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Case Reports

Vincristine Can Induce Regression of Vascular Malformation in Long Standing Refractory Kasabach Merritt Phenomenon

WC ***Chow,*** SY ***Ha,*** GCF ***Chan***

Abstract Vascular lesion with consumptive anaemia and thrombocytopenia (Kasabach Merritt phenomenon, KM phenomenon) is considered to be related to congenital vascular malformation rather than genuine haemangioma. Unlike the classical strawberry haemangioma, patients with KM phenomenon are often resistant to both steroid and interferon treatment, and the vascular malformation does not regress spontaneously. In the past 2 decades, various forms of treatment have been advocated but few with consistent effect. Recently vincristine, a commonly used chemotherapeutic agent with an anti-angiogenesis action, has demonstrated encouraging clinical effect in infants and young children with KM phenomenon with tolerable side effects. Recent data suggested that vincristine could control the vascular malformation in KM phenomenon if used early. However, its efficacy on patients with long-standing, refractory KM phenomenon remains unknown. We reported here a young adolescent girl with long and refractory KM syndrome who responded to weekly vincristine treatment. The thrombocytopenia resolved completely within 12 weeks of treatment and the size of the vascular malformation continued to shrink over a span of 1.5 years. Future study targeted at this group of patients will help to verify its efficacy in this clinical setting.

Key words Haemangioma; Kasabach Merritt phenomenon; Vascular malformation; Vincristine

Case Report

A 10-year-old girl was detected to have large circumscribed vascular lesion over her right lower limb at birth. The antenatal history was unremarkable except for mild gestational hypertension which required no treatment. The size of the vascular lesion increased markedly in the first two months of life and her peripheral blood film showed anaemia and thrombocytopenia (haemoglobin: 6.1 g/dl, platelet: 12 x 10^9/L). Coagulation profile was also deranged [prothrombin time: 14.7 seconds (control: 12.0 seconds), partial activated prothrombin time: 47.6 seconds (control: 27.5 seconds), fibrinogen: 0.7 g/L (N 1.5-4 g/L), and fibrin degradation product >40 μg/ml (N<10 μg/ml)]. She was then diagnosed to have Kasabach Merritt (KM) phenomenon and various forms of treatment including repeated courses of high dose oral and systemic steroid (6 months), alpha interferon injection (3 months) was given. However there was no sign of clinical response. Over the next 5 years, her vascular lesion continued to grow and was complicated by intermittent bleeding, superficial ulceration and infection. Significant hemi-hypertrophy and leg length discrepancy developed. There was hepatomegaly and mild cardiomegaly but no overt clinical heart failure was detected. Plan for local sclerosing or thrombotic therapy was ruled out after CT scan and USG of the vascular lesion failed to identify suitable feeder vessels for occlusion.

Pressure garment was tried at the age of five but with no improvement. Her platelet remains persistently low at below 20 x 10^9/L with deranged clotting profile. Her family also

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sought experimental approach such as daily topical injection of urea, steroid and xylocaine outside Hong Kong when she was 6 years old. This therapy was given daily for six weeks alternated with six months of rest period. A total of 4 courses were given over 2 year's period. Mild clinical response in terms of control of the size of the vascular lesion was noted (Figures 1 & 2). At 8.5 years, vincristine (1.5 mg/M^2 BSA weekly via intravenous route by bolus injection) was commenced and her condition improved drastically with normalisation of her clotting profile after eight weeks of therapy and platelet count increased to 154 x 10^9/L at 11th week treatment (Figure 1). Her thigh and calf circumference decreased from a maximum of 48 cm to 31.5 cm and 44 cm to 34.5 cm respectively (Figures 2, 3a & 3b).

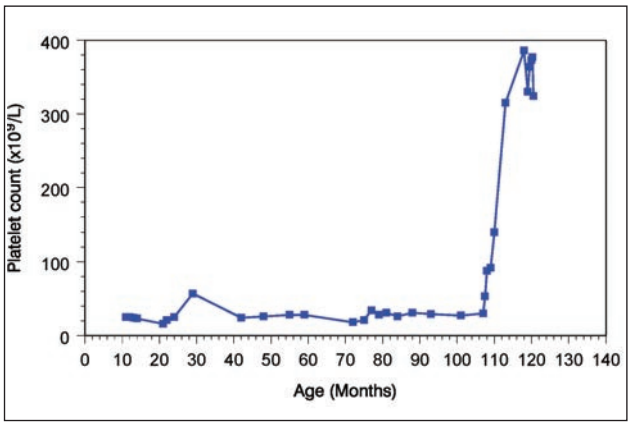

Figure 1 Persistent severe thrombocytopenia (around 20x10^9/L) was noted prior to vincristine treatment and drastic improvement was noted after initiation of vincristine treatment (month #106).

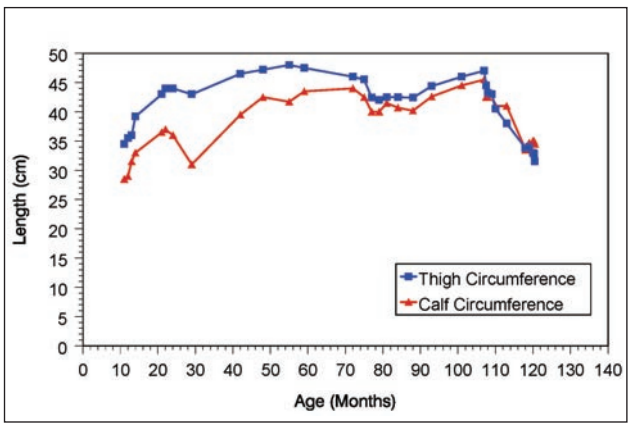

Figure 2 Gradual shrinkage of the vascular malformation with vincristine treatment (after month #106). Taking note that the child is at her secondary growth sprut during the treatment.

Peripheral neuropathy was detected by regular NCV monitoring as an adverse side effect of vincristine after 19 months of therapy (18 months of weekly and one month of biweekly therapy). The nerve conduction velocity test showed absence of responses however clinically all the deep tendon reflexes and sensations were preserved. Three months after stopping the therapy, her thigh and calf circumferences rebounded from 32 cm to 34 cm and 35.3 cm to 38 cm respectively. Repeated peripheral blood film was normal and the platelet count was 278 x 10^9/L.

Discussion

Kasabach Merritt phenomenon is a severe complication induced by an enlarging vascular lesion. The classical phenomenon composed of microangiopathic haemolytic anaemia, profound thrombocytopenia and consumptive coagulopathy. Differences between the vascular lesion that induce KM phenomenon and classical infantile haemangiomas have recently been emphasized. Most

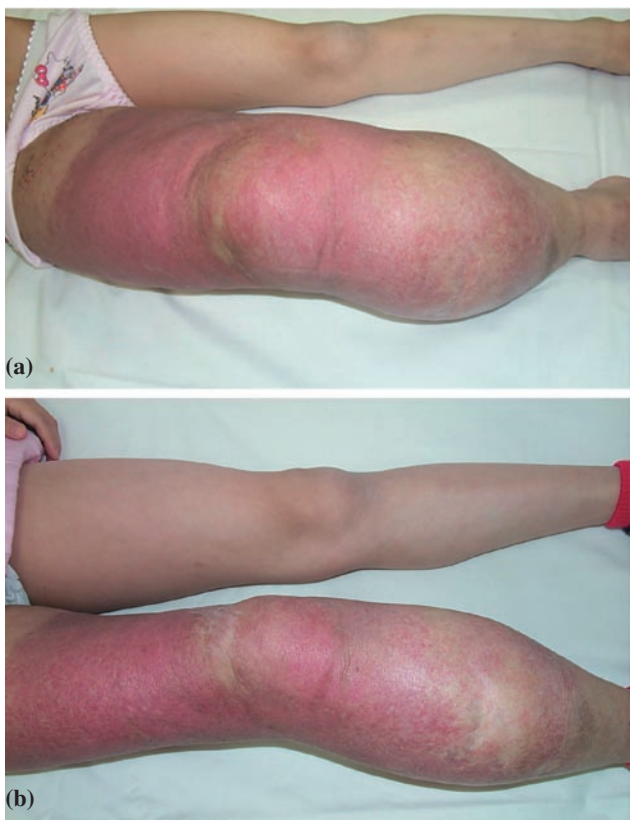

Figure 3 Comparing the size of the malformation at her thigh and calf: (a) 5 months before vincristine treatment and (b) 18 months after weekly vincristine treatment.

patients suffered from large slow progressive "haemangioma" compatible with the diagnosis of KM phenomenon were found to have Kaposiform haemangioendothelioma and/or tufted angioma by biopsy.[1-4] Despite high dose steroid, alpha interferon and intra-lesional steroid which were the classical choice of treatment for classical haemangioma, the vascular lesion in KM phenomenon often resists to these approaches.

Perez Payrols et al first reported the successful use of vincristine (2 mg/M^2 BSA weekly) in two infants with large vascular tumours.[5] Subsequently, Haisley-Royster et al reviewed 15 patients with Kasabach Merritt phenomenon and thirteen out of fifteen cases (87%) responded to weekly vincristine either alone or adjuvant to other therapy.[6] While it is quite convincing that vincristine alone can effectively apply to infants with KM phenomenon, whether similar approach can be applicable to older patients with long standing lesion remain unanswered. Hu et al used a six monthly cycles of combination chemotherapy including vincristine (1.5 mg/M^2 BSA), cyclophosphamide (300 mg/M^2 BSA) and actinomycin D (500 microgram/M^2 BSA) and demonstrated that it was able to normalise the thrombocytopenia of a 6 years old child with KM phenomenon.[7] This patient failed to respond to two months of steroid therapy previously. Reports on using vincristine on KM phenomenon are summarised in Table 1. The current dose of vinvristine that we used is 0.5 mg/M^2 BSA and we have been using this low dose for other patients with similar effect.

Our patient is the first reported case of older child with long standing refractory KM syndrome who responded to vincristine alone. Vincristine was given as the last available option at that time after her family sought for various remedies from different centres around the world with no improvement. The uncertain clinical outcome was discussed and the side effect of vincristine including peripheral neuropathy was informed. Regular monitoring of the NCV was offered. At the end, vincristine did not only induce hematological abnormalities but also resulted in shrinkage of the vascular lesion. In an observation period of 2 years, the vascular lesion continued to regress in size while the patient received weekly vincristine treatment.

We believe that vincristine, as an anti-angiogenesis agent; can serve as a good treatment option for both infants and older patients with this distressing syndrome. It is especially worthwhile to try for those patients who fail to respond to steroid or/and interferon therapy. But the remaining unanswered question is when to stop the therapy. Around 30% of patient will have recurrence of the disease after stopping the vincristine treatment.[6] We initially intended to empirically stop the therapy after a 12 months period but encountered objection from both the patient and her

Table 1 Studies using vincristine as treatment for KM phenomenon

No of case	Resistant to prior Rx	Mean age	Age range	Rx	Response	Location of the KM phenomenon	Adverse effect	Authors
1	Steroids	6 yr	---	VAC	Improved in platelet count & size	Right thigh	Nil	Hu et al[7]
2	Steroid 2 mg/Kg/day 10 to 55 days	4.8 m	20 day to 9 m	V	Improved in platelet count, size & heart failure	Left supra-clavicular & left hepatic lobe	Nil	Perez Payarols et al[5]
21	Steroid, embolisation, radiation	N/A	At birth to 12 m	4 cases with V or VC	1/4 responded	Cervicofacial x 2, truncal x 11, extremities x 8	Nil	Sankar et al[4]
15	Steroid, IFN, FFP, embolisation, aspirin, radiation	7 m	14 day to 28 m	V +/- steroid, IFN	100% Platelet improvement, 87% decrease in size	Cervicofacial x 5 Truncal x 6 Extremities x 4	1/15 with neuropathy, 1/15 with abdominal pain	Haisley-Royster et al[6]
1	Steroid, aminocaproic acid, IFN, radiation	10 m	---	V, steroid, IFN	Improved in platelet & size	Upper chest	Nil	Vin-Christian et al[3]

A=actinomycin; C=cyclophosphamide; FFP=Fresh Frozen Plasma; IFN=interferon alpha; m=months; Rx=treatment; V=vincristine; yr=years

parents due to the continued clinical response. So far, we have given the treatment weekly for 18 months and then tapered to 2 weekly twice. Finally, due to the subclinical abnormal nerve conduction study found in the routine examination, the treatment was withheld and there was mild rebound in terms of the vascular tumour size but no decrease in the platelet level over a period of 8.5 months (24 months since initiation of vincristine treatment). She has no overt neurological deficit detected clinically upon follow up. Future international collaborative study can help to resolve different issues related to this relatively new approach for children or adult with KM phenomenon.

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