

CONCISE COMMUNICATION

# Successful management of steroid-resistant vascular tumors associated with the Kasabach–Merritt phenomenon using sirolimus

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## ABSTRACT

**Vascular tumors associated with Kasabach–Merritt phenomenon (KMP) are life-threatening and the mortality is as high as 10–30%. Steroids are considered the primary choice for drug therapy. However, there are many steroid-resistant cases. In the present study, analyzed data are presented to support the use of sirolimus in clinical practise for the treatment of corticosteroid-resistant vascular tumors with KMP in eight infants between June 2015 and April 2017 in a single hospital. The time to initial response was  $6.8 \pm 2.7$  days. The average stabilization time for the platelet count was  $19.1 \pm 8.5$  days. At the time of publication, the average duration of sirolimus treatment was  $14.1 \pm 4.0$  months, and the average time for sirolimus treatment as a single agent was  $12.6 \pm 4.2$  months. The side-effects were tolerable and included oral ulcer, fever, pain, skin rash and transient ascension of serum transaminase and cholesterol. Our study indicated that sirolimus therapy is an effective and safe method for the treatment of corticosteroid resistant vascular tumors associated with KMP in infants.**

**Key words:** hemangioendothelioma, Kasabach–Merritt phenomenon, mammalian target of rapamycin inhibitor, sirolimus, tufted angioma.

## INTRODUCTION

In 1940, Kasabach and Merritt reported the case of an infant with thrombocytopenic purpura, which was labeled Kasabach–Merritt syndrome (the name was later changed to the Kasabach–Merritt phenomenon, KMP).<sup>1</sup> KMP is rare and mainly found at the distal limbs, trunk or maxillofacial region during the neonatal period or infancy. Typical presentations of vascular tumors with KMP include a rapidly enlarging vascular tumor accompanied by consumptive coagulopathy, which can induce hemorrhage, anemia or even disseminated intravascular coagulation and thus may become life-threatening. Previous studies have shown that mortality in such cases is as high as 10–30%.<sup>2,3</sup>

Steroids are considered the primary choice for drug therapy.<sup>2</sup> However, there are many steroid-resistant cases.<sup>3–5</sup> In the present study, analyzed data are presented to support the use of sirolimus in clinical practise for the treatment of corticosteroid-resistant vascular tumors with KMP in eight infants.

## CASE REPORT

This study was approved by the ethics committee at Guangzhou Women and Children's Medical Center. Clinical data from eight infants with steroid-resistant vascular tumors associated

with KMP treated between June 2015 and April 2017 in a single hospital were retrospectively analyzed. The diagnosis was based on a review of digital photographs, imaging, clinical history, laboratory data and biopsy results. Histopathological confirmation was not required for diagnosis but some patients underwent biopsy following the sirolimus therapy. The biopsy specimens were reviewed by a pathologist with experience in vascular anomalies. Baseline data are detailed in Table 1.

Sirolimus was administrated p.o. at a dose of 0.8 mg/m<sup>2</sup> b.i.d. at 12-h intervals. The dose was adjusted to maintain the level of rapamycin at 10–15 ng/mL. Routine blood parameters, coagulation function, liver and kidney function, serum lipids and sirolimus levels were monitored regularly. The steroid was withdrawn gradually, starting from the onset time of sirolimus. The sirolimus level, platelet (PLT) count, lesion shrinkage and side-effects were monitored regularly throughout the study.

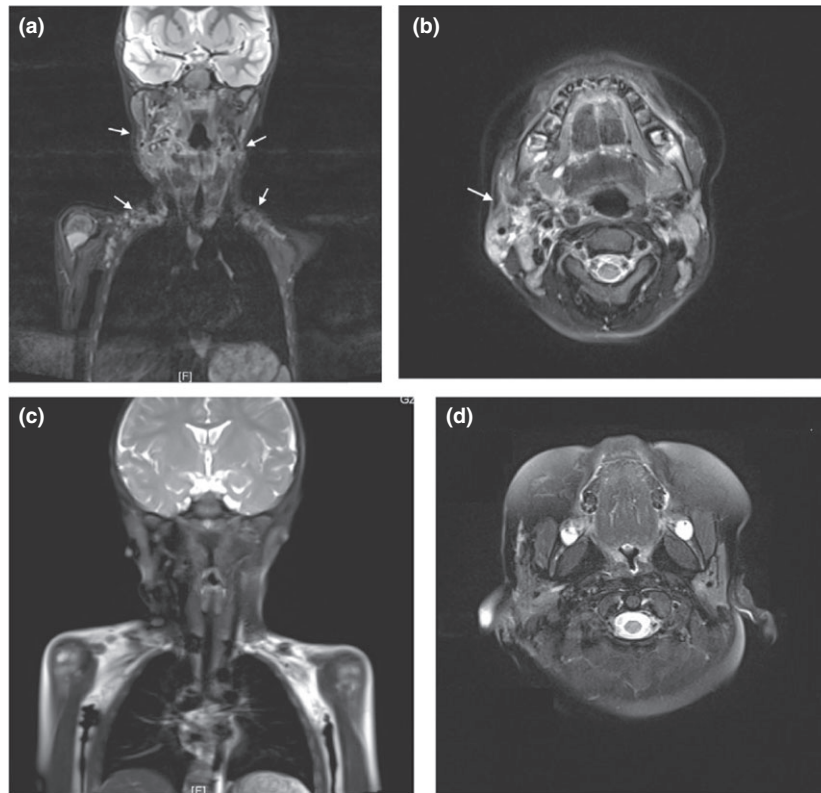
The assessment criteria referred to the Response Evaluation Criteria In Solid Tumors<sup>6</sup> in combination with the clinical features of vascular tumors with KMP. The response was classified as a complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD) or progressive disease (PD) (CR + VGPR + PR + MR = response rate [RR] and CR + VGPR + PR + MR + SD = disease control rate [DCR]).

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**Table 1.** Demographics and evaluation of disease response of patients treated with sirolimus

Case no.	Sex of onset	Affected locations	Previous treatments	Age starting sirolimus therapy (months)	Time of response to sirolimus (days)	Stabilization time of platelet (days)	Duration of sirolimus treatment (months)	Time of sirolimus as single therapy (months)	Efficacy	Side-effects (grade)
1	Male, 1 mo	Neck, maxillofacial region, anterior chest wall	Steroid, embolization, platelets transfusion, vincristine	18	7	12	12	10	CR	Fever (I)
2	Male, 3 mo	Maxillofacial region	Steroid, embolization	5	3	15	18	17	CR	Vomiting, rash (I)
3	Male, 2 mo	Chest wall	Steroid, embolization, sclerotherapy	3	6	21	14	13	PR	Fever (II)
4	Female, 10 d	Thigh	Steroid, embolization, compression	1	8	13	16	16	VGPR	Diarrhea (II)
5	Female, 2 mo	Maxillofacial region	Steroid, embolization, vincristine, platelet transfusion	8	4	17	20	18	VGPR	Pain (I)
6	Male, 14 d	Abdominal wall	Steroid, embolization, vincristine	3	6	38	8	6	MR	Diarrhea (I)
7	Female, 1 mo	Maxillofacial region	Steroid, embolization, platelet transfusion	20	5	14	15	12	PR	Oral mucositis/oral ulcer (II)
8	Male, 4 mo	Thigh	Steroid, embolization, sclerotherapy, platelet transfusion	22	15	23	10	9	PR	Elevated alanine transaminase (I), elevated aspartate aminotransferase (II), elevated total cholesterol (I)

CR, complete response; d, days; mo, months; MR, minimal response; mo, month; PR, partial response; VGPR, very good partial response.



**Figure 1.** A patient aged 18 months with Kasabach–Merritt phenomenon in the maxillofacial region, neck and anterior chest wall. (a–b) Magnetic resonance imaging (MRI) examination showed extensive lesions in the right and left maxillofacial region, neck and anterior chest wall with unclear boundaries, a high signal intensity on enhanced T<sub>1</sub>-weighted images and tracheal compression. The patient had undergone four transcatheter arterial embolizations, more than 2 years of steroid use and intermittent vincristine therapy before sirolimus treatment. However, the condition was recurrent, and the platelet level continued to decline. (c–d) MRI re-examination after 10 months of sirolimus therapy revealed that the lesions had disappeared from the maxillofacial region, neck and anterior chest wall.

The size of the lesion was mainly evaluated by magnetic resonance imaging (MRI). If the patients were unable to undergo the MRI examination, an enhanced computed tomography scan was considered. Adverse drug reactions were evaluated according to the National Cancer Institute – Common Toxicity Criteria version 4.0 and were classified as grade 0–IV.

#### Efficacy of sirolimus therapy

For the eight patients, the current total time of sirolimus therapy was 4–10 months, with a mean of  $6.0 \pm 2.2$  months. Two cases met the criterion for a CR (Fig. 1), two cases met the criterion for a VGPR, three cases met the criterion for a PR and one case approached a MR. The PLT level of all patients returned to normal. The time to an initial response was  $6.8 \pm 2.7$  days. At the time of publication, the average stabilization time for the PLT count was  $19.1 \pm 8.5$  days. The average duration of sirolimus treatment was  $14.1 \pm 4.0$  months, and the average time for sirolimus treatment as a single agent was  $12.6 \pm 4.2$  months. At the time of follow up, sirolimus was discontinued in two patients, while the others were still undergoing sirolimus therapy. Good disease control was achieved in all cases, with an RR and DCR of 100% (Table 1).

#### Adverse drug reactions

The side-effects included oral ulcer (grade II), fever (grade II), pain (grade I), skin rash/vomiting (grade I), diarrhea (grade I/II) and transient ascension of serum transaminase (grade I/II) and cholesterol (grade I). The above parameters returned to normal after symptomatic treatment within 2 weeks. No pulmonary infection, bone marrow suppression or other severe adverse events due to the use of sirolimus were observed (Table 1).

#### DISCUSSION

The development and progression of vascular tumors with KMP is extremely dangerous, resulting in a mortality rate of 12–30% and making treatment extremely difficult.<sup>2,3</sup> Vascular tumors with KMP often show invasive growth in the presence of coagulopathy, making it difficult and risky to surgically resect the lesion. Thus, medication remains the primary treatment. Presently, glucocorticoids and vincristine (VCR) are the two major therapeutic agents for vascular tumors with KMP in clinical practise. In particular, glucocorticoids are the first-line agent in the treatment of vascular tumors with KMP because glucocorticoids are available at a relatively low cost. However, the recurrence rate is generally

high after the treatment has stopped, and there are many steroid-resistant cases.<sup>7</sup> Furthermore, repeated and prolonged use of glucocorticoids can cause hypertension, cushingoid appearance and opportunistic infections. VCR, a plant alkaloid anticancer agent, is often used as a second-line therapy. In 2002, Haisley-Royster *et al.*<sup>8</sup> reported the first use of VCR for the treatment of vascular tumors with KMP and conducted a retrospective analysis. Their results showed that the effective rate of VCR therapy was 87%. However, the major adverse reaction to VCR therapy is transient neurotoxicity, including peripheral neuropathies such as a lack of deep tendon reflex, finger/toe numbness, tingling and autonomic neuropathies such as abdominal pain and constipation.<sup>9</sup> Moreover, the average response time of VCR has been reported to be 5.3 weeks.<sup>8</sup> Therefore, recent research has focused on identifying an agent that can achieve long-lasting efficacy with fewer side-effects. In recent years, several studies, most of which were case reports or case series, have reported the application of inhibitors of the mammalian target of rapamycin (mTOR) for the treatment of vascular tumors with KMP with good results.<sup>10–11</sup> In 2016, Adams *et al.*<sup>12</sup> reported 60 cases of vascular anomalies treated with sirolimus in the *Journal of Pediatrics*, including 10 patients with kaposiform hemangioendothelioma (KHE) or tufted angioma, who obtained a response rate of 100% after 6 months or 1 year of sirolimus therapy. In the present study, our results showed that the average response time to sirolimus was 3–15 days, with a mean of  $6.8 \pm 2.7$  days, which was markedly shorter than that for VCR. With continuous use of sirolimus, the PLT stabilization time (i.e. a PLT level maintained at  $100 \times 10^9/L$  or higher) was 12–38 days, with a mean of  $19.1 \pm 8.5$  days. Furthermore, the efficacy of sirolimus was long-lasting, without the development of resistance. These results indicate that sirolimus combines the rapid onset of steroids and long-lasting efficacy of VCR while avoiding the resistance of steroids and the substantially slow onset of VCR. Therefore, sirolimus shows great clinical value and is worthy of further study.

Sirolimus was the first mTOR inhibitor to be discovered. In an early study, sirolimus was used as an immunosuppressant for anti-rejection following renal transplantation.<sup>13</sup> During the 1970s, sirolimus was found to play an inhibitory role in some tumors (e.g. breast cancer, lung cancer, pancreatic cancer, glioma, prostate cancer, kidney cancer and ovarian cancer), in addition to a medical effect in anti-rejection treatment. Recent studies have shown that sirolimus also exhibits good effects in the treatment of refractory KHE with KMP,<sup>10–12</sup> although more clinical research needs to be conducted. In the present study, eight infants with KMP were treated with sirolimus, and the response rate was 100%, with significant improvement. The eight patients were gradually withdrawn from steroids after the start of sirolimus therapy. It was previously thought that patients can tolerate sirolimus at a level of 10–15 ng/mL.<sup>14</sup> In an international multicenter clinical trial, McCormack *et al.*<sup>15</sup> used a dose of 2 mg/day to treat lymphangiomyomatosis and noted adverse reactions in 89 cases, mainly including gastrointestinal discomfort (28.7%), pain plus shock (13.5%), mucosal inflammation and rash (11.5%), and hypercholesterolemia (5.8%). In our study, no patient was withdrawn from sirolimus therapy due to serious adverse reactions. Despite mild adverse

reactions during the administration of sirolimus, the symptoms were generally alleviated after symptomatic treatment.

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**CONFLICT OF INTEREST:** None declared.

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