

## Review Article

# Successful treatment of kasabach-merritt syndrome with vindesine: a case report and review of literature

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Received January 30, 2018; Accepted October 11, 2018; Epub January 15, 2019; Published January 30, 2019

**Abstract:** Kasabach-Merritt Syndrome (KMS) is associated with profound thrombocytopenia and consumptive coagulopathy caused by vascular tumors. In this report, we described an adult patient with KMS who received chemotherapy including vindesine (VDS), and briefly reviewed the literature on KMS treatment. This female patient was found to be presented with multiple subcutaneous masses at birth. These soft masses increased in size and numbers every year and led to KMS finally, including subarachnoid hemorrhage and coagulopathy. After being treated with combination of glucocorticoid, thalidomide and propranolol, her symptoms did not improve. We started VDS treatment on a 4 mg weekly basis for the first week, and then reduced to 2 mg weekly. After 4 weeks treatment, the platelets count and fibrinogen level both increased and no more newly emerged abnormal lesions was found. Based on these existing literatures, the current major treatments of KMS include physical therapy, traditional chemotherapy and hemostatic therapy. The treatment choice depends on the severity of KMS. For those patients who got widely distributed hemangiomas, and involving deep muscles and many important organs, will lose the opportunity of surgery excision or embolization treatment. The VDS based combination treatment approach may make the disease reached a stable state.

**Keywords:** Kasabach-Merritt syndrome, vascular tumor, coagulopathy, vindesine

## Introduction

Kasabach-Merritt Syndrome (KMS), known as a consumptive coagulopathy associated with giant vascular tumors, is characterized by severe thrombocytopenia, microangiopathic anemia, and hypofibrinogenaemia. In 1940, Kasabach and Merritt first described this syndrome in a male infant with a capillary hemangioma and associated thrombocytopenic purpura. KMS is a rare type of vascular lesion that presents in various ages, but usually in infancy [1]. This report describes an adult patient with KMS who received chemotherapy including vindesine (VDS) in our hospital in June of 2016. And we briefly reviewed the clinical characteristics and therapy of KMS.

## Case report

A 53-year-old woman was found to be presented with multiple subcutaneous masses at birth, involving head, neck, armpits, trunk, upper limbs and hands with no obvious discomfort.

As these soft masses increased in size and numbers every year, she received the right hand mass and throat mass excisions in 2009 and 2010, which on biopsy were found to be hemangioma. Until 4 months ago she started to feel faint and nausea. The CT scan showed signs of subarachnoid hemorrhage and subdural hemorrhage. The MRI images showed multiple lesions in liver, spleen, back and buttocks muscles. As the blood coagulation test showed a decrease of fibrinogen and an increase of D-dimer and FDP, she was diagnosed as KMS. After being treated with combination of glucocorticoid, thalidomide and propranolol, CT scan showed absorption of cerebral hemorrhage. As her dizziness has been getting worse since 2016, she took the MRI examination again which showed newly emerged occipital hemorrhage, forcing her back to our hospital in June 2016. Her past medical history includes the nephrotic syndrome and hypertension. The routine blood test showed moderate anemia and thrombocytopenia (**Table 1**). The coagulation test showed hypofibrinogenaemia with

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**Table 1.** Relevant hematological investigations carried out before and after the treatment of VDS

VDS Doses	Investigations					
	WBC ( $\times 10^9/L$ )	Hb (g/L)	PLT ( $\times 10^9/L$ )	Fib (g/L)	D-D (mg/L)	FDP (mg/L)
Before VDS	7.1	93	69	0.6	86	106.8
After VDS						
After first dose	3.5	89	69	1.0	60.32	106.5
After second dose	1.7	69	90	1.0	73.83	99.1
After third dose	3.6	68	98	0.8	63.85	103.6
After fourth dose	3.6	67	118	1.1	40.12	81.1

increased D-Dimer and FDP (**Table 1**). The serum creatinine level was between 250-300  $\mu\text{mol/L}$ . T1WI and T2WI images of head MRI scan showed multiple high signal lesions in the occipital lobe on both sides, surrounded by low signal rings, which prompted cerebrovascular malformation with chronic hemorrhage (**Figure 1**). The MRI scan of trunk and limbs showed multiple hemangiomas in neck, chest and abdominal wall, arms and legs, right psoas major, right buttock, and perineum; multiple liver hemangiomas; Splenic diffuse lesions, considering multiple hemangiomas (**Figures 2, 3**).

Finally this patient was diagnosed as Kasabach-Merritt Syndrome, chronic renal insufficiency, nephrotic syndrome, intracranial hemorrhage and hypertension. After discussing at a multidisciplinary meeting which included a hematologist, nephrologist, neurologist, and radiologist, vindesine (VDS) was started on a 4 mg weekly basis for the first week, and reduced to 2 mg weekly due to the decreased creatinine clearance for the after three weeks. Thalidomide was started at 50 mg/day basis, but withdrew because of the intractable constipation. As the patient has been taking prednisone for more than one month, which started at a 1 mg/kg/day basis, we gradually reduced the dose to 7.5 mg/day. Intermittent infusion of fresh frozen plasma or cold precipitation was given. During our treatment process, platelets were lowest at  $69 \times 10^9/L$  during the first week, and then progressively improved, as well as the fibrinogen level (**Table 1**). And no more newly emerged abnormal lesions appeared on cranial MRI. Since vindesine may inhibit the proliferation of vascular endothelial cells and block the formation of intravascular microthrombus, it may as a result reduce the destruction and consumption

of platelets and fibrinogen, which were showed in our patient.

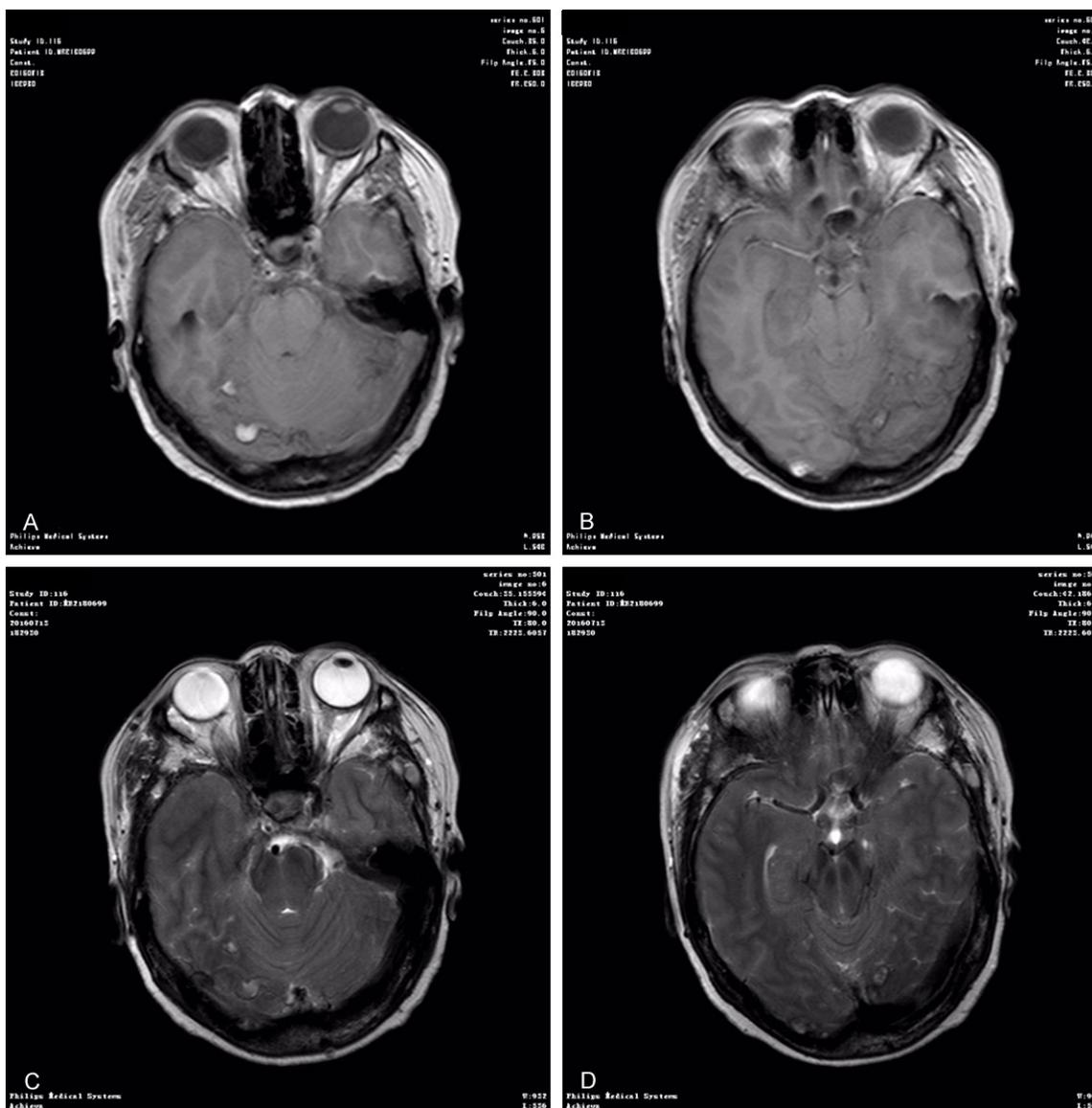
### Discussion

Kasabach-Merritt Syndrome (KMS) is a life-threatening clinical constellation of consumptive coagulopathy and thrombocytopenia associated with an underlying vascular tumor. Kasabach and Merritt first described this

syndrome in a 2-month-old boy in 1940. It was more common in infants, and was initially thought to be associated with infantile haemangiomas. Until 1997, Enjolras and Sarkar reported that KMS was in fact resulted from Kaposiform haemangioendotheliomas (KHE) and tufted angiomas (TA) instead [2].

KHE and TA often arise from the soft tissue of the extremities, trunk, retroperitoneum, head, neck, intracranial lesions and so on [3]. One large retrospective study in U.S. [4] which included 107 patients described that, KMS was often associated with large and deep lesions such as muscles, bones or body cavities rather than in superficial lesion, and this phenomenon appeared less frequently in older children and adults. Similar cases summaries have also been done for Chinese people. Yuan [5] reported 19 cases of KMS in Chinese children, tumors involve head (3), neck (2), trunk (9), buttocks (1) and limbs (4). Lei [6] retrospectively studied 59 cases with KMS, the average age of whom was 2.9 months. 28 cases involved maxillofacial lesions, and 31 cases with lesions at trunks and extremities. Based on the above reports, the vascular tumors in most KMS patients are single and localized distributed, few are multiple and widely distributed. However, in our case, the distribution of hemangiomas of the patient is very wide, involving in the head, neck, chest, abdomen, extremities, buttocks and muscles as well as liver and spleen. There is no similar case reported before. This woman was found to be presented with multiple hemangiomas at birth, but with no obvious discomfort and symptoms at the beginning. The hemangiomas gradually increased and became larger as years passed by, and divided into the deep tissues of muscles and viscera, which resulted in the appearance of KMS.

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**Figure 1.** Head MRI scan (transverse section): T1WI (A, B) and T2WI (C, D) images showed multiple high signal intensity lesions in the bilateral occipital lobes, surrounded by low signal rings, which suggested cerebrovascular malformations with chronic hemorrhage in the brain parenchyma.

Because of the rarity of KMS, there is no data from large randomized clinical trials or prospective studies which the existing treatments can refer to. Based on these existing literatures, we reviewed the current major treatments of KMS as follows.

### *Surgery*

For small and localized lesions, surgery can be a curative treatment, but it will not be a good choice if patients have severe coagulopathy, or lesions are widely distributed or infiltrate into vital structures.

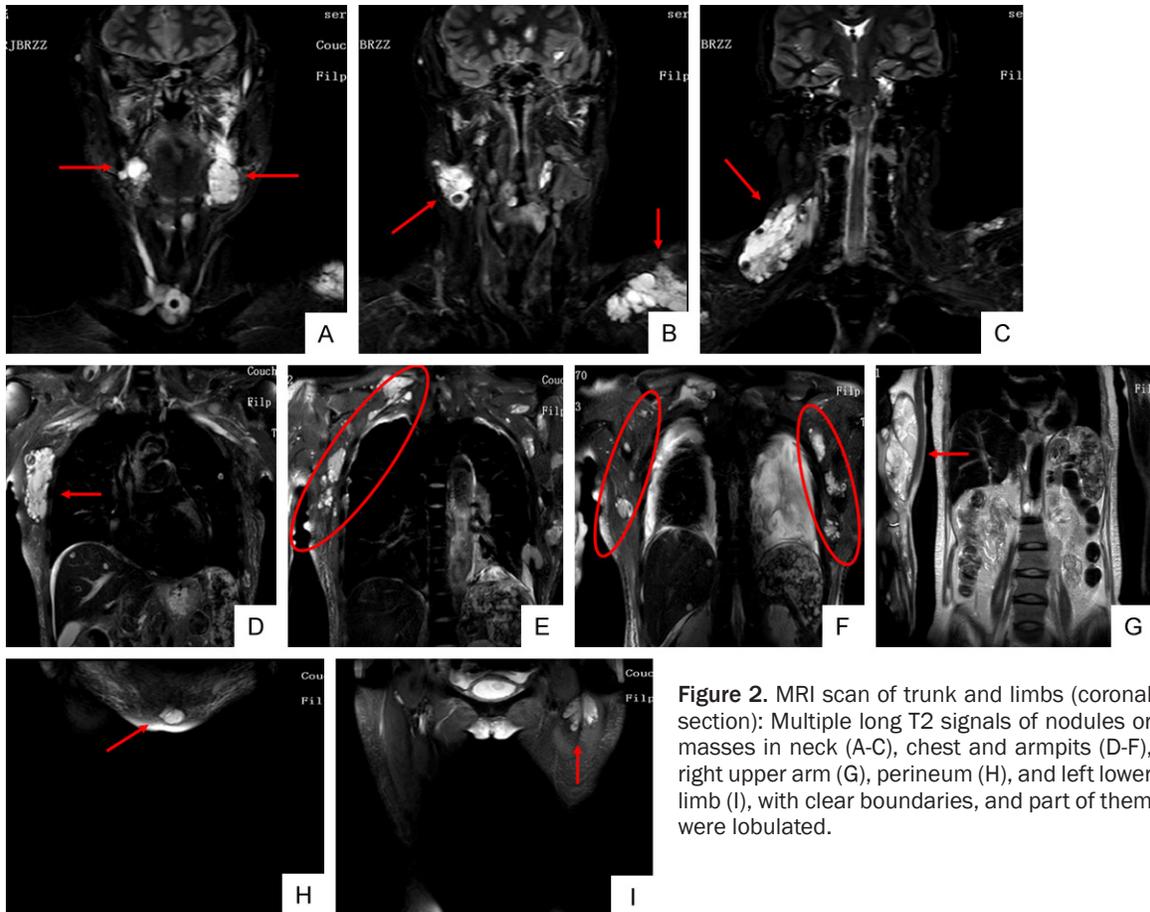
### *Radiotherapy*

Radiotherapy was the curative choice in the first case of KMS in 1940 [3]. Since then, it was widely used in many other cases and proved to be effective. However, with the increasing cycles and doses of treatment, higher incidence of adverse effects would arise, especially in infants, including limb shortening and late malignancy [7, 8].

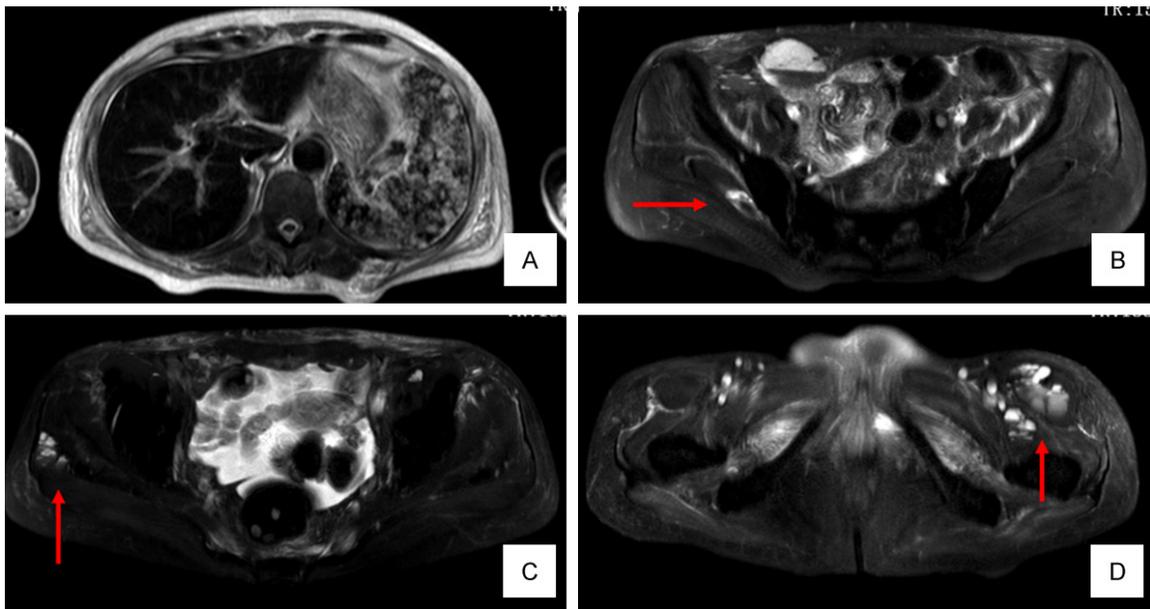
### *Embolization therapy*

Arterial embolization is also a common choice of KMS treatment. As Ryan [9] reported, 10 out

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**Figure 2.** MRI scan of trunk and limbs (coronal section): Multiple long T2 signals of nodules or masses in neck (A-C), chest and armpits (D-F), right upper arm (G), perineum (H), and left lower limb (I), with clear boundaries, and part of them were lobulated.



**Figure 3.** MRI scan of abdominal and legs (transverse section): Diffused heterogeneous signals in spleen (A); Multiple mixed signals in right psoas major (B), right buttock (C), and left thigh (D).

of 15 KMS patients achieved partial response after embolization. However, such treatment

may do harm to the healthy tissue and cause infarction, stroke or limb loss [10, 11]. As a

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result, it ought to be properly used in small and localized lesions.

### *Chemotherapy*

(1) Steroids: Glucocorticoids have been the first-line therapy of KMS treatment because of their low cost and rapid response, but there may be a low response rate and high relapse rate if the corticosteroids are used alone in therapy [9, 12, 13]. (2) Vincristine: Due to the anti-angiogenic properties, vincristine has been successful at treating KMS in numerous case reports. Some multicentre retrospective studies have shown patients with KMS could benefit from vincristine treatment even with refractory diseases. As Haisley [14] reported, more than eighty percent patients response to this approach and get smaller lesions. Wang [15] described 78% of KMS patients who were steroid-resistant could achieving complete response after vincristine treatment, although about 11-20% patient may develop transient symptoms of neuropathy as side effect [14, 15]. Some pediatricians also reported that vincristine could be used together with other regimes such as aspirin, ticlopidine and other antiplatelet agents [16, 17]. (3) Interferon alpha: It is believed that interferon alpha can improve the coagulation function of KMS patients within about one week, and the lesions can be reduced in a few months [18]. But because interferon alpha can cause convulsive paralysis of infants, it is only recommended to be used in life-threatening situations or patients with refractory diseases [19, 20]. (4) Propranolol: As a non-selective beta blocker, propranolone has the effect of constricting capillaries, promoting apoptosis of vascular endothelial cells and inhibiting angiogenesis. But according to the existing literature, the monotherapy of propranolol only have one-third response rate [21, 22]. (5) Thalidomide: Thalidomide has anti-angiogenic activity through inhibiting basic fibroblast growth factor (bFGF) [23]. A single case report has described thalidomide in combination with radiation therapy treating vascular tumors in the spine which can not be extracted [24].

### *Antiplatelet agents*

The activation of platelets and the release of blood vessel growth factors, as well as the interaction between platelets and vascular

endothelial cells, are important parts of KMS's pathogenesis. As a result, the use of antiplatelet agents is rationale and proved to be safe. For examples, aspirin, ticlopidine and dipyridamole are all in the list of KMS treatment [25]. Furthermore, Enjolars [2] proved that dual antiplatelet therapy was more efficacious than monotherapy.

### *Antifibrinolytics*

Antifibrinolytics therapy in KMS is still controversial. As the main cause of coagulopathy in KMS is not fibrinolysis but thrombocytopenia, antifibrinolytics therapy will not reverse the progression of the disease. So that it may only be used if there is persistent bleeding with raised FDPs or reduced fibrinogens. Drolet [26] believed when fibrinogen was less than 1.0 g/L, frozen plasma or cryoprecipitate could be taken into account.

### *Platelet transfusions*

Patients with KMS should be very cautious in platelet transfusion, only if with active bleeding or emergency surgery. The main reasons are as follows: (1) The platelet half-life is less than 24 hours because of the intralesional destroy. (2) The platelet will gather in lesions, which causes hardening and growth of hemangioma. (3) The platelets may release growth factors causing proliferation of vascular endothelial cells [1, 3, 27].

After cerebral hemorrhage, this female patient was treated with combination of glucocorticoid, thalidomide and propranolol. The platelets count and coagulation function were once improved, but soon getting worse again. Due to the widely distributed and deep tissue divided hemangiomas, surgery excision, radiation therapy or embolization therapy could not efficiently and safely reduce the tumor load of the whole body. As a result, we took pharmacotherapeutic approaches as the main regimen. Given the recent history of cerebral hemorrhage, we didn't choose any antiplatelet agents such as aspirin or ticlopidine, but added vindesine weekly for four weeks based on the original small dose prednisone regimen. The platelet and fibrinogen levels were gradually increased after the treatment, and no more newly emerged abnormal lesions appeared on cranial MRI. The main side effects were minor gastro-

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intestinal toxicity and peripheral neurotoxicity, which both relieved after withdraw. The grade 3 hematologic toxicity also can be reduced after use of granulocyte colony stimulating factor and blood transfusion.

According to this patient, we can see that the severity of KMS is closely related to the tumor load of systemic hemangioma in patients. In this case, when the patient started to develop the KMS related symptoms, her hemangiomas had been widely distributed, involving deep muscles and many important organs, which made her lost the opportunity of surgery excision or embolization treatment. Taking the VDS based combination treatment regimen, her disease reached a steady state.

In conclusion, we proved VDS based regimen to be a safe and effective choice to treat KMS with heavy tumor load of systemic hemangioma. However, there is no consensus of the future maintenance treatment, and long-term follow-up and summary of existing cases are needed. Another question is when to intervene with the patient. Whether we can intervene in the early course of disease and reduce the load of hemangioma when KMS related symptoms haven't developed, so as to delay the progress of disease, is also worthy of study and discussion.

### Disclosure of conflict of interest

None.

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