

Successful treatment of an adult with Kasabach-Merritt syndrome using thalidomide, vincristine, and prednisone

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Abstract

Objective: Kasabach-Merritt syndrome is a rare disease that mainly occurs in infants and adolescents. It usually manifests as disseminated intravascular coagulation and severe bleeding, and is associated with high mortality. However, its low incidence and clinical rarity in adults mean that there is currently no well-verified treatment regimen for this disease. We report on an effective novel therapeutic regimen in a patient with Kasabach-Merritt syndrome.

Methods: A woman with Kasabach-Merritt syndrome presented with a recurrent subcutaneous mass and disseminated intravascular coagulation, and was treated with prednisone, vincristine and thalidomide.

Results: This treatment regimen successfully resolved the patient's symptoms, with tumor regression. The patient remained disease-free after 6 years of follow-up.

Conclusions: Prednisone combined with vincristine and thalidomide may be an effective treatment for Kasabach-Merritt syndrome, but further studies are needed to verify the use of this regimen.

Keywords

Disseminated intravascular coagulation, Kasabach-Merritt syndrome, prednisone, vincristine, thalidomide, combination therapy

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Introduction

Kasabach-Merritt syndrome (KMS) is a rare disease that mainly occurs in infants and adolescents. It usually manifests as disseminated intravascular coagulation and severe bleeding, and is associated with high mortality. However, its low incidence and clinical rarity in adults mean that there is currently no well-verified treatment regimen for this disease. We report a woman with KMS who presented with a recurrent subcutaneous mass and disseminated intravascular coagulation, and was treated with prednisone, vincristine, and thalidomide.

Case report

A 42-year old Chinese woman was admitted to our hospital on November 19, 2012, with a recurrent subcutaneous mass and disseminated intravascular coagulation (DIC). A gradually growing subcutaneous mass in her middle left thigh had been noted 10 months prior to presentation to our hospital. She subsequently developed ecchymosis on her left calf and suffered from swelling pain, which restricted her daily activities. She initially attended her local hospital, where her full blood count, liver and renal function tests, and coagulation profile were normal. Magnetic resonance imaging of the left lower extremity showed a circular mixed signal (about 10.53×3.12 cm) inside the lateral muscle of the left femur, with no clear border. Resection of the mass was performed in the local hospital. Pathological examination revealed an intramuscular hemangioma accompanied by degenerative changes, but no detailed immunohistochemistry staining characteristics were provided. Her postoperative recovery appeared uneventful, but extensive ecchymosis appeared successively on her right thigh, left thigh, and right elbow joint after the operation, accompanied by muscle pain and limited

joint flexion. Further investigations revealed anemia, thrombocytopenia, and reactive bone marrow proliferation. A repeat coagulation function test revealed prolonged prothrombin time (PT) (16.9 s), low fibrinogen (1.1 g/L), and increased D-dimer ($>20 \mu\text{g/mL}$), indicating DIC. She was initially treated with methylprednisolone 80 mg/day for 10 days. However, given the enlarging subcutaneous mass and severely abnormal coagulation test results, 10 U of cryoprecipitate were infused and her condition transiently stabilized.

The patient was admitted to our hospital for further management. Extensive investigations were performed to determine the underlying cause of her DIC. Complete blood count showed white blood cells $8.2 \times 10^9/\text{L}$, hemoglobin 92 g/L, platelets $33 \times 10^9/\text{L}$, and reticulocytes 6.9%. Her coagulation profile revealed PT 15.8 s, activated partial thromboplastin time (APTT) 46.9 s, fibrinogen 0.82 g/L, D-dimer 243.04 mg/L fibrinogen equivalent units, and fibrin degradation products 671 mg/L. Mixed test showed that both PT and APTT were corrected completely. Hemolytic studies, including Coombs test, glucose 6-phosphate dehydrogenase activity, erythrocyte permeability experiments, and CD55/CD59 were all normal. Serum protein electrophoresis and immunofixation showed no monoclonal band. Cytomegalovirus and Epstein-Barr virus DNA tests were both negative. Autoimmune panel, including antinuclear antibody, anti-neutrophil cytoplasmic antibodies, lupus anticoagulant, and anti-cardiolipin antibody, were also negative. Positron emission tomography/computed tomography showed increased metabolic signals (standardized uptake value 1.1–2.7) in multiple muscles (left leg, right forearm, left hip, right thigh muscle), and ultrasound suggested a hemangioma. Review of the pathology slides from the previously resected mass demonstrated an intramuscular hemangioma, positive for CD31, CD34,

and F8, and with a Ki-67 index of about 10%, according to immunohistochemical staining. These findings were consistent with KMS. After correction of her coagulopathy with prothrombin complex concentrates, she was treated with prednisone 60 mg/day (tapered after 3 weeks), vincristine 2 mg/week (9 times), and thalidomide 150 mg/day. The patient's hematomas shrunk markedly and the subcutaneous mass in her left thigh disappeared. Her complete blood count and coagulation profiles also gradually returned to normal, with white blood cells $6.54 \times 10^9/L$, hemoglobin 125 g/L, platelets $167 \times 10^9/L$, PT 11.8 s, APTT 22.7 s, fibrinogen 3.06 g/L, and D-dimer 0.47 mg/L fibrinogen equivalent units. No obvious adverse drug reactions were observed. The patient was discharged with thalidomide 150 mg/day as maintenance therapy, and remained stable during 6 years of follow-up.

The study protocol was approved by the Ethics Review Committee of Peking Union Medical College Hospital and the patient provided written informed consent.

Discussion

DIC is characterized by abnormal activation of the coagulation cascade, consumption of platelets and coagulation factors, and secondary hyperfibrinolysis, leading to systemic bleeding and microcirculatory failure. Rather than being an independent disorder, DIC is a clinicopathological syndrome caused by various underlying disorders, including sepsis, malignancy, large hemangiomas, severe trauma, and obstetric problems. Its management thus includes treatment of the underlying causes and correction of the coagulopathy.

KMS is a rare disorder, mainly reported in neonates but occasionally seen in adults. Croteau et al.¹ conducted an epidemiological study among children in Boston, and found incidence and prevalence rates of

0.071/100,000 and 0.91/100,000, respectively, with 60% of patients falling ill within 1 month after birth. The initial manifestation is usually a vascular lesion on the skin, frequently located on the limbs or trunk, but occasionally in the viscera and retroperitoneal space. Lesions involving the limbs and retroperitoneal space tend to have an earlier presentation. The lesions grow progressively in line with body growth, infiltrating the surrounding tissues or organs, often accompanied by obvious hemorrhagic tendencies in the lesion sites or other parts of the body. Thrombocytopenia and consumptive coagulopathy are key findings, secondary to sequestration of platelets and activation of the coagulation cascade in the local hemangioma. Diagnosis is based on a composite of clinical, laboratory, and pathological features. The condition can be life threatening if DIC occurs, with a mortality of 20% to 40%.^{2,3}

There is currently no consensus on the optimal first- or second-line therapy for KMS, because therapeutic experiences in adults are limited by the low incidence of the condition. If possible, surgical removal of the lesion is the only curative treatment, preferably within the first 3 months of the disease. However, surgery carries a high risk of perioperative complications associated with possible coexisting DIC and hemorrhagic tendency, which are often present at the onset of the disease. The main goals of treatment are to correct DIC, control disease progression, and improve the patient's quality of life. Considering its tumor characteristics, various treatments have been reported for KMS, including glucocorticoids, interferon, cytotoxic drugs, radiotherapy, and arterial embolization.⁴⁻¹² Glucocorticoids (prednisone 2-3 mg/kg/day) are commonly used, and megadose methylprednisolone (30 mg/kg/day) may be administered for 3 consecutive days before administering prednisone in severe cases.¹³

In the current case, we designed a combined regimen comprising prednisone, vincristine, and thalidomide. The mechanisms of thalidomide action include anti-angiogenesis, immunomodulation, and interference with cell adhesion. It has been widely used to treat patients with multiple myeloma, myelodysplastic syndrome, and other neoplastic diseases, as well as rheumatological diseases,^{14–18} and has also been used successfully in other vascular malformations and bleeding disorders.^{19,20} KMS usually involves vascular lesions, and we therefore chose thalidomide in the current patient. This case represents the first reported use of thalidomide in an adult with KMS. Although the apparent efficacy of the treatment in this case was probably the result of various therapeutic measures, we suggest that thalidomide may have played a crucial role.

In 2013, the Journal of Pediatrics published expert consensus guidelines recommending the combination of steroid and vincristine as first-line therapy for KMS.²¹ Steroid monotherapy can be used if vincristine is not readily available,²¹ but most patients respond poorly to glucocorticoid monotherapy and often require a combination of various treatments. If regression cannot be achieved by the above treatments, cytotoxic drugs, interferon, and mTOR inhibitors such as sirolimus may also be used.²²

In summary, KMS is a rare cause of DIC in adults. The current case suggests that thalidomide may have a unique potential to treat this disorder, but its combined use with vincristine and prednisone in this patient made it difficult to ascribe the success of treatment to thalidomide alone. Further studies are therefore needed to explore the role of thalidomide in the treatment of KMS.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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