

Multimodal treatment of Kasabach-Merritt syndrome arising from tufted angioma: A case report

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Abstract. Kasabach-Merritt syndrome (KMS) is a rare type of vascular tumor associated with a severely decreased platelet count. No standard guidelines for the treatment of the disease have been established so far. In the present study, a 1-year-old pediatric patient with KMS arising from tufted angioma was successfully and variously treated with steroids, vincristine, surgery and propranolol for 18 months. Systemic steroids stabilized the platelet count stable, while vincristine reduced the size of the tumor. Due to unpredictable response, the patient was operated. Combination of vincristine and propranolol was introduced post-surgery to improve the severely low platelet count of the patient. Following multimodal therapy for 18 months, there has been no evidence of recurrence or metastasis during 2 years of follow-up. Currently, the patient is alive and well. The management of KMS presents a challenge, and well-designed studies are required to clearly determine the benefits and risks of multidisciplinary treatment.

Introduction

Kasabach-Merritt syndrome (KMS) is a rare, aggressive type of vascular tumor associated with thrombocytopenia and consumptive coagulopathy. KMS was first reported by Kasabach and Merritt in 1940, in a boy presenting with enlarging hemangioma with thrombocytopenia on the left thigh (1). KMS has been associated with Kaposiform hemangioendothelioma or tufted angioma, but not with the more common infantile hemangioma (2). Le Nouail *et al* (3) estimated the mortality rate to be between 13% and 24%, depending on the series. Numerous regimens have been employed for the management of KMS, without, however, a consistent response, since patients exhibit a variable and unpredictable response to traditional

pharmacological agents, including steroids, vincristine and interferon (IFN). Recently, excellent response rates and prompt results have been achieved by combining antiplatelet therapy with vincristine, without the use of steroids. Sirolimus, which is directed against the phosphatidylinositol-4,5-bisphosphate 3-kinase/AKT/mechanistic target of rapamycin downstream signalling pathway and is involved in lymphangiogenesis, has also shown promising results (4). No standard guidelines for the treatment of the disease have been established so far. In certain cases, multimodal therapy is necessary. The main therapeutic options include systemic corticosteroid therapy, IFN α 2a or 2b, vincristine and platelet aggregation inhibitors, possibly in combination with acetylsalicylic acid or ticlopidine (3).

Case report

A 1-year-old pediatric patient was admitted to the Department of Reconstructive Plastic Surgery, The Children's Hospital of Zhejiang University School of Medicine (Hangzhou, China) for the management of an erythematous and swollen process on his right shoulder in July 2010. The lesion was a reddish-violaceous plaque measuring 8x6 cm, irregularly shaped, poorly demarcated and showed signs of swelling and inflammation (Fig. 1). The lesion first appeared as a small skin lesion the size of a peanut. Six months later, it had increased in size and become slightly tender and warm upon palpation. Treatment with antibiotics (cefmenoxime, 80 mg/kg) for 1 month failed. Laboratory tests revealed the following: Platelet count, $77 \times 10^9/l$ (normal range, $100-400 \times 10^9$ cells/l); hemoglobin, 115 g/l (normal range, 110-140 g/l); leukocyte count, 9.49×10^9 cells/l (normal range, $4.00-12.00 \times 10^9$ cells/l); D-dimer, $302 \mu\text{g/l}$ (normal range, $<500 \mu\text{g/l}$). Doppler ultrasound (IU Elite; Philips Healthcare, Amsterdam, The Netherlands) showed a fluid collection in the subcutaneous tissue and muscle plane of the patient's right shoulder and computed tomography scan (Somatom Emotion 16; Siemens AG, Munich, Germany) demonstrated a vascular tumor extending to the right clavicle. Based on thrombocytopenia, consumptive coagulopathy and purpura associated with a huge vascular tumor, the patient was diagnosed as KMS. Informed consent was obtained from the patient's parents prior to treatment and the present study was approved by the Ethical Committee of Zhejiang University.

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Treatment with methylprednisolone was administered intravenously at a dose of 10 mg/kg/day for 3 days and tapered off over 2 weeks. Subsequently, 5 intralesional injections of compound betamethasone (diprospan) were administered at a dose of 1 ml (7 mg) twice a week, which was equivalent to 10 mg/kg/day methylprednisolone. Despite the stabilization of the platelet count following treatment, the lesion continued to enlarge. A weekly intravenous injection of 1.5 mg/m² vincristine was therefore added upon termination of the treatment. Following 6 injections of vincristine at a dose 0.68 mg (according his body surface area), the platelet count was found to have increased to 264x10⁹/l, and the mass in the right shoulder to have shrank. The patient was discharged and received weekly blood tests to ensure that the platelet count was stable.

A month later, the patient was readmitted to the Department of Reconstructive Plastic Surgery, The Children's Hospital of Zhejiang University School of Medicine, presenting with a cough and a decreased platelet count of 78x10⁹/l. A posterior-anterior view of the chest was obtained using X-rays, which demonstrated pneumonia. Several antibiotics were altered for dealing with pneumonia and the weekly injection of vincristine was reinitiated for 2 weeks. No further improvement in the platelet count was observed. Laboratory test results showed the following: Platelet count, 86x10⁹ cells/l (normal range, 100-400x10⁹ cells/l); white blood cell count, 5.96x10⁹ cells/l (normal range, 4.00-12.00x10⁹ cells/l); hemoglobin, 97 g/l (normal range, 110-140 g/l); C-reactive protein, <1 mg/l (normal range, <1 mg/l); D-dimer, 853 µg/l (normal range, <500 µg/l); prothrombin time, 11.6 sec (normal range, 9.0-14.0 sec); activated partial thromboplastin time, 23.0 sec (normal range, 23.0-28.0 sec); thrombin time, 18.8 sec (normal range, 15.0-22.0 sec). An emergency surgery was scheduled. Intraoperatively, completely resecting the tumor and stopping the bleeding around the right clavicle was challenging. In the end, partial resection (>90%) was performed and the wound was repaired by skin grafting. The patient was intraoperatively supplied with 3 units platelets (60x10⁹ cells), 1 packed unit red blood cells (20 g hemoglobin) and 200 ml plasma transfusions. On day 3 following surgery, the platelet count was 170x10⁹ cells/l, and on day 10 it was 233x10⁹ cells/l. The surgical specimen was fixed with 10% neutral formaldehyde (Shanghai Ling Feng Chemical Reagent Co., Ltd., Changshu, China) for >24 h and paraffin embedded. The tissue slices (thickness, 4 µm) were stained with hematoxylin and eosin. Histopathology of the KMS revealed tufted angioma (TA). A tumor-like distribution of visible clustered capillary plexus in the dermis and subcutaneous tissue was observed. Low-magnification microscopy (DMLB2; Leica Microsystems GmbH, Wetzlar, Germany) showed a cannon-like appearance of the lesion (Fig. 2). No atypia was identified. Immunohistochemical staining revealed the following: Cluster of differentiation (CD)31⁺ (mouse; 1:100 dilution; GA610; DakoCytomation, Glostrup, Denmark), CD34⁺ (mouse; 1:100 dilution; IR632; DakoCytomation), smooth muscle actin⁺ (mouse; 1:100 dilution; IR611; DakoCytomation), vascular endothelial growth factor⁺ (mouse; 1:100 dilution; M7273; DakoCytomation), vimentin⁺ (mouse; 1:100 dilution; IR630; DakoCytomation) and glucose transporter 1⁺ (polyclonal rabbit; 1:250 dilution;

ab652; Abcam, Cambridge, MA, USA). Upon changing the dressing, the wound was found to be clear and fresh. Two weeks later, however, wound dehiscence and skin graft necrosis were reported, while the platelet count was 187x10⁹/l, white blood cell count 7.33x10⁹/l and C-reactive protein <1 mg/l. Unluckily, a decrease in the platelet count (79x10⁹/l) was again recorded 3 weeks after the surgery, so vincristine injections were repeated postoperatively. Following 4 injections over 1 month, the patient was discharged with a platelet count of 166x10⁹/l and a healing wound.

Half a year later, the patient was readmitted to the Department of Reconstructive Plastic Surgery, The Children's Hospital of Zhejiang University School of Medicine presenting with a severely low platelet count of 36x10⁹/l. During preparation for platelet transfusion, a 63.08% positivity for platelet antibodies was detected (normal value, <30%). Platelet transfusion was delayed and propranolol was introduced to the parents. Due to refractoriness to previous treatments, the parents agreed to oral administration of propranolol for the treatment of KMS. First, the dose of propranolol was increased from 6 mg/day to 24 mg/day (split into 3 equal doses) for three days. The dose was maintained at 24 mg/day in 3 equal doses (2 mg/kg/day) for 3 weeks until the platelet count increased to 134x10⁹/l. During that period, a bone marrow puncture was made to confirm the origin of platelet was normal. Following discharge from the hospital, oral propranolol at the dose of 30 mg/day in 3 equal doses was administered for 5 months and subsequently tapered off. Meanwhile, vincristine was administered intravenously once a month, which resulted in a continued response for 5 months.

At the time of writing the present study, the patient was healthy without evidence of relapse for 2 years.

Discussion

KMS is a rare, aggressive type of vascular tumor that has been associated with thrombocytopenia and consumptive coagulopathy, which can result in a high risk of bleeding (5). KMS was first noted by Kasabach and Merritt in 1940 (1). Enjolras *et al* (2) suggested that KMS was caused by either hemangioendothelioma (KHE), TA or a combination of the two. KHE and TA probably belong to the same neoplastic spectrum and histological continuum (6).

The histopathology of the present case revealed that KMS was associated with TA, which is an infrequently observed benign vascular tumor that was first described by Nakagawa in 1949 under the name angioblastoma (7). The term TA was introduced by Wilson-Jones and Orkin in 1976, based on the characteristic histology of the lesion (8). TA is a solitary tumor or infiltrated plaque believed to have more of an inflammatory appearance than a vascular abnormality (5). The lesion has been described as small, cannonball-like, circumscribed angiomatous tufts and nodules in the dermis and subcutaneous tissue with characteristic lymphangioma-like vessels (9).

The pathogenesis of KMS remains unknown. Platelet trapping by an abnormally proliferating endothelium within the hemangioma may lead to the platelet activation, followed by secondary activation of coagulation cascades, eventually resulting in the consumption of various clotting factors (3,10). Immunohistochemical analysis, using monoclonal antibodies

Table I. Clinical profile of patients with tufted angioma with Kasabach-Merritt syndrome arising from tufted angioma.

Author, year	Age	Gender	Site	Treatment	Outcome	Follow-up	Year of treatment	Country	Ref.
Ferrandiz-Pulido et al, 2010	1 m	Female	Chin	Prednisone + aspirin + VCR + VAC combination + IFN α -2a + Megadose methylprednisolone	Partial response	5 y	2005	Spain	(5)
Kim et al, 2010	2 m	Male	Left pubis	Systemic corticosteroid (DXM + prednisone)	Complete response	1 y	2008	Korea	(11)
Rodriguez et al, 2009	6 w	Female	Left elbow	High-dose methylprednisolone (30 mg/kg/day) + VCR	Near-complete response	4 y	2002	USA	(16)
Wang et al, 2014	2 m	Male	Left knee	Prednisolone + propranolol + VCR + surgery	Complete response	3 y	2010	China	(17)
Chiu et al, 2012	2 d	Female	Right thigh	Propranolol (3 mg/kg/day)	Complete response	6 m	2011	USA	(18)
Choi et al, 2013	15 d	Male	Left cheek	IFN α -2b + prednisolone + propranolol + VCR + VAC combination	No response	6 m	2011	Korea	(19)

w, week; m, month; d, day; y, year; VCR, vincristine; VAC, vincristine, actinomycin D and cyclophosphamide; IFN, interferon; DXM, dextromethorphan.



Figure 1. Preoperative photograph of the mass on the patient's shoulder.

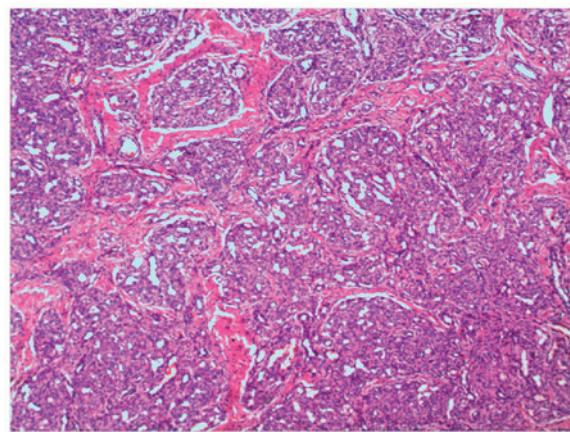


Figure 2. Cannonball-like distribution of small discrete vascular tufts fissured capillary and interstitial fibrosis (hematoxylin and eosin stain; magnification, x40).

against platelet marker CD61, and isotope analysis, using ^{111}In -indium- and ^{51}Cr -labeled platelets, have supported the importance of platelet trapping for the development of KMS (10). In addition, excessive blood flow and sheer stress, secondary to arteriovenous shunts within the tumors, could lead to further platelet activation (11).

The management of KMS is challenging due to its rarity and the lack of well-established systematic treatment strategies (11). Numerous therapeutic modalities have been employed for KMS, with no clear evidence that any type of treatment

is superior over others. It has been suggested that multidisciplinary treatment is required for KMS (5). Several treatment regimens for KMS have been reported, including topical or systemic corticosteroid, IFN, chemotherapy, radiation, laser, propranolol, sirolimus and surgery (5,11-19; Table I).

In the present study, multimodal treatment with steroids, vincristine, surgery and propranolol was selected. An intralesional injection of compound betamethasone (diprospan) was administered at a dose of 1 ml (7 mg) twice a week, equivalent to 10 mg/kg/day of methylprednisolone. As a megadose of a normal intralesional injection, compound betamethasone (diprospan) provided fast-acting and slow-acting treatment to ensure the drug concentration in the lesion was stable.

The reported adverse effects of steroid treatment include hypertension, cushingoid appearance and opportunistic infections (10). Vincristine is considered to be an effective treatment option for TA/KHE; it has been associated with a low incidence of side-effects and should, therefore, be used as first-line treatment (12). Vincristine is a vinca alkaloid antimitotic agent able to block the formation of microtubules in cells (20). Toxicities associated with myelosuppression and neurotoxicity require relevant precautions. In particular, vincristine has been reported to cause loss of deep tendon reflexes, peripheral neuropathy and abdominal autonomic disturbance, such as constipation (21). The effects of angiography and embolization have been shown to be temporary and are used primarily as an adjunct to surgery, in order to minimize bleeding during a planned resection (22). In certain refractory cases, in which the patient cannot be tapered off of the corticosteroids, chemotherapy is used. Therefore, the most common chemotherapy used in such cases is cyclophosphamide, either alone or combined with agents such as vincristine and actinomycin-D (23). Propranolol is a non-selective β -adrenergic antagonist, widely used in the treatment of infantile hemangioma; KMP-associated tumors have been shown to have a variable response to propranolol, and therefore the optimal dose has not yet been established (13,18). Sirolimus, a mammalian target of rapamycin inhibitor, was previously tested in a prospective clinical trial for complicated vascular anomalies (15). However, due to the refractoriness of the treatment, the study did not conclude the best way to deal with KMS.

In a previous study, no platelet antibodies or evidence of an anti-immune process were found to be responsible for the destruction of platelets, which suggests that their destruction may have been due to another mechanism (24). In the present case, however, a positivity of 63.08% for platelet antibodies was detected (normal value, <30%). Prothrombin time and activated partial thromboplastin time have been shown to be either normal or slightly elevated in KMS (16). There were no signs of bleeding and platelet transfusion may have been unnecessary in the present study.

The present study reports a case of KMS as a result of TA, which was managed with multimodal treatment. Although the present patient obtained an optimal objective long-term response with disease control, well-designed, large-scale studies are required in order to clearly determine the benefits and risks of multidisciplinary treatment for KMS. However, accumulating sufficient patients for such studies may be challenging.

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