Int J Clin Exp Med 2015;8(6):10006-10010
www.ijcem.com /ISSN:1940-5901/IJCEM0008246

*Original Article*

# Kasabach-Merritt phenomenon in Chinese children: Report of 19 cases and brief review of literature

Si-Ming Yuan[1], Wei-Min Shen[2], Hai-Ni Chen[2], Zhi-Jian Hong[1], Hui-Qing Jiang[1]

*[1]Department of Plastic Surgery, Jinling Hospital, School of Medicine, Nanjing University, Nanjing 210002, Jiangsu, China; [2]Department of Plastic Surgery, Nanjing Children's Hospital, Nanjing 210008, Jiangsu, China*

Received March 19, 2015; Accepted June 3, 2015; Epub June 15, 2015; Published June 30, 2015

**Abstract:** Kasabach-Merritt phenomenon (KMP) is life-threatening, charactered by the profound thrombocytopenia and consumptive coagulopathy associated with vascular tumors. The therapy of KMP still remains challenging. In this study, we retrospectively analyzed the clinical data of KMP treated in Nanjing Children's Hospital and Jinling Hospital, China, and brief reviewed the literature on KMP. From Jan. 2005 to Dec. 2014, a total of 19 cases of KMP were enrolled into this study. Laboratory results showed that seven patients had typical disseminated intravascular coagulation (DIC), and others were atypical DIC. CT scanning showed the low-density tumor with obvious intensification in enhanced scanning, and the large distorted arteries in association with the tumor. After the admission, the patients received the infusion of platelets and the applying of dipyridamole, steroids, and other necessary drugs. Eight patients underwent complete surgical removal of the tumor, or partial removal with subsequent chemotherapy of vincristine. Three patients underwent only the chemotherapy of vincristine. Eight patients underwent the intralesional injection of absolute ethanol. Pathological examination showed eighteen samples were kaposiform hemangioendothelioma, and one tufted agioma. In our cases, six patients died from extensive hemorrhage and subsequent multiple organ failure. The others survived. In conclusion, KMP in Chinese children has typical symptoms. Kaposiform hemangioendothelioma is the most frequent vascular tumor associated with KMP. The individual treatments with surgical management, chemotherapy with vincristine, and intralesional injection of absolute ethanol can achieve good results in most of the patients with KMP.

**Keywords:** Kasabach-merritt phenomenon, kaposiform hemangioendothelioma, diagnosis, therapy

## Introduction

Kasabach-Merritt phenomenon (KMP) is a rare and life-threatening disease in childhood with high mortality rate. It is charactered by the profound thrombocytopenia, microangiopathic hemolytic anemia, and subsequent consumptive coagulopathy in association with vascular tumors, including kaposiform hemangioendothelioma (KHE), tufted angioma, lymphangioendotheliomatosis, and angiosarcoma, etc. [1-4]. Among them, KHE is most frequently reported. Infantile hemangioma doesn't lead to KMP [5].

Treatments of KMP include surgical management, systemic corticosteroids and interferon, chemotherapy with vincristine, inventional embolization, and radiotherapy [6]. Recently, sirolimus and propranolol were used in the treatment of KMP [6]. In spite of above options, there isn't a consensus on the optimal medical management due to the variable response of patients. In this study, we retrospectively analyzed the clinical data of 19 cases of KMP treated in our clinic. And we briefly reviewed the diagnosis, therapy and pathogenesis of KMP.

## Patients and methods

### *Clinical data*

We retrospectively collected the data of patients with KMP treated in Nanjing Children's Hospital and Jinling Hospital, Jiangsu, China, from Jan. 2005 to Dec. 2014. The following criteria were used for diagnosis: (1) Vascular tumor. (2) Profound thrombocytopenia and consumptive coagulopathy. (3) Treatment of the tumor can improve clinical symptoms. (4) Other diseases that can cause thrombocytopenia or

consumptive coagulopathy were excluded, such as hypersplenism and idiopathic thrombocytopenic purpura. The results of ecsomatics, imageology, and pathology were summarized. The treatments and outcomes of patients were reviewed.

*Statistics*

Microsoft® Office Excel was used to calculate the average and standard deviation.

## Results

*Clinical features*

Nineteen patients were included in this study, eleven of which were male. The average age of patients at admission was 43.5 days (age range, 1 day~120 days). The surface area of the tumor estimated by physical examination ranged from 6 $cm^2$~210 $cm^2$, with an average of 78.3 $cm^2$. Tumors were located in the head (n=3), neck (n=2), trunk (n=9), buttocks (n=1), upper extremity (n=2), and lower extremity (n=3). In some cases, the tumors extended into the thoracic cavity and retroperitoneum.

*Laboratory results at admission*

*Platelets and coagulation:* The average number of platelets was $22.8\times10^9$/L. The lowest number of PLT was $6.22\times10^9$/L in a 25-day-old boy with a 30 $cm^2$ tumor in the right lower extremity. The averages of PT, TT, KPTT, and FIB were 15.85 s, 23.64 s, 44.26 s, and 1.21 g/L, respectively. The most severe abnormality of PT, TT, KPTT, and FIB were 20.6 s, 31.6 s, 54.2 s, and 0.57 g/L in a just born boy with a 96 $cm^2$ tumor in the back. According to the criteria of disseminated intravascular coagulation (DIC) [7], seven patients had typical DIC and the others had atypical DIC.

*Erythrocytes:* The averages of erythrocytes and hemoglobin were $3.16\times10^{12}$/L and 86.73 g/L. The lowest value of erythrocytes and hemoglobin was $1.71\times10^{12}$/L and 55 g/L in a 52-day-old girl with a 176 $cm^2$ tumor in the Left buttock. According to the criteria of anemia, three patients had severe anemia; seven patients had moderate anemia; and nine patients had slight anemia.

*Leukocytes:* The averages of leukocytes, percent of neutrophils, and percent of lymphocytes were $13.18\times10^9$/L, 38.56%, and 52.35%, respectively. The value of leukocytes in twelve cases was higher than normal value.

*CT scanning*

CT scanning showed diffused or clumping low-density tumor with dot or stripe calcification. In enhanced scanning, there was uniform intensification in small tumor or marginal intensification in large tumor. Large distorted arteries flowing into tumor were detected.

*Treatment*

The patients received the infusion of platelets and the applying of dipyridamole, steroids, and other necessary drugs after admission. Eight patients underwent complete surgical removal of the tumor, or partial removal with subsequent chemotherapy of vincristine. Three patients underwent only the chemotherapy of vincristine. Eight patients underwent the intralesional injection of absolute ethanol. The samples were acquired from all the tumors by the operation or core needl biopy. Eighteen samples were diagnosed as kaposiform hemangioendothelioma and one tufted agioma.

*Outcome*

Among the nineteen patients, six patients died from extensive hemorrhage and subsequent multiple organ failure. The others survived and were still in follow-up.

## Discussion

*Diagnosis of KMP*

KMP can be diagnosed by symptoms (extensive hemorrhage), signs (purple tumors), laboratory results (profound thrombocytopenia and consumptive coagulopathy), and imaging [8]. CT scanning can show tumor clearly. MRI scanning also can supply useful information [9]. But it needs longer time than CT scanning. The differential diagnosis for vascular tumors complicated by KMP includes KHE, tufted angioma, and lymphangioendotheliomatosis, angiosarcoma, etc. Pathological examination is necessary for the exact diagnosis [3, 10].

*Therapy of KMP*

KMP is life-threatening with high mortality rate. Extensive hemorrhage, respiratory failure due

to a pressured airway, and high-output heart failure are the major causes for the death of children. Effective therapy should be started as soon as possible once the diagnosis of KMP is established. The treatments are summarized as following.

*Supportive treatment:* This includes infusion of blood components (platelets, erythrocytes, and blood plasma), coagulation factors (thrombin and fibrinogen), and anticoagulant or anti-platelet drugs (heparin, warfarin [11] and dipyridamole [12]). Platelets are a particular problem in KHE, as their VEGF content might stimulate tumor growth and thus promote complications. So the infusion of platelets is discouraged in the absence of acute bleeding [13].

*Surgical management:* Surgical intervention is the first choice if operation will not destroy patient's appearance or function. Complete removal of the tumor can cure KMP [14]. Partial removal of the tumor with subsequent chemotherapy of vincristine also can effectively release KMP [15].

*Embolization:* This can be performed on huge tumors which aren't suitable for surgical management. Interventional or percutaneous puncture was used to embolize the nutritional arteries of tumor [16, 17]. Antitumor drugs (such as vincristine and bleomycin A) can be injected simultaneously. Intralesional injection of absolute ethanol also was effective for KMP [18].

*Oral corticosteroids:* Oral steroids were reported to have effect on KMP a long time ago [12]. The recommended dosage of oral prednisone was 3~5 mg/kg/d [12]. For those patients resistant to steroids, alterative treatments, such as vincristine and interferon, should be adopted in time.

*Chemotherapy:* Vincristine was reported to successfully treat KMP with mild side effects, and had satisfying long-term outcome so it was recommended as the first choice for KMP [19, 20]. Cyclophosphamide and actinomycin-D also was applied in the treatment of KMP [21].

*Interferon:* Interferon was reported to release KMP which didn't respond to corticosteroids [12, 22]. Notably, spastic diplegia resulted from interferon has been observed in the infants less than 12-month-old [23].

*Propranolol:* Since the first report in 2008, propranolol has showed many advantages in the treatment of infantile hemangioma [24]. But its effect on KMP still has controversy [25] although there was case report suggesting it may be useful in the mild KMP [26].

*Sirolimus (also called rapamycin):* It's an immunosuppressive preparation, but also shows the effects of inhibiting the vasculogenesis and angiogenesis [27], and has been reported to successfully treat blue rubber bleb nevus syndrome [28]. Recently, several studies reported its use in refractory KMP acquired rapid response [29, 30]. Sirolimus may be a new therapeutic option for KMP.

*Radiotherapy:* It was used on life-threatening KMP which didn't response to the above treatments [31, 32]. But long-term adverse effects after radiotherapy have been reported, including skin atrophy, ulcer, growth retardation, and possible malignant tumor [33].

*Pathogenesis of KMP*

The mechanism of KMP still remains unclear till now. Radioactive labeling and immunohistochemical markers have demonstrated platelet trapping in KHE [34, 35]. Our ultrastructural observation and immunohistochemistry staining revealed the trapping of blood components, not only platelets [36]. The abnormality of PT, TT, KPTT, and fibrinogen reflected the hypofibrinogenemia and fibrinolysis caused by disseminated intravascular coagulation. And sequestration and damage of red cells in the tumor led to severe anemia. Although above results supplied some evidences for explaining the occurring of KMP, but the mechanism of the trapping of platelets and intratumoral coagulopathy still need further study.

**Acknowledgements**

This work was supported by the National Natural Science Foundation of China (No. 81272989). We thank Dr. Jie Cui, Dr. Jian-Bin Chen, Dr. Xiu-Kun Wang for their help in patients recruition.

**Disclosure of conflict of interest**

None.

**Address correspondence to:** Dr. Si-Ming Yuan, Department of Plastic Surgery, Jinling Hospital, School of Medicine, Nanjing University, 305 East Zhongshan Road, Nanjing 210002, Jiangsu, China. Tel: 086-25-80860020; Fax: 086-25-80860211; E-mail: yuansm@163.com

## References

[1] Zukerberg LR, Nickoloff BJ, Weiss SW. Kaposiform hemangioendothelioma of infancy and childhood; an aggressive neoplasm associated with Kasabach-Merritt syndrome and lymphangiomatosis. Am J Surg Pathol 1993; 17: 321-328.

[2] Yesudian PD, Parslew R, Klafowski J, Gould D, Pizer B. Tufted angioma-associated Kasabach-Merritt syndrome treated with embolization and vincristine. Plast Reconstr Surg 2008; 121: 692-693.

[3] North PE, Kahn T, Cordisco MR, Dadras SS, Detmar M, Frieden IJ. Multifocal lymphangioendotheliomatosis with thrombocytopenia. Arch Dermatol 2004; 140: 599-606.

[4] Grellety T, Italiano A. Angiosarcoma associated with a Kasabach-Merritt syndrome: report of two cases treated with paclitaxel. Future Oncol 2013; 9: 1397-1399.

[5] Sarkar M, Mulliken JB, Kozakewich HP, Robertson RL, Burrows PE. Thrombocytopenic coagulopathy (Kasabach-Merritt phenomenon) is associated with kaposiform hemangioendothelioma and not with common infantile hemangioma. Plast Reconstr Surg 1997; 100: 1377-1386.

[6] Tlougan BE, Lee MT, Drolet BA, Frieden IJ, Adams DM, Garzon MC. Medical management of tumors associated wit h Kasabach-Merritt phenomenon: an expert survey. J Pediatr Hematol Oncol 2013; 35: 618-622.

[7] Bakhtiari K, Meijers JC, de Jonge E, Levi M. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. Crit Care Med 2004; 32: 2416-2421.

[8] Rodriguez V, Lee A, Witman PM, Anderson PA. Kasabach-merritt phenomenon: case series and retrospective review of the mayo clinic experience. J Pediatr Hematol Oncol 2009; 31: 522-526.

[9] Chen YJ, Wang CK, Tien YC, Hsieh TJ. MRI of multifocal kaposiform haemangioendothelioma without Kasabach-Merritt phenomenon. Br J Radiol 2009; 82: e51-54.

[10] North PE, Waner M, Buckmiller L, James CA, Mihm MC Jr. Vascular tumors of infancy and childhood: beyond capillary hemangioma. Cardiovascular Pathology 2006; 15: 303-317

[11] Mori K, Suzuki S, Ishikawa M, Akutsu Y, Toyota T, Sakai H. A case of Kasabach-Merrit syndrome complicated with DIC treated effectively by long term oral administration of warfarin. Rinsho Ketsueki 1995; 36: 200-205.

[12] Wananukul S, Nuchprayoon I, Seksarn P. Treatment of Kasabach-Merritt syndrome: a stepwise regimen of prednisolone, dipyridamole, and interferon. Int J Dermatol 2003; 42: 741-748.

[13] Mulliken JB, Anupindi S, Ezekowitz RA, Mihm MC Jr. A Newborn Girl with a Large Cutaneous Lesion, Thrombocytopenia, and Anemia. N Engl J Med 2004; 350: 1764-1775.

[14] Velin P, Dupont D, Golkar A, Valla JS. Neonatal Kasabach-Merritt syndrome healed by complete surgical excision of the angioma. Arch Pediatr 1998; 5: 295-297.

[15] Shen W, Cui J, Chen J, Zou J, Ji Y, Chen H. Kasabach-Merritt syndrome with partial resection of tumor, reduction of tumor blood, and vincristine chemotherapy. J Craniofac Surg 2010; 21: 215-216.

[16] Billio A, Pescosta N, Rosanelli C, Zanon GF, Gamba PG, Savastano S, Coser P. Treatment of Kasabach-Merritt syndrome by embolisation of a giant liver hemangioma. Am J Hematol 2001; 66: 140-141.

[17] Hosono S, Ohno T, Kimoto H, Nagoshi R, Shimizu M, Nozawa M, Fuyama Y, Kaneda T, Moritani T, Aihara T. Successful transcutaneous arterial embolization of a giant hemangioma associated with high-output cardiac failure and Kasabach-Merritt syndrome in a neonate: a case report. J Perinat Med 1999; 27: 399-403.

[18] Shen W, Cui J, Chen J, Zou J, Xiaoying Z. Treating kaposiform hemangioendothelioma with Kasabach-Merritt phenomenon by intralesional injection of absolute ethanol. J Craniofac Surg 2014; 25: 2188-2191.

[19] Fernandez-Pineda I, Lopez-Gutierrez JC, Chocarro G, Bernabeu-Wittel J, Ramirez-Villar GL. Long-term outcome of vincristine-aspirin-ticlopidine (VAT) therapy for vascular tumors associated with Kasabach-Merritt phenomenon. Pediatr Blood Cancer 2013; 60: 1478-1481.

[20] Wang Z, Li K, Yao W, Dong K, Xiao X, Zheng S. Steroid-resistant kaposiform hemangioendothelioma: A retrospective study of 37 patients treated with vincristine and long-term follow-up. Pediatr Blood Cancer 2015; 62: 577-580.

[21] Hu B, Lachman R, Phillips J, Peng SK, Sieger L. Kasabach-Merritt syndrome-associated kaposiform hemangioendothelioma successfully treated with cyclophosphamide, vincristine, and actinomycin D. J Pediatr Hematol Oncol 1998; 20: 567-569.

[22] Hartman KR, Moncur JT, Minniti CP, Creamer KM. Mediastinal Kaposiform hemangioendothelioma and Kasabach-Merritt phenomenon in an infant: treatment with interferon. J Pediatr Hematol Oncol 2009; 31: 690-692.
[23] Fledelius HC, Illum N, Jensen H, Prause JU. Interferon-alfa treatment of facial infantile haemangiomas: with emphasis on the sight-threatening varieties. A clinical series. Acta Ophthalmol Scand 2001; 79: 370-373.
[24] Sans V, de la Roque ED, Berge J, Grenier N, Boralevi F, Mazereeuw-Hautier J, Lipsker D, Dupuis E, Ezzedine K, Vergnes P, Taïeb A, Léauté-Labrèze C. Propranolol for severe infantile hemangiomas: follow-up report. Pediatrics 2009; 124: e423-431.
[25] Wang Z, Li K, Dong K, Xiao X, Zheng S. Variable response to propranolol treatment of kaposiform hemangioendothelioma, tufted angioma, and Kasabach-Merritt phenomenon. Pediatr Blood Cancer, 2014, 61: 1518-1519.
[26] Choeyprasert W, Natesirinilkul R, Charoenkwan P. Successful treatment of mild pediatric kasabach-merritt phenomenon with propranolol monotherapy. Case Rep Hematol 2014; 2014: 364693.
[27] Greenberger S, Yuan S, Walsh LA, Boscolo E, Kang KT, Matthews B, Mulliken JB, Bischoff J. Rapamycin suppresses self-renewal and vasculogenic potential of stem cells isolated from infantile hemangioma. J Invest Dermatol 2011; 131: 2467-2476.
[28] Yuksekkaya H, Ozbek O, Keser M, Toy H. Blue rubber bleb nevus syndrome: successful treatment with sirolimus. Pediatrics 2012; 129: e1080-1084.
[29] Wang Z, Li K, Dong K, Xiao X, Zheng S. Refractory Kasabach-Merritt phenomenon successfully treated with sirolimus, and a mini-review of the published work. J Dermatol 2015; 42: 401-4
[30] Blatt J, Stavas J, Moats-Staats B, Woosley J, Morrell DS. Treatment of childhood kaposiform hemangioendothelioma with sirolimus. Pediatr Blood Cancer 2010; 55: 1396-1398.
[31] Kwok-Williams M, Perez Z, Squire R, Glaser A, Bew S, Taylor R. Radiotherapy for life-threatening mediastinal hemangioma with Kasabach-Merritt syndrome. Pediatr Blood Cancer 2007; 49: 739-744.
[32] Watanabe Y, Onuma M, Looi CY, Saito Y, Kitazawa H, Niizuma H, Rikiishi T,Sakamoto O, Sasahara Y, Kumaki S, Watanabe M, Ushio S, Tsuchiya S. Vincristine-resistant Kasabach-Merritt phenomenon successfully treated with low-dose radiotherapy. Int J Hematol 2011; 93: 126-128.
[33] Mitsuhashi N, Furuta M, Sakurai H, Takahashi T, Kato S, Nozaki M, Saito Y, Hayakawa K, Niibe H. Outcome of radiation therapy for patients with Kasabach-Merritt syndrome. Int J Radiat Oncol Biol Phys 1997; 39: 467-473.
[34] Warrell RP Jr, Kempin SJ, Benua RS, Reiman RE, Young CW. Intratumoral consumption of indium-111 labeled platelets in a patient with hemangiomatosis and intravascular coagulation (Kasabach-Merritt syndrome). Cancer 1983; 52: 2256-2260.
[35] Seo SK, Suh JC, Na GY, Kim IS, Sohn KR. Kasabach-Merritt syndrome: Identification of platelet trapping in a tufted angioma by immunohistochemistry technique using monoclonal antibody to CD61. Pediatr Dermatol 1999; 16: 392-394.
[36] Yuan SM, Hong ZJ, Chen HN, Shen WM, Zhou XJ. Kaposiform hemangioendothelioma complicated by Kasabach-Merritt phenomenon: ultrastructural observation and immunohistochemistry staining reveal the trapping of blood components. Ultrastruct Pathol 2013; 37: 452-455.