



# Sirolimus for treatment of kaposiform hemangioendothelioma associated with Kasabach-Merritt phenomenon

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## INTRODUCTION

Kaposiform hemangioendothelioma (KHE) was first described by Zuckerberg et al in 1992.<sup>1</sup> KHE is defined as a rare, locally aggressive infiltrative vascular neoplasm that typically occurs during infancy and childhood. KHE generally originates on the skin as a distinctive cutaneous lesion with ill-defined borders, later affecting deeper tissue by infiltrative growth.<sup>1,2</sup> This lesion occurs most commonly over the extremities and other sites such as the head, neck, trunk, and retroperitoneal or thoracic cavity.<sup>3,4</sup> According to a previous case series at a large referral center, the incidence of KHE is estimated at 0.07 per 100,000 children per year.<sup>2</sup>

KHE is commonly associated with Kasabach-Merritt phenomenon (KMP). KMP is triggered by intralesional platelet trapping within a vascular tumor leading to profound thrombocytopenia and consumptive coagulopathy.<sup>4-6</sup> KHE is associated with a relatively high mortality rate (around 30%). However, deaths are almost always related to local invasion and compression of vital structures or are a result of KMP.<sup>1,3</sup>

To date, it is particularly challenging to treat KHE complicated by KMP, as no controlled trials have been conducted to describe variable responses of the therapeutic options for this relatively rare neoplasm. According to the consensus-derived practice standards plan for complicated KHE published in 2013

### Abbreviations used:

KHE: kaposiform hemangioendothelioma  
KMP: Kasabach-Merritt phenomenon

there are several treatment modalities for KHE complicated by KMP, such as corticosteroids, vincristine, intravascular embolization, and surgery. These treatments are described with variable responses and many side effects.<sup>7</sup> Recently, sirolimus, a mammalian target of rapamycin inhibitor, was reported to be effective and safe and seems to be a promising agent in treating patients with life-threatening refractory KHE.<sup>4,6,8</sup>

We report for the first time, to our knowledge in the Middle East, a successful outcome using oral sirolimus to treat refractory KHE complicated with KMP in a neonate who did not respond to multiple medical therapies.

## CASE REPORT

Three-month-old female twins were delivered at full term by cesarean section. Twin A (birth weight, 3.8 kg) was referred to our hospital on November 3, 2013 for further workup; she had a large vascular anomaly over the right side of the face with respiratory distress. Twin B was healthy and medically free with an unremarkable postnatal

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**Fig 1.** Kaposiform hemangioendothelioma. A huge mass involving right side of the face, almost obscuring the right eye, with extension to the upper chest before sirolimus therapy.

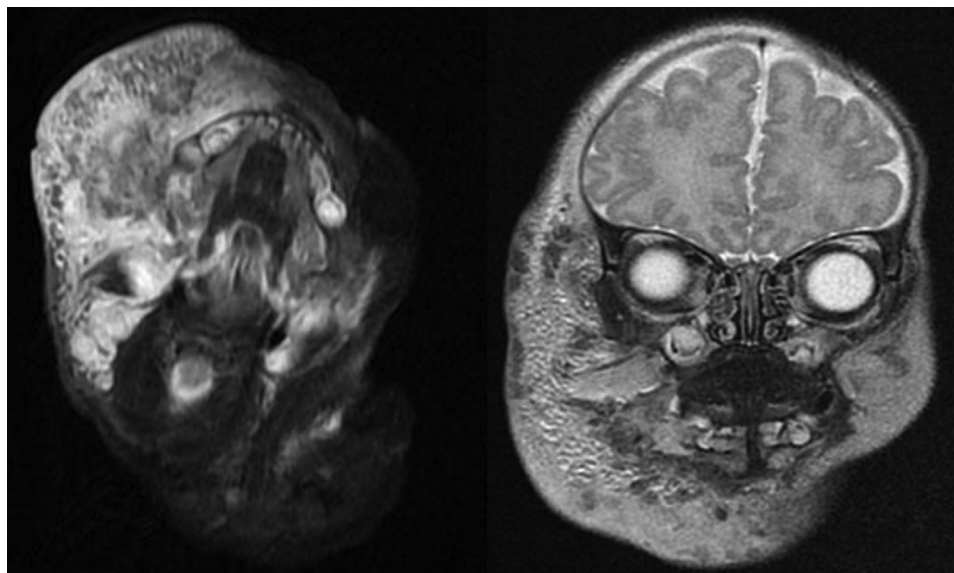
period. On admission, the baby was in respiratory distress with altered level of consciousness. Initial examination found a large vascular tumor involving the right side of the face, almost obscuring the right eye, with extension to the upper chest, disfiguring facial symmetry, and an area of ulceration over the chin (Fig 1). The swelling had a firm deep reddish component over the cheek with no other vascular tumor visible on the skin. The patient had been admitted previously to a local hospital with a diagnosis of infantile hemangioma with KMP treated with prednisolone (3.2 mg/kg) and propranolol (2 mg/kg/day) 3 times per day without any effect. Subsequently, she was transferred to our hospital. Her hemoglobin level was 11.8 g/dL, platelet count was  $13 \times 10^3/\mu\text{L}$ , and fibrinogen level was 153 mg/dL. Prothrombin time was 15.2 seconds, partial thromboplastin time was 39.6 seconds, and international normalized ratio was 1.2.

Magnetic resonance imaging (MRI) found a large vascular tumor occupying the right scalp; it was minimally crossing the midline posteriorly. There was significant involvement of the soft tissue of the right side of the neck, the right posterolateral side of the neck, the right periorbital area, the right masticator space, the right carotid space, the right parapharyngeal space, and along the right carotid sheath. The evaluation of the pharynx and larynx was limited on this examination because of the incomplete fat suppression; there was suggestion of involvement in the submental region and midline soft tissue of the neck. There was no cerebellar tonsillar herniation. Pituitary gland was normal. The corpus callosum was present. Myelination was present in the posterior limb of the internal capsule

and brainstem. Ventricles were of normal size. No intracranial abnormality was seen, and there was no intracranial involvement. No intracranial abnormality was noted (Fig 2).

MRI and laboratory investigations strongly suggested the diagnosis of KHE with KMP. Biopsy of the tumor was not attempted because of the potential risk for hemorrhage. After the diagnosis, we began treating the patient by adjusting the dose of propranolol to 2 mg/kg/day divided into 3 equal doses and increased prednisone to 3.5 mg/kg with no response. Within 2 weeks, we started the patient on vincristine, 5 doses per week for 2 months. Interferon alfa-26 was added and stopped after 4 days because of fever and shortness of breath. However, the patient did not show any response; either in the size of the tumor or improvement in the platelet count. Two more cycles of vincristine with aspirin and clopidogrel were tried unsuccessfully.

Because the patient was not responding to conventional therapy (platelet count,  $45 \times 10^3/\mu\text{L}$ ), a trial of sirolimus was warranted on February 15, 2014 on a compassionate basis. The risks and benefits were explained to the family, and their consent was obtained. Conventional therapy with steroids was still ongoing then tapered slowly. The patient was treated with the liquid formulation of oral sirolimus for ease of titration. Initial dose was  $0.8 \text{ mg/m}^2$ , administered twice daily at approximately 12-hour intervals. Subsequently, the administration route was changed temporarily to gastric tube because of the massive swelling of the mass, and dosing adjustments were made to optimize the drug level to 7 to 10 ng/mL. Pneumocystis



**Fig 2.** MRI with fat suppression before sirolimus therapy showed extensive bright areas involving the right side of the face, from skin almost reaching the airways.

prophylaxis with cotrimoxazole was also started for the potential risk of immunosuppression. Her platelet count improved initially then it decreased again, but at the time of discharge, it was back to normal.

During her hospital stay, the patient underwent several procedures, including port-A-catheter insertion to receive intravenous medication. She then had a gastrostomy tube inserted because she could not tolerate oral feeding because of the size of the tumor. She was discharged in good condition and continued on 0.8 mg/m<sup>2</sup> of sirolimus per dose twice daily.

After 2 months of sirolimus therapy, the patient was doing well with a normal platelet count. Currently she remains on sirolimus, and there is no recurrence of thrombocytopenia or further growth of the mass after 18 months of follow-up (Fig 3). Coronal and axial T2 MRI with fat suppression showed remarkable 90% to 95% reduction of the bright T2 signal with few residual areas of high signal in the skin and deeper tissue. Axial T1 postcontrast imaging at the level of the upper teeth showed parallel 95% reduction of the volume of the enhancing tissue favoring excellent response to sirolimus (Fig 4). The patient has experienced no toxicity from sirolimus.

## DISCUSSION

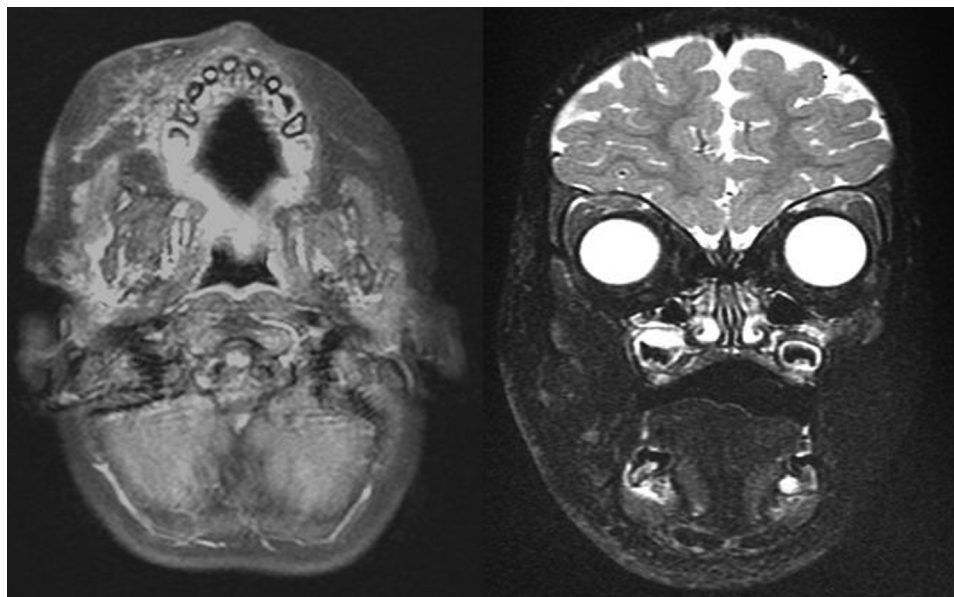
KHE is a rare, locally aggressive vascular neoplasm characterized as a rapidly growing bluish-red, nodular, irregular lesion.<sup>1,9</sup> Therefore, most of the literature dealing with these lesions consists of case reports.



**Fig 3.** After 15 months of sirolimus therapy.

Management of KHE complicated by KMP, a profound thrombocytopenia resulting from intraleisional platelet trapping, is particularly difficult and challenging, as it shows a wide variation and unpredictable response to different treatment modalities.<sup>2</sup> To date, no standard treatment guidelines exist for KHE complicated by KMP because of their rare nature and lack of prospective trials. Therefore, researchers are still working on new methods and strategies to control the life-threatening complications with minimal side effects.<sup>8</sup>

Theoretically, surgical extraction is the definitive treatment, as it will normalize coagulopathy promptly, but most lesions are unresectable because



**Fig 4.** MRI with fat suppression after 15 months of sirolimus therapy showed a remarkable 90% to 95% reduction of the volume of the enhancing tissue with few residual areas of high signal in the skin and deeper tissue.

of location, size, or tissue infiltration. Additionally there is the probability of bleeding profusely and thrombocytopenia contributing to systemic bleeding. Therefore, surgery is unfeasible in most cases. Vascular embolization or sclerotherapy are minimized by the hardship of cannulating small feeder vessels and the serious complications, including pulmonary embolism and acute kidney failure.<sup>9</sup> Radiotherapy has been used successfully, but its use is limited by the risk of growth delay and the secondary malignancies in later childhood.<sup>8,10</sup>

Several pharmacologic treatments are reported in the literature, including high doses of systemic corticosteroids. Many clinicians used to consider this treatment as the initial treatment of choice despite the low response rate and significant side effects, including hypertension, growth limitation, cushingoid appearance, osteoporosis, opportunistic infections, and psychological changes. Propranolol is also used as an adjuvant therapy with systemic corticosteroids in treating KHE associated with KMP. However, the literature reports that it is ineffective to be used alone.<sup>4,6</sup>

Recently, vincristine, by blocking the formation of microtubules in cells, has been reported in the literature to improve KHE complicated by KMP once corticosteroid treatment has been proven insufficient. Vincristine seems to be well tolerated and has a good response in the severe cases; therefore, it can be combined with other medications for unresponsive cases. On the other hand, vincristine has many hematologic and neurologic

complications such as myelosuppression, peripheral mixed sensory and motor neuropathy, abdominal pain, and irritability.<sup>6,11</sup> However, in our case, both steroid and vincristine treatment failed.

The use of interferon in infants has been limited by the significant potential long-term neurologic side effects such as spastic diplegia.<sup>5</sup> The literature describes a variable response to propranolol therapy for the treatment of KHE.<sup>6</sup>

Our patient seemed to be in serious condition and near death after not responding to several treatment modalities.<sup>10</sup> Sirolimus is a macrocyclic triene antibiotic produced by *Streptomyces hygroscopicus*, a streptomycete isolated from a soil sample collected from Easter Island (Rapa Nui). Although sirolimus is a potent antifungal agent, several studies found that sirolimus is a serine/threonine kinase regulated by phosphoinositide 3-kinase and acts as a master switch of numerous cellular processes, including cell growth and angiogenesis; it has a potent antitumor and immunosuppressive activity.<sup>12,13</sup>

Sirolimus is found to be efficacious with a safe profile that has temporary and acceptable side effects in some patients with life-threatening KHE. Evidence of success in using sirolimus is accumulating, representing a promising tool in treating refractory KHE.<sup>4,8</sup>

Sirolimus was initially administered in a young patient with a KHE with KMP in 2007. This patient had significant response to sirolimus treatment and rapid improvement in platelet count and fibrinogen level after failure of all standard treatment

algorithms.<sup>14</sup> In the last few years, multiple studies, including case reports and retrospective case series, have been reported using sirolimus for treatment of different vascular anomalies with positive results.<sup>4,12,15-22</sup> A 2011 study on 6 patients found that sirolimus is a reasonable treatment for children and young adults with complicated vascular anomalies, even when they have proven refractory to several other treatments.<sup>23</sup> The most recent study published regarding sirolimus treatment in a KHE patient was done by Denise Adams and colleagues in February 2016.<sup>22</sup>

KHE is a rare challenging vascular tumor of childhood that might have a potentially devastating clinical presentation. To our knowledge, our case represents the first case in the Middle East to show the efficacy of sirolimus in treating life-threatening KHE associated with KMP. We conclude that sirolimus is a promising agent that is safe and effective in treating KHE with KMP refractory to other treatment modalities and is recommended as a frontline treatment. Our experience shows that sirolimus is superior to vincristine and other modalities in the treatment of life-threatening KHE.

More trials with sirolimus in the treatment of KHE are required before it can be set as the first-line therapy. The goal of this study is to encourage the development of further multicenter prospective trials to determine the effectiveness of different therapeutic agents to reach the proper guidelines for treating patients with potentially life-threatening KHE.

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