

SUCCESSFUL TREATMENT OF KASABACH-MERRITT SYNDROME WITH PREDNISONE AND EPSILON-AMINOCAPROIC ACID

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The Kasabach-Merritt syndrome is characterized by thrombocytopenia and localized coagulopathy associated with a hemangioma. Most techniques applied to eradicate the tumor or accelerate its involution (surgery, radiation therapy, embolization) are invasive and require transfusion of large amounts of blood products. In some cases, medical treatment is the only alternative. Efficacy of steroids and antifibrinolytic agents has already been described, but even this approach is associated with the administration of blood products. We report two cases of infants with Kasabach-Merritt syndrome associated with cardiac and hepatic hemangiomas. At admission, both had signs of cardiac failure. They were successfully treated with prednisone and epsilon-aminocaproic acid (EACA). Blood products were not required once the diagnosis was made. These observations have important implications for the management of patients with Kasabach-Merritt syndrome because they show that even in severe cases blood transfusions can be avoided by the use of prednisone and EACA.

KEY WORDS: antifibrinolytic agents, epsilon-aminocaproic acid, hemangioma, Kasabach-Merritt syndrome, steroids.

INTRODUCTION

Hemangioma is the most common vascular neoplasm in childhood. It is usually cutaneous, of small size, asymptomatic, and most often resolves spontaneously.¹ In rare instances it may be life-threatening. Possible complications include hemorrhage, heart failure, liver rupture,² and Kasabach-Merritt syndrome. This syndrome is characterized by thrombocytopenia and a localized consumptive coagulopathy associated with a hemangioma.³ The treatment consists of eradicating the tumor or accelerating its involution, which usually cures the coagulopathy. A variety of strategies have been applied to achieve

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remission. Many of these are invasive and require transfusion of large amounts of blood products. We report two cases of infants with Kasabach-Merritt syndrome associated with cardiac and hepatic hemangiomas respectively. Both were treated and cured with prednisone and epsilon-aminocaproic acid (EACA). In both cases, administration of blood products was avoided.

CASE REPORTS

Case Report 1

A 2-month-old boy was admitted to the hospital with congestive heart failure. Chest x-ray showed cardiomegaly. Cardiac sonography revealed a pericardiac effusion with signs of pre-tamponade and a mass in the posterior wall of the left atrium. A pericardiac drainage was performed for treatment of the tamponade. The liquid was serous and contained lymphocytes. At admission, the patient's complete blood count revealed a platelet count of $56 \times 10^9/L$. The prothrombin time was 18 sec (control, 12 sec), the partial thromboplastin time was 40.9 sec (control, 30 sec), fibrinogen was 0.57 g/L, and fibrin-split products were 40 $\mu g/mL$. Because of the cardiac failure, surgery was delayed until 10 days after admission. Preoperatively, the patient received 2 units of platelets and 100 mL of plasma. At the time of operation the platelet count was $96 \times 10^9/L$ and the consumptive coagulopathy was still active. Fibrinogen was 0.96 g/L and fibrin-split products were 40 $\mu g/mL$. After sternotomy and pericardiotomy, the mass was found to be inoperable and a biopsy was performed. A diagnosis of benign hemangioendothelioma was made. Hemostasis was difficult to achieve at the biopsy site. Administration of an intravenous bolus of 100 mg/kg of EACA instantly controlled the bleeding.

Treatment with prednisone (2 mg/kg/day divided into two doses) and EACA (100 mg/kg/dose every 6 hours, intravenously for 7 days and per os subsequently) was initiated. Although there was only a slight decrease in the size of the mass, there was substantial clinical improvement. The platelet count rapidly rose to normal. Over a 1-month period prednisone was gradually tapered, then discontinued. However, following discontinuation of prednisone the platelet count fell again to $56 \times 10^9/L$. At that time, the patient was still receiving EACA but his fibrinogen had severely decreased to 0.35 g/L. Corticotherapy was therefore resumed for a total of 6 months. EACA was continued for 14 months until complete resolution of the lesion. One year after cessation of treatment, the child is asymptomatic with normal growth and development. The only sign at cardiac sonography is a thickening of the posterior wall of the left atrium. Complete blood count, fibrinogen levels, and coagulation studies remain within the normal range.

Case Report 2

A female infant presented at birth with massive hepatomegaly and congestive heart failure. Sonography and echo Doppler revealed a large hepatic hemangioma measuring $5 \times 6 \times 7$ cm. The white blood count was normal at $13.8 \times 10^9/L$ with a normal differential. The hemoglobin was 148 g/L, and the platelet count $40 \times 10^9/L$. Examination of the blood smear revealed no other abnormalities. The prothrombin time was 13 sec (control, 11.9 sec). The partial thromboplastin time was 45 sec (control, 30.9 sec). Fibrinogen was decreased at 0.7 g/L and the thrombin time was prolonged at 50.8 sec (control, 18.9 sec). Fibrin-split products were elevated at $80 \mu g/mL$.

A treatment with digitalis and diuretics was initiated for cardiac failure. The patient was treated with prednisone 2 mg/kg/day (in two doses) and EACA 100 mg/kg/day four times a day. Within a few days the patient improved dramatically, the platelet count rose sharply to normal, and the signs of consumption coagulopathy disappeared. The cardiac failure was rapidly controlled and the size of the hemangioma gradually decreased. Prednisone was continued for 4 months and EACA for 5 months. After a treatment-free period of 7 months, physical examination, complete blood count, and coagulation studies are normal. Sonography shows a calcified hemangioma measuring $2 \times 3 \times 4$ cm.

DISCUSSION

The Kasabach-Merritt syndrome is characterized by a localized intra-hemangioma consumptive coagulopathy, with increased turnover of both platelets and fibrinogen.^{4,5,6} Use of indium-111 oxine-labeled platelets has clearly demonstrated platelet trapping in the hemangioma.⁷ Vascular stasis and a possible abnormality of the endothelial wall of the hemangioma probably lead to clotting and depletion of platelets and coagulation factors. The fibrinolytic pathway is activated secondarily.⁸ Classical treatment of the Kasabach-Merritt syndrome consists of tumor eradication. It can be achieved by different techniques: surgery,⁹ radiation therapy,^{3,10} and embolization.¹¹ The size of the hemangioma and its location often hinder surgical excision. Moreover, uncontrolled coagulopathy is a contraindication for surgery. Radiation therapy often results in good hemangioma regression but could be associated with local tissue damage and potential long-term risk of carcinogenesis. Embolization can be performed with suitable vascular anatomy only.¹² When eradication is contraindicated or unfeasible, medical treatment is the only alternative. Steroids were shown to be effective.¹³⁻¹⁵ Zweifach et al demonstrated that, in adrenalectomized rats, corticosteroids restore the sensitivity of the terminal vascular beds to vasoconstrictive agents.¹⁶ Other studies in ani-

TABLE 1. Previous Studies on Successful Treatment of Kasabach-Merritt Syndrome by Antifibrinolytic Agents

Study	Sex	Age	Site of lesion	DIC*	Transfusion	Steroids	Treatment		
							Antifibrinolytic	Other	Other
Hanna et al ²⁴	F	Newborn	Chest	Yes	Yes	12 mo	Tranexamic acid	16 mo	None
Henriksson et al ²⁶	F	3 mo	Arm	Yes	Yes	No	EACA		None
Neidhart et al ²⁵	M	19 yrs	Femur	Yes	Yes	2 mo	EACA	6 wks	None
Orchard et al ²³	M	4 mo	Colon, rectum, retroperitoneal	Yes	Yes	7 mo	EACA		Laser embolization, surgery, interferon
Ortel et al ²⁷	M	32 yrs	Scapula	Yes	Yes	Single dose (pretransfusion)	EACA	49 days	Embolization
Warrel et al ⁸	F	17 yrs	Chest, intraabdominal	Yes	Yes	No	EACA		Heparin, anti-inflammatory

*Disseminated intravascular coagulation.

mal models show that steroids decrease the fenestration of endothelial cells.¹⁷ Steroids inhibit the production of tissue plasminogen activators¹⁸ and increase the plasminogen activator inhibitors,¹⁹ both effects leading to reduction of fibrinolysis. Despite the administration of high-dose prednisone for 6 and 4 months, no side effects were observed in our two cases and they grew normally. Antiplatelet drugs such as aspirin and dipyridamole have also been used with prednisone to treat the coagulopathy of the Kasabach-Merritt syndrome,²⁰ but the risk of hemorrhage limits their use. Heparin has the same side effect.²¹ Cyclophosphamide has been successfully used,²² but this agent is associated with an unacceptably high risk of mutagenesis and should be reserved only for life-threatening lesions unresponsive to other therapies. Recently, interferon was shown to be effective for a retroperitoneal hemangioma.²³ By promoting intralesional thrombosis, EACA may contribute to decreasing the blood flow in the abnormal vessels of hemangioma. Table 1 presents studies in which EACA and other antifibrinolytic agents such as tranexamic acid have been used alone or combined with other therapies. It includes cases of corticosteroid-resistant patients who had major evidence of active fibrinolysis, but EACA was associated with the administration of cryoprecipitates.^{8,25,26,27} Why blood transfusions could be avoided in the two cases presented here and not in the cases listed in Table 1 is difficult to ascertain. Possible explanations may be that the hemangiomas were diagnosed early, which limited their size as well as the associated coagulopathy, initiation of EACA and prednisone without delay, and different criteria for transfusion. It is also noteworthy that the effects of EACA in case 1 is not clear, and it is possible that prednisone alone would have been sufficient to cure the coagulopathy, which may reflect a different pathologic process.

In conclusion, our observations have important implications for the management of patients with Kasabach-Merritt syndrome because they show that invasive procedures and blood transfusions are not always essential for managing the associated coagulopathy.

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