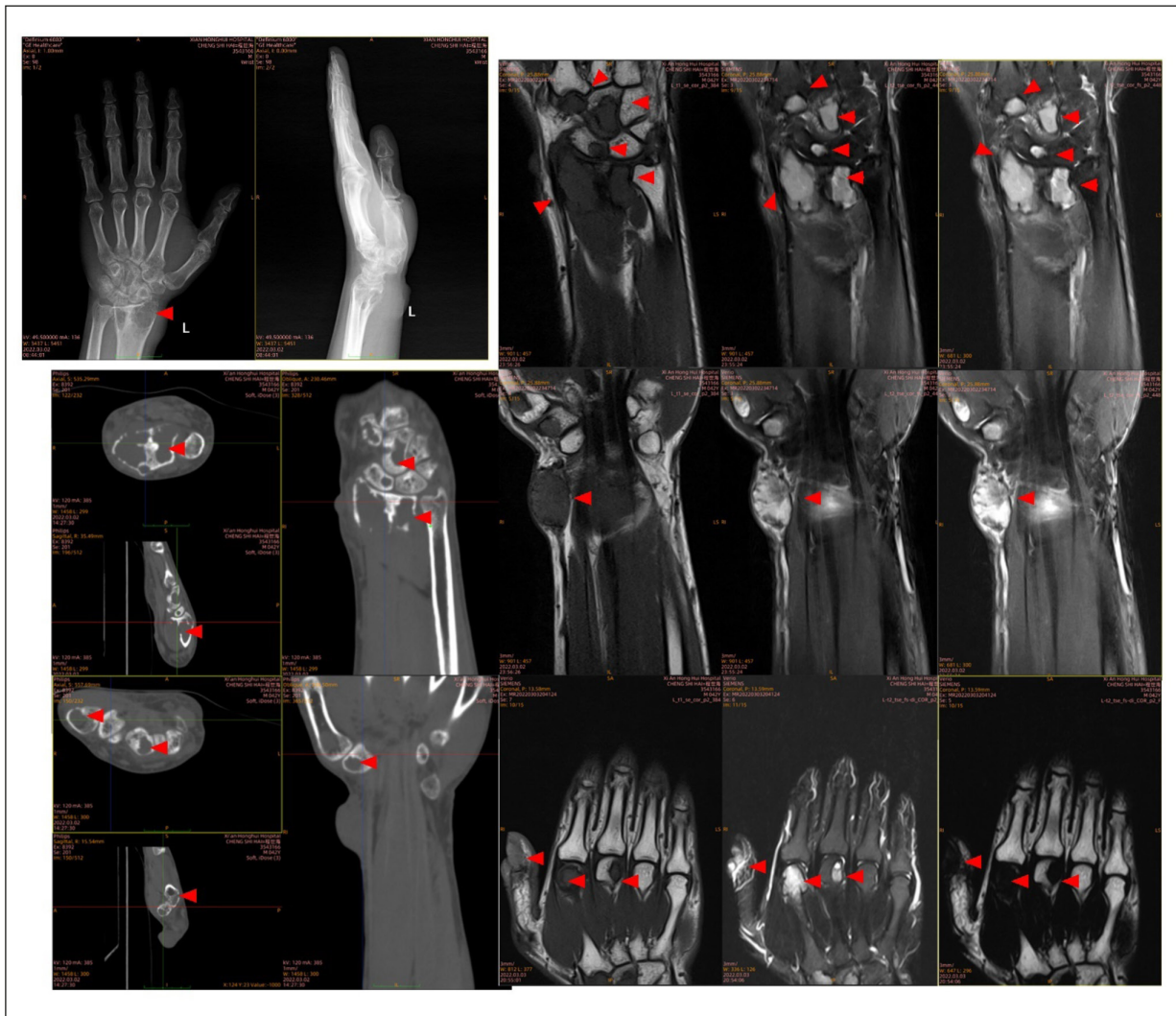


Figure 2. Preoperative X-ray, computed tomography (CT) and magnetic resonance imaging (MRI) (T1- and T2-weighted images, and fat-suppressed sequence) of the patient's left forearm. Osteolytic destruction and soft tissue mass were observed. In the T1-weighted image, the tumor presented equal or hypointensity signaling. In the T2-weighted image and fat-suppressed sequence, the mass clearly showed high signals. The red arrowheads marked bony lesions in X-ray, CT, and MRI, respectively.

was invaded. We resected the invaded nail bed and scraped the tumor in the phalange of the distal thumb. Afterward, all focuses were flushed out by hydrogen peroxide solution and 98% ethyl alcohol to inactivate tumor cells. Polymethylmethacrylate cement (PMMA) was shaped into the distal radius and filled the bone defect. Other bone defects were filled by allogeneic artificial bone (Figure 4).

Postoperatively, the patient only received nutrition support and infection prevention therapy, but not chemotherapy, radiotherapy, hormone therapy, sirolimus, or other treatments.

At three months postoperatively, tumors were observed on the nail bed's root in the first and second fingers, which showed similar MRI signals as previously observed (Figure 5). Therefore, postoperative KHE recurrence was considered as a result of missed diagnosis of microlesions. To avoid tumor recurrence, the first and second fingers beyond the intermediate interphalangeal joint were amputated. Amputated fingers underwent postoperative biopsy, which confirmed KHE diagnosis (Figure 6). Nutrition support and infection prevention therapy was continued, and recurrence

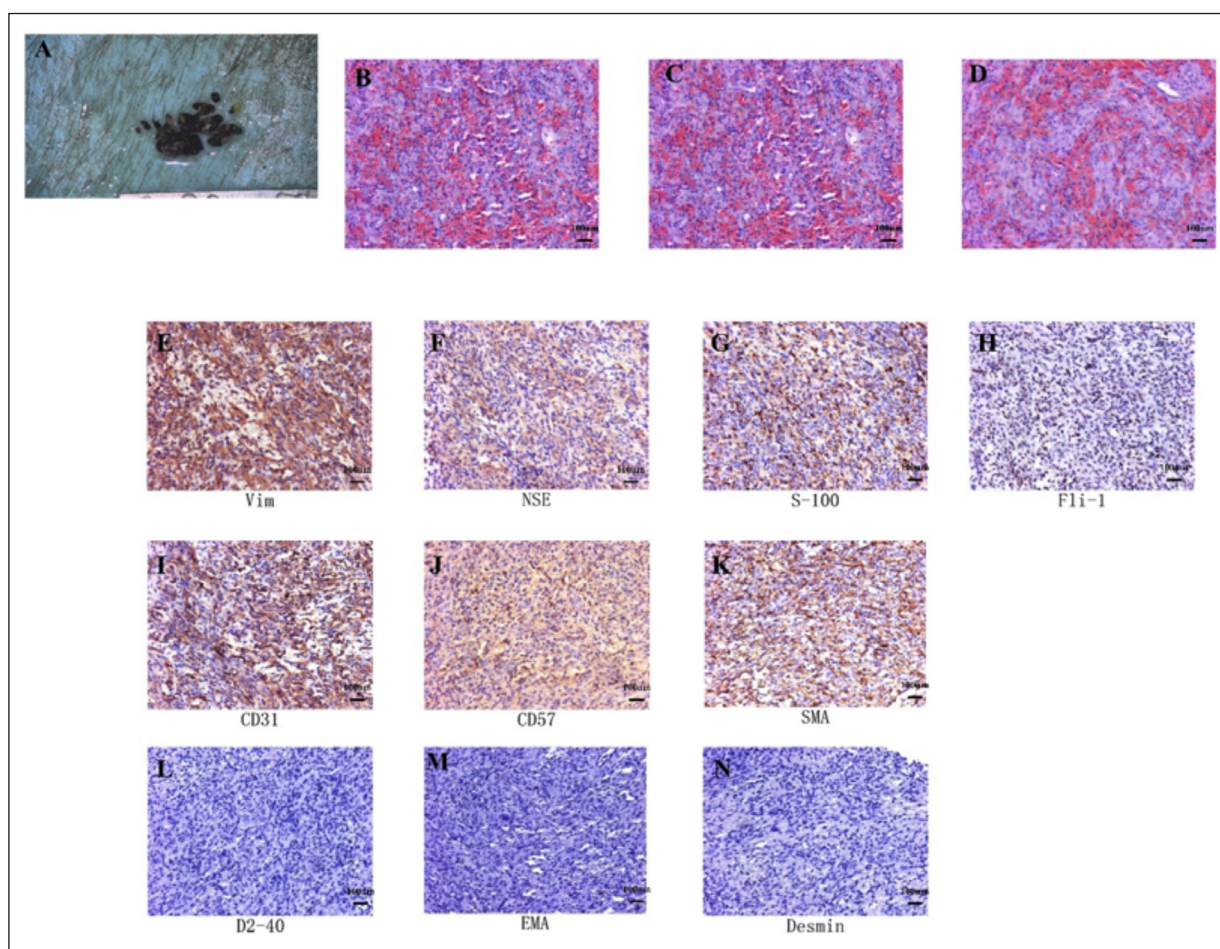


Figure 3. Puncture biopsy. **A**, Gross view of the organization. **B-D**, Hematoxylin-eosin staining of the lesions. Immunohistochemical positivity for *vimentin* (**E**), *neuron-specific enolase* (**F**), *S-100* (**G**), *flil-1* (**H**), *CD31* (**I**), *CD57* (**J**), and *smooth muscle actin* (**K**). Immunohistochemical negativity for *D2-40* (**L**), *epithelial membrane antigen* (**M**), and *desmin* (**N**). The magnification is 100x.

was not observed at the 6-month postoperative follow-up.

Discussion

To our best knowledge, this is the first report of a rare KHE case with multiple bony lesions in the forearm and hand (Table I). KHE always involves musculoskeletal tissues around the joint, which causes obvious pain and dysfunction due to its invasive and destructive growth⁹. Therefore, active treatment is required for KHE with skeletal involvement, even in the absence of KMP². In our case, the mass in the distal radius grew rapidly after 6 months with approximately 8 cm in

diameter, which might increase KMP risk⁷. Therefore, the patient should receive active therapy. There were four potential treatment methods: 1) complete excision (the most effective therapy)^{8,10}; 2) systemic treatment with prednisolone, vincristine, cyclophosphamide, aspirin, interferon- α 2b, and sirolimus; 3) systemic medication after excision; and 4) arterial embolization. Considering the uncertain effectiveness of systemic medication and possible excision postponement after arterial embolization, the patient refused treatment types 2 and 4^{2,11}. Therefore, we planned to perform a complete excision and postoperative systemic medication, as complete lesion resection was difficult. However, postoperative MRI and X-ray showed complete lesion

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Table I. Reports of Kaposiform hemangioendothelioma with bony lesions.

Authors	Year	Patient number	Age (years)	Gender	Lesion	Treatment	Surgery	Follow-up (years)	Function
Lalaji et al ¹⁴	2001	1	1	female	temporal bone	oral prednisone, vincristine	excision	NA	NA
Liu et al ¹⁵	2019	1	40	female	cervical spine (C4-C5)	oral thalidomide	excision	34 months	ANED
Bsisu et al ¹⁶	2019	1	9	female	left proximal tibial metaphysis, eccentric lateral distal tibial metaphyseal	vincristine	NA	NA	NA
Lisle et al ¹⁷	2009	1	6	female	Thoracic/lumbar spine (T10-L2)	thalidomide, celecoxib	No	8 months	ANED
Wang et al ¹⁸	2014	1	51	female	ilium	cyberknife	NA	2	NA
Alonso Arroyo et al ¹⁹	2017	2	7	male	ipsilateral scapula	prednisolone, vincristine, cyclophosphamide, aspirin, interferon-a2b	No	NA	ANED
Mac-Moune Lai et al ³	2001	5	4-month-old	female	right scapula	prednisolone, vincristine, interferon-a2b, ticlopidine, aspirin	No	6	Severe scoliosis
			5-month-old	male	distal radius and ulna	NA	amputation	16	ANED
			7-month-old	male	left subcostal skin, rectus muscle	NA	excision	14	ANED
			infant	female	proximal right thigh	interferon	No	8	ANED
			39	female	distal right humerus, proximal radius	NA	iliac bone graft, hydroxyapatite	35	ANED
Ma et al ²⁰	2011	2	23	male	entire left limb and buttock	interferon, Chinese herbal medicine	amputation	17	ANED
			9	female	right distal femur	NA	excision	15	recurrence
			5	male	right cortex and medulla of the proximal humerus	NA	wide local excision	5	ANED
Patel et al ²¹	2017	1	2	male	left scapula	sirolimus	excision	18 months	considerably smaller
Zhu et al ⁴	2011	1	14	female	thoracic spine (T8-T9)	NA	deformity correction and fusion	3	ANED
Birchler et al ¹⁰	2013	3	2	NA	femur	NA	NA	NA	NA
			4	NA	sacrum	NA	NA	NA	NA
			6	NA	vertebrae	NA	NA	NA	NA
Gruman et al ⁷	2005	1	2	female	left cheek, mandible	interferon alfa-2b, prednisone	Incomplete excision	7	Recurrence
DeFatta et al ²²	2005	1	3	male	hard palate	NA	Excision	1	ANED
Lyons et al ²³	2004	1	2	male	temporal bone	NA	Excision	4	ANED

ANED=alive with no evidence of disease, NA=not available, No = without surgery.

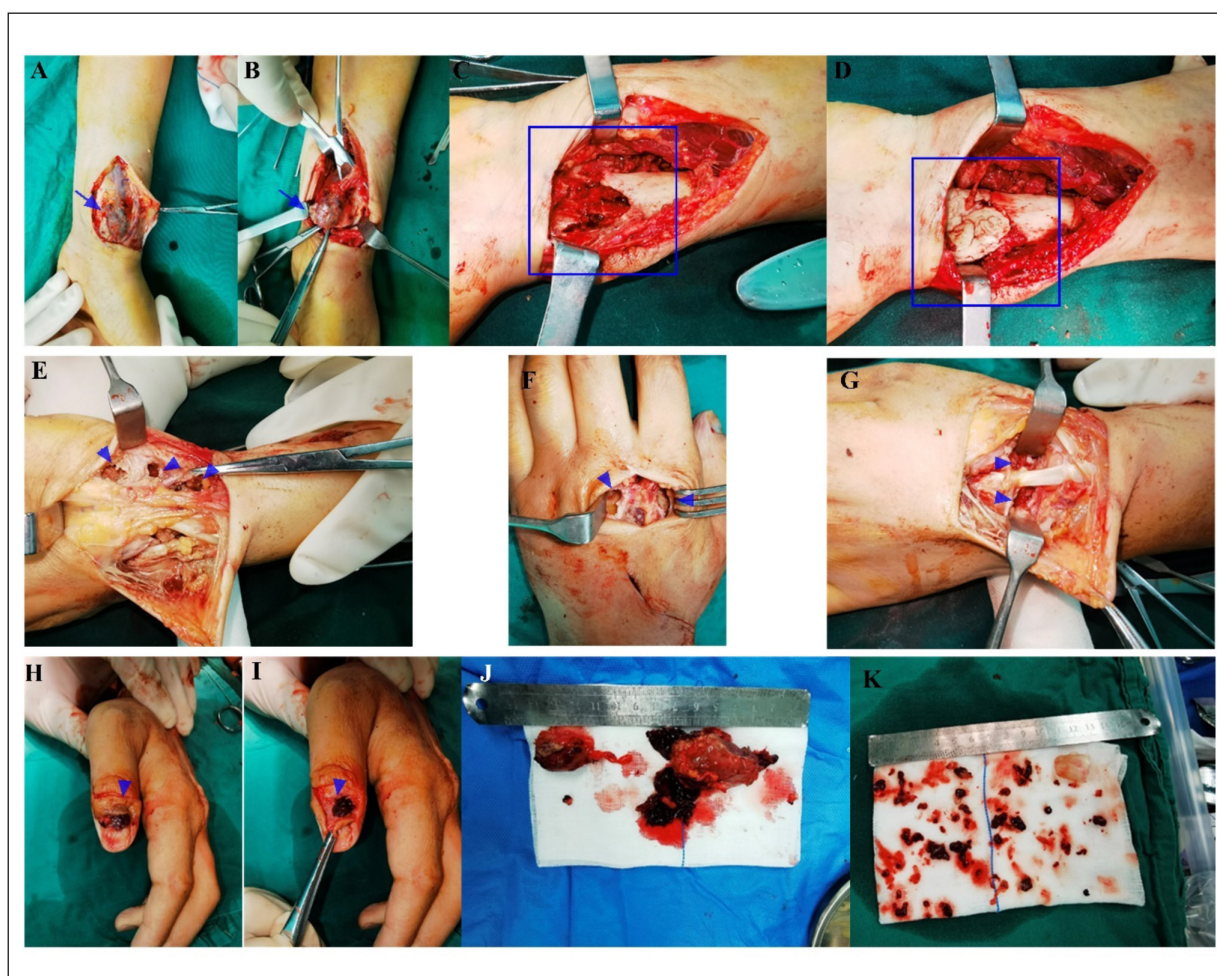


Figure 4. Excision records. **A**, The mass in the distal radius was exposed. **B**, Radial artery and concomitant veins penetrated into the mass. **C**, The wrist mass was removed. **D**, Bone defect was filled by molded polymethylmethacrylate cement. **E-G**, The mass in the lunate bone, scaphoid bone, trapezium bones, the first metacarpal bone, and second and third metacarpal heads were resected. **H-I**, Lesion of the phalange of the distal thumb was exposed. **J-K**, Gross masses were presented. The blue arrows showed the tumor in the radial bone. The blue square highlighted the bony defect (C), and which was filled with bone cement (D). The arrowheads presented a small bony lesion in the wrist joint and thumb.

removal with no abnormal signs (Figure 5), and we did not provide postoperative systemic medication for recurrence prevention. Unfortunately, KHE recurred at the nail root of the thumb, and a new focus was observed in the phalangette of the index finger. Kuo et al¹² reported that two bony KHE cases with gross total resection showed postoperative recurrence, while another with complete excision did not. Therefore, recurrence and new focus resulted from rapid residual lesion growth, triggered by the surgery². There are no current consensus regarding systemic medication for KHE⁹. Surgery and trauma can stimulate

rapid residual lesion growth or even KMP². While Kuo et al¹² reported positive clinical efficacy of isolated systemic medication after KHE recurrence, previous literature also noted that amputation was effective for KHE recurrence. Therefore, our patient underwent post-recurrence amputation, even if older age and superficial lesion might be negative KMP predictors^{2,11}. Generally, KHE is a single soft tissue mass⁷, and KHE with multiple bony lesions is extremely rare. Notably, multiple resectable lesions were found in the distal limb, for which complete resection might not present typical features (high-intensity

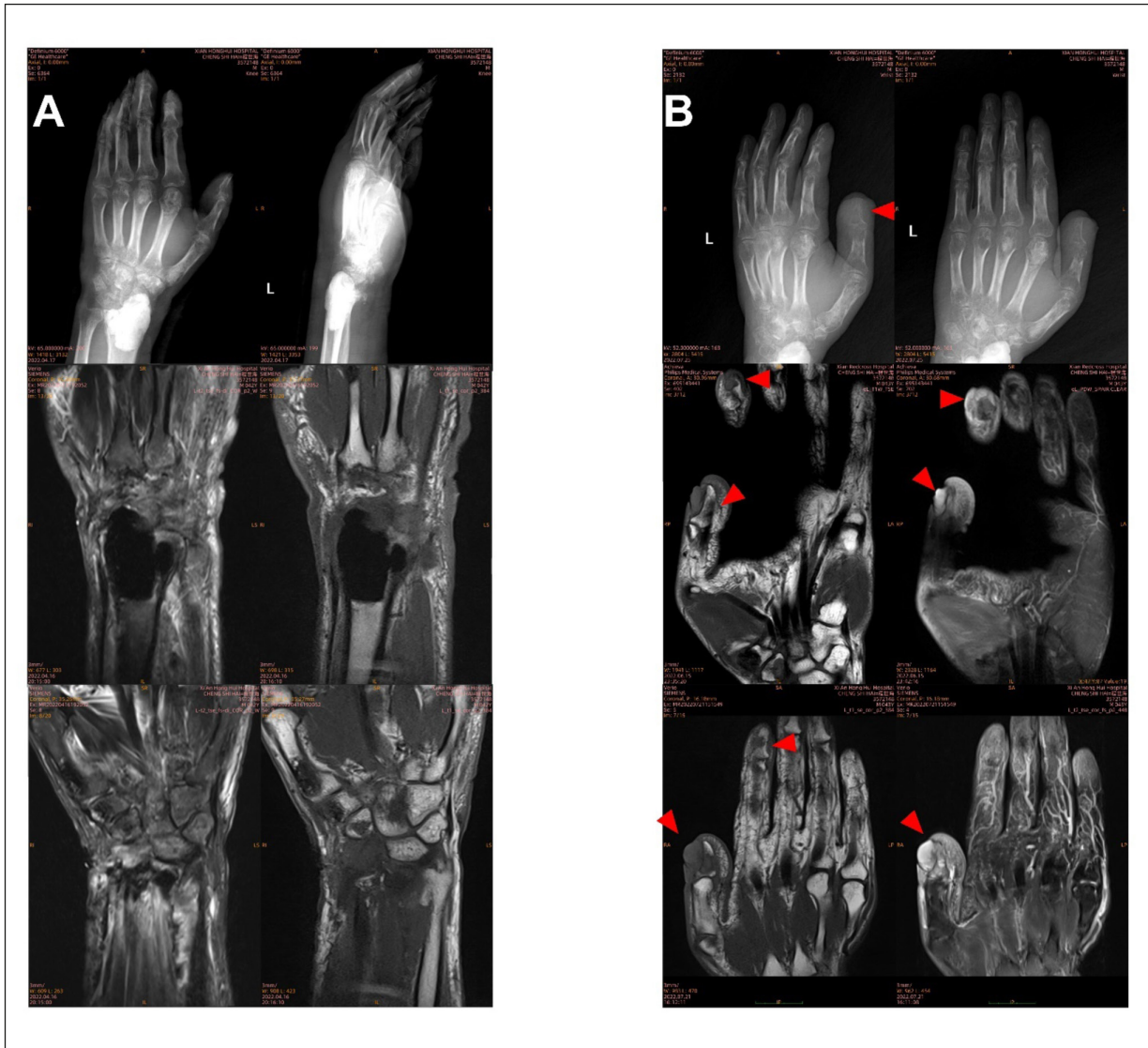


Figure 5. Postoperative X-ray and magnetic resonance imaging (MRI). **A**, X-ray and MRI at 3 months postoperatively. **B**, Osteolytic destruction was observed in the phalanges of the distal thumb and index finger by X-ray with equal or hypointense T1 signal and hyperintense T2 signal. The red arrowheads marked the tumor recurrence in the index finger and thumb.

T2-weighted MRI¹³), which might fail to detect all KHE lesions. Therefore, complete excision is not optimal for multiple resectable KHE lesions.

Limitations

Here we first reported a rare KHE case with multiple bony lesions in the forearm and hand, however, there were limitations in the research. First, we only reported one case with a short follow-up. The KHE recurrence or KMP may be observed with a longer follow-up. Second, the

patient refused systemic treatment and arterial embolization, which were reported as effective methods. Therefore, our work cannot evaluate the effectiveness of systemic therapy and arterial embolization for KHE with multiple bony lesions.

Conclusions

We first reported an adult KHE case with >10 bony lesions in the forearm and hand. The patient underwent complete KHE excision, which recurred at 3 months postoperatively.

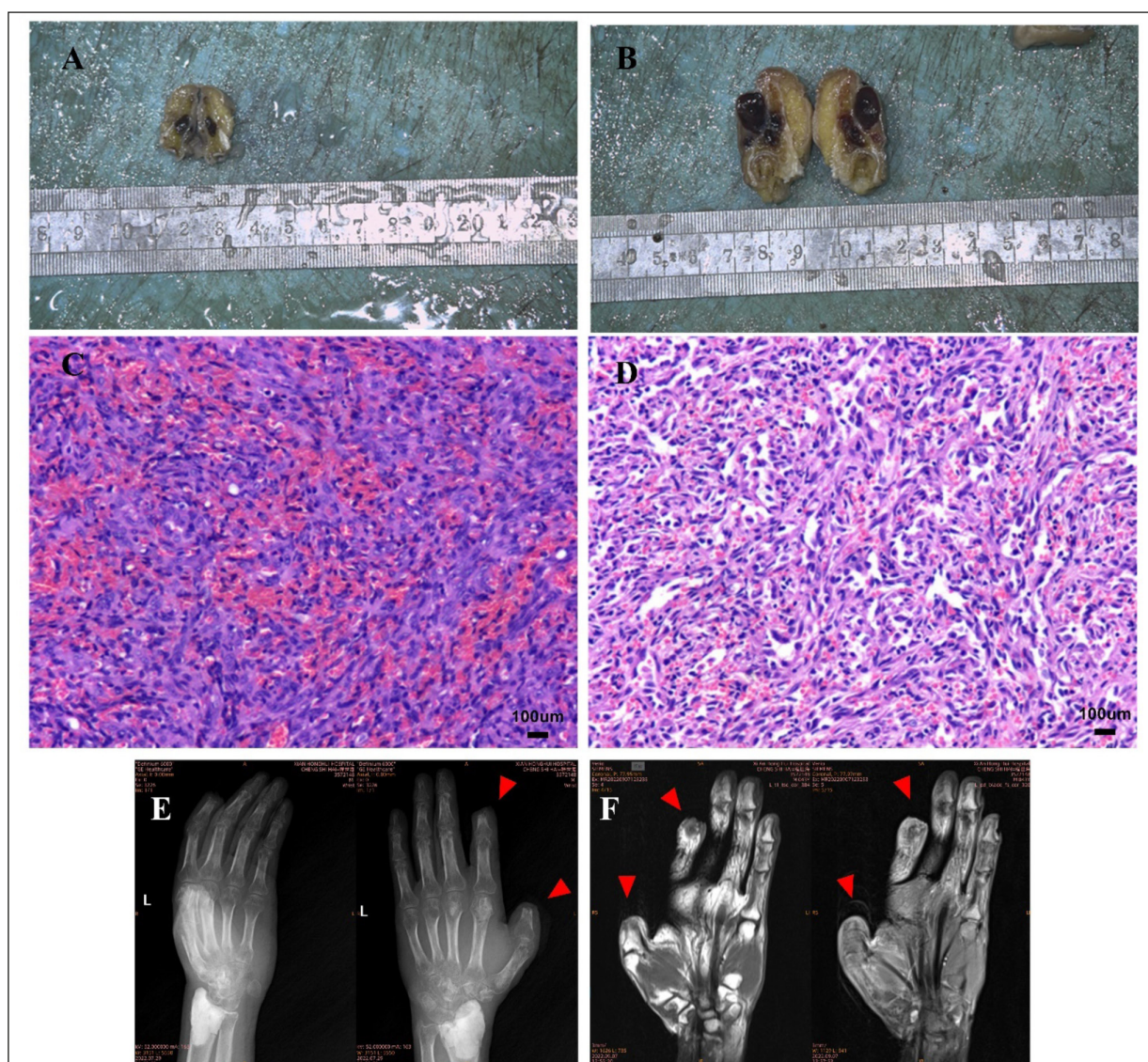


Figure 6. Biopsy and MRI after secondary operation. **A-B**, Gross view of the organisation. **C-D**, Hematoxylin-eosin staining of the masses. **E-F**, Post-amputation X-ray and magnetic resonance imaging (MRI) from the phalangettes of the thumb and index finger. Red arrowheads presented the absence of distal end of index finger and thumb. The magnification is 100x.

He was treated by amputation and was alive with no recurrence evidence at the six-month follow-up. During the entire treatment, the patient did not receive systemic therapy. Multiple resectable lesions were found in the distal limb, for which complete resection might not present typical features (high-intensity T2-weighted MRI), which might fail to detect all KHE lesions. Therefore, complete excision is not optimal for multiple resectable KHE lesions.

Informed Consent

The patient provided informed consent to publish the information/image(s) in an online open-access publication.

Conflict of Interest

All authors declare no relevant financial or non-financial interests and no conflicts of interest relevant to the article content.

Data Availability

Data are available upon reasonable request from corresponding authors.

Authors' Contributions

Jian Xing performed the study and draft the manuscript. Nan Zhang and Bo Chen help with manuscript drafting. Zhichao Tong helped to summarize previous literature. Jian Xing and Haizhen Zhou designed the study. All authors read and approved the final manuscript.

Ethics Approval

All study procedures involving human participants followed the ethical standards of the institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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