Cocktail therapy with prednisolone, vincristine and sirolimus for Kasabach-Merritt phenomenon in 10 infants

QIANLONG LIU[1], NA XIONG[1], XINYUAN GONG[2], HAOCHONGYANG TONG[1], XUANFENG TAN[3] and XINKUI GUO[1]

[1]Department of Pediatric Surgery, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi 710004; [2]Department of Science and Education, Tianjin First Central Hospital, Tianjin 300192; [3]Department of Dermatology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi 710004, P.R. China

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Abstract. Kasabach-Merritt phenomenon (KMP) is a life-threatening condition caused by rare vascular tumors. To reduce drug resistance observed in monotherapy of KMP with prednisone, vincristine (VCR) or sirolimus, the present study evaluated the efficacy and safety of triad therapy in the treatment of KMP. A total of 10 KMP infants managed with prednisolone, VCR and sirolimus in The Second Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China) between April 2017 and August 2021 were retrospectively reviewed. The three female and seven male infants with KMP underwent cocktail therapy with prednisone, VCR and sirolimus. At diagnosis, the infants, aged 49.1±41.0 days, showed laboratory test results with platelet counts 22±15.4x10^9/l, fibrinogen 81.7±26.9 mg/dl and D-dimer 38649±13443.6 ng/ml. The average maximal diameter of the tumors at diagnosis was 84.5±25.1 mm. KMP risk is increased by large tumors with deep lesions infiltrating the muscle. Platelet counts normalized after a median 10 days (range, 5-69 days) of treatment. With combination therapy maintained for 46.8±24.4 days, ultrasound showed that the thickness of the tumors decreased by 51% from 28.9±12.1 to 13.9±6.2 mm. Neutropenia and gastrointestinal disorders were the most common adverse effects. The present study found that the cocktail therapy with prednisolone, VCR and sirolimus has favorable tolerance and efficacy for life-threatening KMP. Once a stable condition has been achieved, cocktail therapy should be replaced by sirolimus monotherapy to reduce potential side effects.

Correspondence to: Professor Xinkui Guo, Department of Pediatric Surgery, The Second Affiliated Hospital of Xi'an Jiaotong University, 157 Xiwu Road, Xi'an, Shaanxi 710004, P.R. China
E-mail: guoxinkui66@126.com

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Introduction

Kaposiform hemangioendothelioma (KHE) is a rare vascular tumor with an incidence of less than 1 in 100,000 (1,2), but Kasabach-Merritt phenomenon (KMP), which often develops secondary to KHE, has a high infants mortality rate of 10-30% (3). KMP, mostly associated with KHE and less frequently tufted angioma (TA), is characterized by profound thrombocytopenia and hypofibrinogenemia (1). Originally designated as Kasabach-Merritt syndrome, as described by Kasabach and Merritt in 1940 in the case of an infant with a 'giant hemangioma' with severe coagulopathy (1,4), deeper identification has led to it being described as Kasabach-Merritt phenomenon since 1997 (1,4).

There has been no unified treatment strategy for KMP to date. Treatments including systemic drug application, local compression, intraluminal intervention and surgical resection have been used (4). A consensus statement published by Drolet *et al* (5) in 2013, recommended medical treatment including corticosteroids and/or vincristine (VCR) for KHE. Recently, increasing evidence has suggested that sirolimus is a promising treatment for refractory KHE (6-8). Combination therapy with two of drugs such as corticosteroid plus VCR or corticosteroid plus sirolimus is usually applied in the clinical practice (1). However, drugs resistance has led to KMP patients being in critical conditions for longer time periods (7-10). Results from cocktail therapy used for acquired immunodeficiency syndrome (11) and triad therapy for KHE (12,13) suggest that cocktail therapy with prednisolone, VCR and sirolimus may be a more efficient treatment for KMP and may help to avoid prednisolone, VCR, or sirolimus resistance and accelerate the improvement of coagulopathy, thereby reducing KMP infant mortality. The present study evaluated the efficacy of the triad combination of prednisolone, VCR and sirolimus as cocktail therapy of life-threatening KMP in 10 infant patients.

Patients and methods

Patients. KMP is defined as KHE/TA with profound thrombocytopenia (thrombocytes<50x10^9/l), hypofibrinogen (fibrinogen<1.5 g/l) and elevated D-dimer. A total of 10 KMP

patients managed with cocktail therapy at The Second Affiliated Hospital of Xi'an Jiaotong University between April, 2017 and August, 2021 were retrospectively reviewed; five KMP patients with monotherapy or duplex therapy were excluded. A total of three female and seven male infants, with mean age at diagnosis of 49.1±41.0 days (range, 13-122 days), were included (Table I). Of the 10, three infants were diagnosed by puncture biopsy before KMP presented. Unfortunately, one of them was misdiagnosed with congenital hemangioma and treatment was postponed. During this time, the tumor enlarged and hardened rapidly with associated severe coagulopathy and KHE was confirmed by pathology consultation. The other seven patients were clinically diagnosed with KMP on the basis of the combination of KHE characteristics (Figs. 1 and 2) and hematologic abnormalities.

Treatment regimen. In the cocktail regimen, sirolimus was initiated at 0.05 mg/kg/12 h, prednisolone at 2 mg/kg/day and VCR at 0.05 mg/kg/week. The clinical data were collected from electronic medical records of The Second Affiliated Hospital of Xi'an Jiaotong University. Prednisolone was tapered after platelet counts returned to the normal range (100-300x10^9/l) for ≥7 days. A total of four cycles of VCR were usually recommended, followed by monotherapy with sirolimus. Sirolimus monotherapy was used for maintenance treatment because of increasing evidence of its efficacy in the management of KHE (6,10). The use of the triad combination of prednisolone, VCR and sirolimus as cocktail therapy was approved by The Medical Ethics Committee of The Second Affiliated Hospital of Xi'an Jiaotong University (approval number: 2022204). Informed consent was obtained from the parents.

Statistical methods. Normally distributed continuous variables were expressed as mean ± standard deviation. The tendency of platelet count, fibrinogen and D-dimer during the combination therapy were analyzed by ANOVA with polynomial linear trend test. Thickness of tumor before and after treatment were analyzed using paired t-test. Data analysis was performed using GraphPad Prism 7 (GraphPad Software, Inc.). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Variables before treatment. At KMP diagnosis, the mean platelet count was 22±15.4x10^9/l (range, 5-54x10^9/l), mean fibrinogen was 81.7±26.9 mg/dl (range, 55-137 mg/dl) and D-dimer was 38,649±13,443.6 ng/ml (range, 16,940-60,530 ng/ml) (Table II). Tumors had infiltrated the muscle in 10 patients according to the ultrasound (US) or magnetic resonance imaging (MRI). When US and MRI were performed simultaneously at KMP diagnosis, MRI results were preferred.

Treatment and efficacy. Anti-tumor treatment was initiated with cocktail therapy including sirolimus (0.05 mg/kg/12 h), VCR (0.05 mg/kg/wk) and prednisolone (2 mg/kg/d) in all 10 KMP patients. The sirolimus dose was subsequently modified to reach the target blood level of 10-15 ng/ml (14,15). Cotrimoxazole or metronidazole was administrated orally to prevent concurrent pneumocystis, which is a potential risk of immunosuppression. When platelet counts exceeded 100x10^9/l for ≥7 days, prednisolone was tapered off. Prednisolone was used for an average of 39.6±19.6 days (range, 24-84 days). A mean of 3.7 cycles of VCR (range, 2-7 cycles) was used in the cocktail therapy. Of the 10, four patients were only administrated two cycles of VCR, three of whom had received previous VCR treatment. The parents of the fourth patient (case number eight) declined the additional two VCR cycles because they were concerned about the adverse effects of chemotherapy. In this case, platelet counts decreased below 100x10^9/l and the tumor hardened again once prednisolone was tapered. Prednisolone was therefore required at the initial dose (2 mg/kg/d) until KHE reached a stable condition on treatment day 65. Finally, sirolimus monotherapy was administered as maintenance therapy for KHE in all patients. Where necessary, KMP was treated throughout with supportive treatments, including blood product transfusion (Table I), to improve coagulation and anemia. Of the 10, eight patients received blood product transfusion, including platelet (n=3) because of potential risk of bleeding; suspension red blood cell (n=6) because of severe anemia; fresh frozen plasma (n=5), cryoprecipitate (n=2) and human fibrinogen (n=3) due to severe hypofibrinogen.

Visibly improved appearance in response to treatment offered confidence for the parents but still posed difficult quantification criteria (Fig. 1). During cocktail therapy, platelet counts were very low (mean 16.6±12.6x10^9/l, range 3-39x10^9/l) and required a median of 10 days (range, 5-69 days) to exceed 100x10^9/l (Table II). The tendency of platelet count, fibrinogen and D-dimer are shown in Fig. 3 and significant improvement of platelet count ($P<0.001$), fibrinogen ($P=0.001$) and D-dimer ($P=0.02$) were analyzed ($P<0.05$) by ANOVA trend test analysis during combination therapy. KMP in all 10 patients was completely resolved after combination therapy with mean duration of 46.8±24.4 days (range, 27-92 days) and did not recur in the subsequent monotherapy stage. US and/or MRI imaging indicated, maximal tumor diameter of 84.5±25.1 mm (range, 44-120 mm) at initiation of treatment. US imaging showed significant ($P<0.01$) reduction of thickness from 29±11.5 mm at diagnosis to 13.9±5.5 mm after combination therapy. Sirolimus was only discontinued after a stable condition was maintained and no significant reduction in tumor size was observed over three months. At the time of writing, only three patients were still receiving sirolimus treatment. No recurrence or severe adverse effects were observed during sirolimus monotherapy.

Safety and tolerance. During cocktail therapy, eight of the 10 patients suffered from adverse effects including neutropenia (n=7); gastrointestinal disorders such as vomiting (n=4), diarrhea (n=4), anorexia (n=1) and oral mucositis (n=1); leukopenia (n=1); pneumonia (n=1); and upper respiratory tract infection (n=1).

Adverse effects were evaluated in accordance with the Common Terminology Criteria for Adverse Events version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf). At the end of cocktail therapy, case three presented with grade 4 pneumonia, had to discontinue sirolimus and required transfer to the intensive care unit for assisted mechanical ventilation. Once the complications improved, sirolimus was reintroduced because of a significantly decreased platelet count. Grade 3 neutropenia was observed in three patients, but all neutropenia cases were rapidly improved by recombinant human granulocyte colony stimulating factor and did not recur after VCR cessation. Other

Table I. Demographic and clinical data of patients.

No	Sex	Age at diagnosis (days)	Confirmed diagnosis	Lesion location	Blood product transfusion	Previous treatment
1	Male	20	Clinically	Neck	No	No
2	Male	34	Clinically	Neck	RBC/FFP/PLT	No
3	Female	63	Clinically	Left upper arm	RBC/PLT	No
4	Male	13	Clinically	Right thigh and knee	No	VCR
5	Male	122	Clinically	Left axilla	RBC/FFP/FIG	Pro+CS+VCR
6	Male	42	Biopsy	Temple	RBC/PLT/ALB	No
7	Female	31	Clinically	Occiput	RBC/FFP	CS+VCR
8	Male	29	Biopsy	Right thigh	Cryoprecipitate/RBC/FIG/FFP	No
9	Female	15	Clinically	Abdominal wall	Cryoprecipitate	Pro
10	Male	122	Biopsy	Right axilla	FIG/FFP	No

ALB, albumin; CS, corticosteroid; FFP, fresh frozen plasma; FIG, human fibrinogen; PLT, platelet; Pro, Propranolol; RBC, red blood cell; VCR, vincristine.

Table II. Variables during the combination therapy.

	Platelet ($x10^9$/l)			Coagulation results at diagnosis			Thickness (mm)[b]		
No	At diagnosis	At the minimum	Time to rise to normal (days)	Fibrinogen (mg/dl)	D-dimer (ng/ml)	Maximal diameter of tumor (mm)	At diagnosis	After combination therapy	Duration of combination therapy (days)
1	39	34	10	102	16,940	44	24	9	92
2	27	27	12	67	46,580	87	-	12	42
3	5	4	37	86	26,390	68	21	13	30
4	17	17	8	103	36,430	92	32	15	29
5	10	10	6	55	22,070	84	23	10	27
6	14	3	69	66	38,770	63	28	15	84
7	29	11	17	137	47,940	64	24	15	31
8	17	13	11	57	60,530	105	57	28	65
9	8	8	7	55	43,760	120	19	9.1	35
10	54	39	5	89	47,080	118	33	13	33
M±SD	22±15.4	16.6±12.6	10 (5-69)[a]	81.7±26.9	38649±13443.6	84.5±25.1	29±11.5	13.9±5.5	46.8±24.4

M, mean; SD, standard deviation; [a]represents the median value with the range; [b]represents that thickness of tumor shrank significantly following combination therapy (P=0.0001).

adverse events were evaluated as grade 1 or 2 and improved with appropriate treatment. Overall, although some severe side effects were observed, all 10 patients tolerated the cocktail therapy and showed a significant response. During the subsequent sirolimus monotherapy, only mild oral mucositis and repeated upper respiratory tract infection were reported in two patients.

Discussion

KMP caused by KHE is a very rare but life-threatening disorder. Therapy used for KMP management primarily includes corticosteroids, VCR, sirolimus, ticlopidine, interferon-α and propranolol (1,4). However, only corticosteroids, VCR and/or sirolimus are recommended for KMP (1). Corticosteroids, such as prednisolone, reduce abnormal endothelial cell proliferation and the inflammatory response (4) with rapid effect (1,9). VCR, an anticancer agent, markedly promotes apoptosis of vascular endothelial cells and tumor cells (4). Sirolimus is a mammalian target of rapamycin inhibitor that enhances apoptosis and inhibits angiogenesis (4). Drug responsiveness of emergent KMP cannot be accurately predicted. These different mechanisms of anti-tumor action and reduced likelihood of

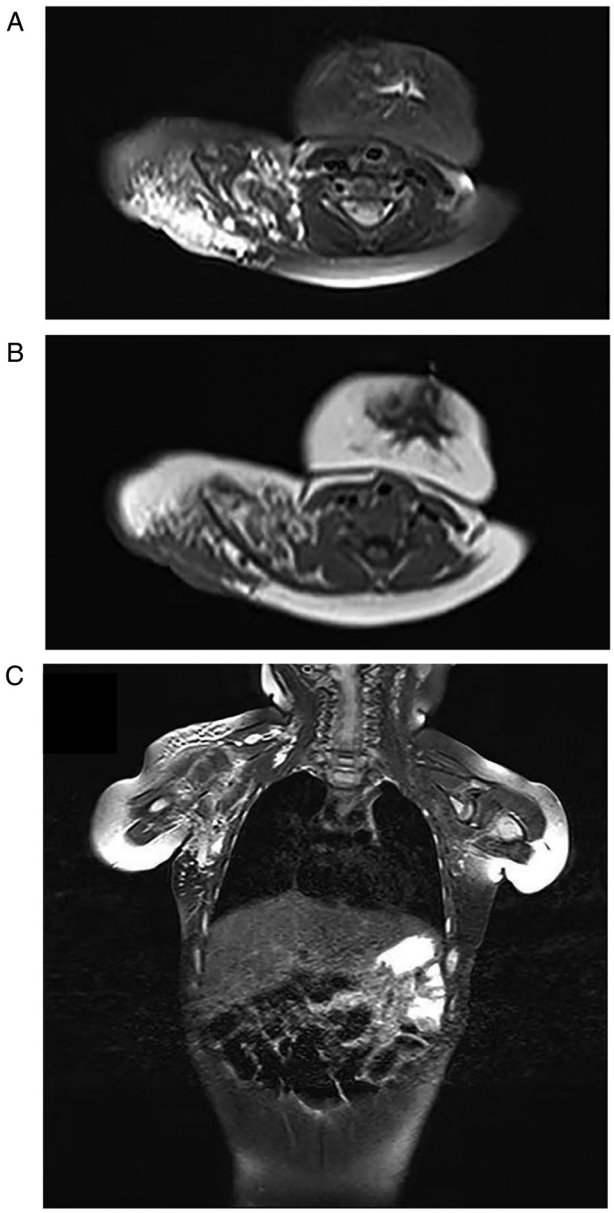

Figure 1. KHE with diffuse abnormal signal with ill-defined border and irregular shape in MRI. (A) Horizontal plane shows KHE lesion involved right neck and scapula with hyperintense signal on T2WI in fat saturation sequence and (B) low-intensity on T1WI. (C) Coronal plane shows lesion in right axilla, shoulder and neck with high signal on T2WI in fat saturation sequence. KHE, Kaposiform hemangioendothelioma; MRI, magnetic resonance imaging.

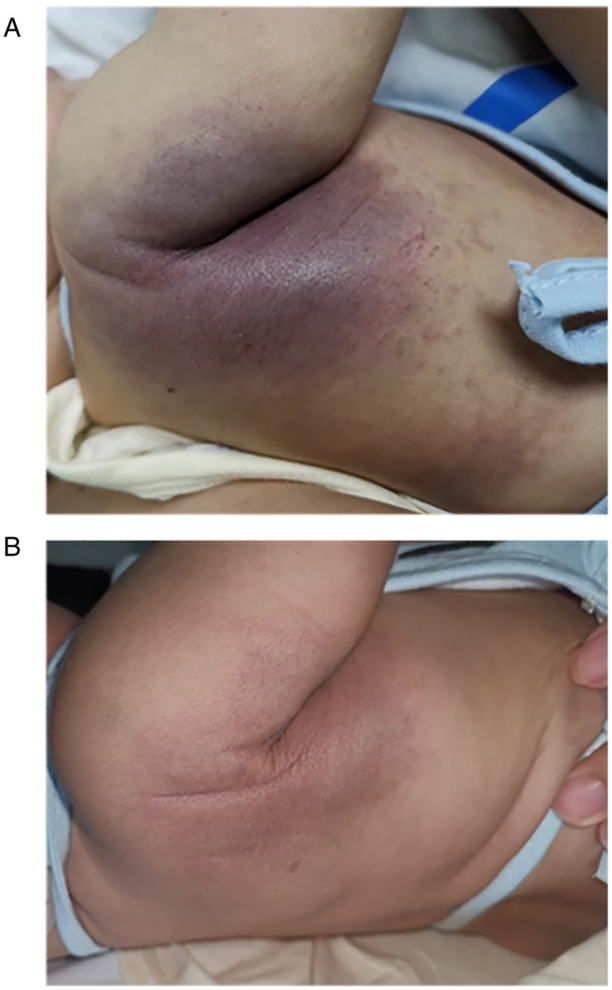

Figure 2. Appearance of Kaposiform hemangioendothelioma with purplish red color and ill-defined border. (A) Prior to treatment; (B) following cocktail therapy for one week.

drug-resistance to cocktail therapy may render it a promising alternative (12,13). The present study, with more patients than the 2018 study by Cashell *et al* (12), demonstrated significant response and good tolerance of cocktail therapy with the triad combination of prednisolone, VCR and sirolimus for infants with KMP.

KMP is more common in young patients and/or larger tumors and deeper lesions (4). All 10 patients in this study were diagnosed with KMP before five months of age, which supports previous reports of KMP developing secondary to KHE being more prevalent in younger patients (16), especially in those under six months old (17). Gruman *et al* (2005) found that KHE tumors <8 cm in diameter are less likely to be associated with the development of KMP (18). In a cohort study of 146 patients, univariate analysis showed that large (>5 cm) KHE tumors were associated with KMP (17). In 2018, Schmid *et al* (16) showed that the median tumor size in KHE patients with KMP (48.75 cm^2) is significantly larger than in patients without KMP (12 cm^2). A recent multicenter prospective controlled study by Yao *et al* (9) reported that the tumor volume in KMP patients (77.63±54.00 cm^3) is significantly greater than in patients without KMP (36.70±34,41 cm^3). However, it is very difficult to accurately measure tumor area and volume due to the irregular and ill-defined morphology of KHE (3) and there are no available methods for calculating the area or volume (9,16). In the present study, only four KMP patients had a maximal tumor diameter of <8 cm and the results suggested that KMP occurred in patients with large tumors with a maximal diameter of 84.5±25.1 mm. Furthermore, the results suggested that KMP occurred in patients with deep lesions extending into the muscle, which confirmed previous research indicating that higher KMP risk is associated with muscle infiltration (19). Although a previous study found that KHE located within the retroperitoneum or mediastinum is more aggressive and associated with greater risk (19), none of the patients in the present study had KHE in these locations.

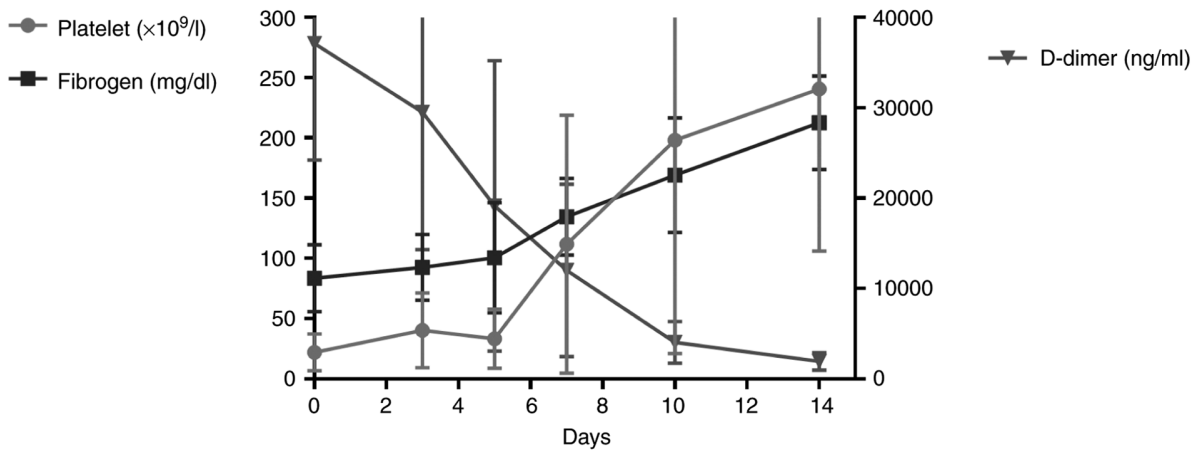

Figure 3. The tendencies of platelet count, fibrinogen and D-dimer during the combination therapy.

In the multicenter prospective randomized controlled trial of methylprednisolone (MP) and VCR, Yao *et al* (9) report complete platelet recovery in 44% of the MP group and in 80% of VCR group after one month of treatment. A previous study of VCR-resistant KMP by our group reported platelet counts >100x10^9/l after four-week VCR treatment followed by an average two-week sirolimus treatment (8). Another case series of steroid-resistant KMP reports elevation of platelet counts to the normal range after 19.1±8.5 days of sirolimus treatment (data for prior duration of steroid treatments were unavailable) (7). Due to the development of resistance in monotherapy, which necessitates the use of additional or alternative drugs (7-9), it was hypothesized that the timely management of thrombocytopenia and coagulopathy was required to save the lives of infants with KMP. The results of the present study showed that cocktail therapy led to complete resolution of thrombocytopenia after median 10 days of treatment, which indicated that cocktail therapy was superior to monotherapy for improvement of thrombocytopenia and KMP. During the treatment, platelet transfusion, which could exacerbate platelet trapping, was not recommended unless there was active bleeding or the potential risk of intracranial bleeding (4,20).

Despite the potential benefits, more attention should be paid to adverse events during cocktail treatment. To avoid common side effects such as Cushing-like appearance and growth retardation, prednisolone should be tapered as soon as medically feasible (1). Neutropenia was common in the present study, probably due to VCR in accordance with results of the prospective trial (9). Gastrointestinal disorders and other adverse effects were mainly considered as side effects of the triad regimen. Therefore, to minimize potential side effects of triad therapy, sirolimus monotherapy is recommended as soon as a stable condition is attained. Similar to reports of other studies of KHE (9,10,21), the side effects were well tolerated and improved with symptomatic treatment.

To date, to the best of the authors' knowledge, no uniform regimen has been used in the treatment of KMP and no accurate predictor of KMP development has been found. Although, a promising response to cocktail therapy has been demonstrated, which drug is acting on the tumor has not been established because of anti-tumor effects and drug resistance (4,7-10). Furthermore, the risk of adverse effects may be greater for a combination of three drugs. To reduce the side effects and rapidly control KMP, the drug-specific character of KMP needs to be elucidated. As KHE is such a rare tumor, our retrospective data with few patients provided limited evidence. Although some multicenter retrospective and prospective studies with small sample sizes have investigated the efficacy and safety of various drugs (9,22). Collaboration is necessary to complete prospective studies of KMP with long-term follow-up.

In summary, the present study was the first report, to the best of the authors' knowledge, of prednisolone-VCR-sirolimus cocktail therapy producing a promising response in KMP patients. When triad therapy was initiated at the onset of KMP, significant decrease of tumor thickness and complete resolution of KMP was achieved. It is worthwhile managing critical KMP rapidly with cocktail therapy, despite potential side effects of the triad regimen and transitioning to sirolimus monotherapy for KHE only once a stable condition has been attained.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

QL and HT participated in study design and data collection, carried out the initial analyses and drafted the article. NX, XYG and XT analyzed and interpreted the data of patients and gave critical revisions of the article. XYG performed the statistical analysis of data, and presentation of results. XKG conceptualized and designed the study and performed critical

revisions of the article. QL, HT and NX confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval was obtained from the Medical Ethics Committee of The Second Affiliated Hospital of Xi'an Jiaotong University (approval number: 2022204). Written informed consent was obtained before treatment from every infant's parents.

Patient consent for publication

Written informed consent was obtained before treatment from every infant's parents and photographs in the article were obtained with the parents' permission for publication in this study.

Competing interests

The authors declare that they have no competing interests.

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