Littoral cell angioma of the spleen revealed by a Kasabach-Merritt syndrome in a 22-month-old child

Marie-Amelyne Le Rouzic[1], Julie Valduga[1], Aurélie Phulpin-Weibel[1], Ludovic Mansuy[1], Audrey Contet[1], Fanny Fouyssac[1], Imane Athmani[1], Marie-Agnès Galloy[2], Michel Wassef[3], Pascal Chastagner*,[1]

[1]Department of Pediatric Hematology and Oncology, Children's University Hospital, Nancy, France, [2]Department of Pediatric Radiology, Children's University Hospital, Nancy, France, [3]Department of Pathological Anatomy, Lariboisière Hospital, Paris

Abstract

Introduction: Kasabach-Merrit syndrome (KMS) is characterized by the association of a vascular tumor, thrombocytopenia and potentially life-threatening coagulopathy. Observation: A 22-month-old child was referred to our center for incidental discovery of thrombocytopenia in a context of recurrent throat infections. Clinical examination showed petechial purpura, subicterus, no tumoral syndrome and good overall condition. His biological parameters showed regenerative hemolytic anemia (10.2 g/dL), thrombocytopenia (32 G/L), no schistocytes, moderate fibrinopenia and positive D-dimer test. The results of bone marrow analysis and auto-immune tests were normal. No treatment was undertaken given the absence of diagnosis and complication. The child was regularly followed-up in consultation. Complementary investigations ruled out Wilson's disease, thrombotic thrombocytopenic purpura and constitutional red blood cell disorders. The main hypothesis remained a thrombotic microangiopathy despite absence of schistocytes on repeated blood tests. Two months later, he was rehospitalized for acute clinical and biological worsening with splenomegaly and severe consumption coagulopathy leading to suspect a myeloproliferative syndrome, finally refuted. Steroids were started due to worsening hemorrhagic symptoms, daily transfusion requirements and increasing splenomegaly. Due to worsening health status and risk of threatening rupture, splenectomy was performed and histopathological analysis revealed a vascular lesion infiltrating the whole spleen, compatible with a littoral cell angioma. The child showed rapid clinical improvement and complete hematological normalization within 48 hours post-splenectomy. Conclusion: Littoral cell angioma is a very rare and benign vascular lesion which may be complicated by a life-threatening KMS. This diagnosis should be suspected in patients presenting with splenomegaly and features of thrombotic microangiopathy.

Keywords: *Kasabach-Merritt syndrome, thrombotic microangiopathy, littoral cell angioma, child*

Introduction

Kasabach-Merritt syndrome (KMS) is characterized by the association of a vascular tumor, a major thrombocytopenia and a potentially life-threatening coagulopathy. It develops in infancy and is associated with a high morbidity and mortality rate [1], as a result of severe bleeding, sepsis or invasion in vital organs [2].

Received: October 2017; Accepted after review: December 2017; Published: December 2017.

*Corresponding author: Prof. Pascal Chastagner, Department of Pediatric Hematology and Oncology, Children's University Hospital, 11 Allée du Morvan, 54511 Vandoeuvre, France.
Email: p.chastagner@chru-nancy.fr

Interaction between platelets and endothelial cells, and the resulting proangiogenic phenotype, has been recognized to underlie the pathogenesis of this disorder [3].

KMS is not associated with infantile hemangiomas (which are common benign vascular lesions) but occurs almost exclusively as a complication of other rare entities such as kaposiform hemangioendotheliomas (KHE) and tufted angiomas (TA). Many arise from the soft tissue of the extremities and slightly more than 10% of all cases lack cutaneous manifestations [4]. Littoral cell angioma (LCA) is another rare and benign vascular lesion, first described in 1991 by Falk et al [5], which may be complicated by life-threatening KMS.

We report here on a patient with a littoral cell angioma of the spleen who displayed a severe KMS with complex diagnosis. The occurrence of this uncommon internal tumor is very rare and may be considered as an unusual presentation.

Case Report

A 22-month-old child was referred to our hospital for incidental discovery of thrombocytopenia in a context of asthenia. He was the second child of Caucasian parents and had no medical history except for recurrent ear, nose and throat (ENT) infections.

Clinical examination showed ecchymotic purpura of the lower limbs and petechial purpura of the upper limbs. He was also found with mild conjunctival icterus, no tumoral syndrome, no hepato-splenomegaly and good general condition.

His laboratory parameters showed regenerative hemolytic anemia (hemoglobin: 10.2 g/dL, reticulocytosis: 180 G/L, haptoglobin < 0.08 g/dL) and thrombocytopenia (platelets: 32 G/L with normal mean platelet volume). The rest of his laboratory evaluation revealed elevated white blood cells count (15.3 G/L), normal liver and pancreatic function tests, decreased prothrombin ratio (59%), low fibrinogen level (1.4 g/L), presence of fibrin degradation products, positive D-dimer test and low factor V level. Abdominal ultrasound showed an enlarged homogeneous spleen (131 mm) with no other abnormalities observed. Bone marrow aspiration and biopsy were performed and showed a high megakaryocyte count with no neoplastic infiltration. Complementary investigations ruled out Wilson's disease, viral infections, thrombotic thrombocytopenic purpura and constitutional red blood cell disorders. Our main hypothesis remained a thrombotic microangiopathy (TMA) despite the absence of schistocytes on repeated blood tests.

Given the absence of diagnosis and complication, no treatment was undertaken. The child was regularly followed-up in consultation for two months, during which time his platelet count ranged between 25 and 45 G/L. He was then re-examined in consultation for acute clinical and biological worsening. Physical examination revealed persistent purpura and conjunctival icterus, associated with appearance of palpable splenomegaly (measuring 158 mm on ultrasound control with a heterogeneous pattern). He presented hematomas after venipunctures and active bleeding after a second bone marrow aspiration was performed (yielding the same results as in the first analysis). At admission to hospital, his hematological parameters revealed thrombocytopenia (27 G/L), anemia (Hb: 9.7 g/dL), high reticulocytosis (368 G/L), persistent stigmata of hemolysis, decreased prothrombin ratio (48%), low fibrinogen (0.8 g/L) and low factor V level (45%). The following days, we noted a rapid deterioration of his biological parameters with daily transfusion requirements. The patient presented prolonged prothrombin time and unmeasurable fibrinogen levels. Partial and transitory improvement was observed after fibrinogen supplementation followed by secondary deterioration.

Even if no schistocytes were found on repeated peripheral blood smears, TMA remained our main hypothesis with suspicion of an unusual spleen-localized presentation. However, successive blood cell counts showed fluctuating leukocytosis with monocytosis at the upper limit of normal, stressing out the need to rule out a hemopathy like juvenile myelomonocytic leukemia, finally refuted.

At day 6 of hospitalization, a bluish subcutaneous nodular skin lesion appeared on the anterior face of the tibia. A biopsy was performed in search for leukemia cutis but no neoplastic infiltration was found and histopathology yielded non-contributory results.

Due to worsening hemorrhagic symptoms and persistent daily transfusion requirements, steroids therapy was started at a dose of 2 mg/kg/day, with no improvement in the following 48 hours. Indeed, the patient continued to display severe disseminated intravascular coagulation associated with a rapid enlargement of the spleen after each transfusion.

At day 7, a CT scan was performed and found a voluminous spleen with a persistent heterogeneous pattern, measuring 185 mm, extending to the pelvis, along with increased pancreas and posterior mediastinal masses which were interpreted at this time as lymphadenopathies (Figure 1).

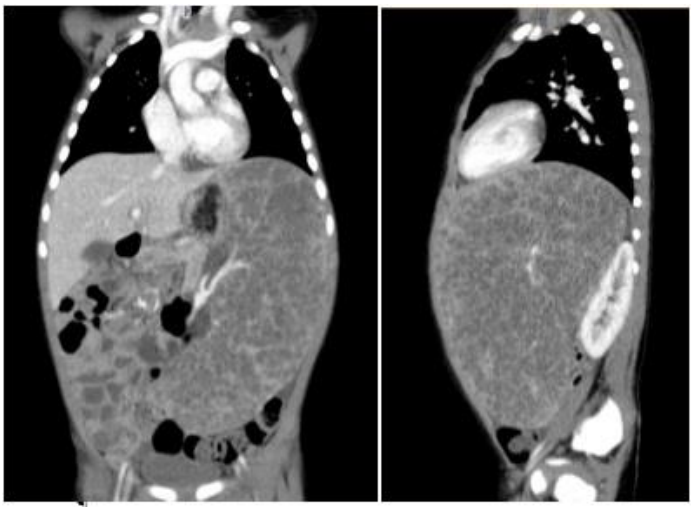

Fig. 1. Coronal and sagittal thoraco-abdominal CT scan showing huge heterogeneous spleen extending to the pelvis, along with increased pancreas and posterior mediastinal masses

Despite supportive care, the patient's general condition gradually worsened. In fear of a life-threatening spleen rupture, splenectomy was performed at day 8 under cover of platelet and fresh frozen plasma transfusions. No peroperative bleeding complication occurred. The surgeon macroscopically described diffuse angiomatosis and splenic lymphangiectasia. Anatomo-immunohistochemical analysis revealed a vascular lesion infiltrating the whole spleen, compatible with a littoral cell angioma.

Within 48 hours after splenectomy, the patient showed rapid clinical improvement and complete hematological normalization (except for post-splenectomy thrombocytosis at 738 G/L). One month later, a CT scan control showed normal pancreas and disappearance of the posterior mediastinal masses (which were then interpreted as lymphangiomas in the light of the previous diagnosis of littoral cell angioma of the spleen). No major complication occurred during follow-up.

Discussion

In 1940, Kasabach and Merritt reported the case of an infant with a capillary hemangioma associated with extensive purpura responsible for thrombocytopenia, thrombotic microangiopathy and consumption coagulopathy [6]. This condition, although benign, can be life-threatening due to hemorrhagic complications with a mortality rate ranging from 30 to 40 % [7].

KMS pathophysiology is presumed to be related to platelet trapping, activation and consumption within the abnormal vascular structure [3] leading to activation of the coagulation cascade. Intra-lesional bleeding may occur as well as distant bleeding and purpura due to systemic coagulation abnormalities.

KMS is mostly described in cutaneous hemangiomas. Rare cases of splenic hemangiomatosis associated with KMS have been reported in literature. The spleen is a highly vascular organ and is susceptible to a wide range of complications, including vascular and hematological disorders. Splenic hemangiomas are usually asymptomatic and incidentally discovered [8] but patients may also present with abdominal pain, large splenomegaly or KMS at diagnosis.

When associated with external vascular tumors, the diagnosis of KMS is more easily performed. It gets harder when hemangiomas

develop in organs such as liver and spleen. Biopsy is rarely performed because of the high risk of hemorrhage and even more so when KMS is associated. Moreover, imaging characteristics of splenic hemangiomas vary depending of their size and composition and are usually nonspecific [8]. In our patient, the heterogeneous pattern of the spleen on sonography and CT scan oriented towards a malignant process. The posterior mediastinal masses on CT scan were interpreted at first as lymphadenopathies, thus supporting diagnosis of hematological malignancy. However, both bone marrow aspiration and biopsy refuted this diagnosis.

Given the poor specificity of imaging and the hemorrhagic risks associated with percutaneous biopsy, splenectomy was performed for both diagnostic and therapeutic purposes.

The diagnosis of littoral cell angioma (LCA) was finally made, which is a different vascular tumor with a resemblance pathologically to either tufted angioma (TA) or kaposiform hemangioendothelioma (KHE) in association with lymphatic-like vessels [9]. It is important to point out that most reported cases of KMS were associated with KHE and TA, rarely with LCA [10].

Our main hypothesis had remained a thrombotic microangiopathy despite the absence of peripheral schistocytosis and intra-splenic TMA was finally confirmed by these vascular lesions.

Management of KMS is still controversial as the choice of treatment is usually empirical and response to treatment, unpredictable. Non-surgical treatment of KMS classically includes steroids therapy, interferon alpha2, vincristine, ticlopidine/aspirin association, radiation and embolization [3, 7, 10, 11]. Combined use of steroids and propranolol can be considered under careful monitoring of the side-effects with the aim of improving coagulopathy and thrombocytopenia as well as reducing tumor size [12] with a variable response [13]. Sirolimus (also known as rapamycin) is an inhibitor of the mammalian target of rapamycin (mTOR) and has been shown to be a safe and effective treatment option in some children [14, 15] and may be used as a first-line therapy [16]. Antiangiogenic treatment (such as anti-VEGFR drugs) could play a role in these new treatment regimens but more trials are needed before it can be recommended [17]. When possible, tumor resection provides complete cure. Platelet transfusions should be avoided, except in life-threatening situations. Indeed, exacerbations of bleeding and swelling of the tumors have been reported presumably due to intra-tumoral trapping and activation of platelets [18] (as seen in our patient with rapid deterioration after daily transfusions). Although first described as benign, LCA may have malignant potential and has been shown to be rarely associated with visceral malignancies [19, 20], thus requiring long-term follow-up.

In our patient, the diagnosis of littoral cell angioma of the spleen associated with intra-splenic KMS was established following splenectomy and histopathological analysis. KMS should be suspected in patients presenting with splenomegaly and features of thrombotic microangiopathy. This rare case illustrates the diagnostic difficulties met in dealing with such internal tumors, with possible atypical biological parameters and nonspecific imaging characteristics at presentation.

Conclusion

Littoral cell angioma is a rare and benign vascular tumor which can be discovered incidentally or in a context of various signs and symptoms such as abdominal pain, splenomegaly and hypersplenism. This condition may be complicated by a life-threatening Kasabach-Merritt syndrome due to high risk of hemorrhage. Vascular lesions of the spleen (such as LCA, KHE and TA) should be suspected in patients presenting with splenomegaly and features of thrombotic microangiopathy. Long-term follow-up is necessary in patients diagnosed with LCA due to increased risk of developing malignant diseases.

Conflict of interest

The authors have no conflict of interest to declare.

Patient consent

Written informed consent was obtained from the patient's legal guardians for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

References

1. Haisley-Royster C, Enjolras O, Frieden IJ, et al. Kasabach-Merritt phenomenon: a retrospective study of treatment with vincristine. *J Pediatr Hematol Oncol* 2002; 24(6):459-462.
2. Verheul HMW, Panigrahy D, Flynn E, et al. Treatment of the Kasabach-Merritt syndrome with pegylated recombinant human megakaryocyte growth and development factor in mice: elevated platelet counts, prolonged survival, and tumor growth inhibition. *Pediatr Res* 1999; 46:562-565.
3. O'Rafferty C, O'Regan GM, Irvin AD, et al. Recent advances in the pathobiology and management of Kasabach-Merritt phenomenon. *Br J Haematol* 2015; 171(1):38-51.
4. Croteau SE, Liang MG, Kozakewich HP, et al. Kaposiform hemangioendothelioma: atypical features and risks of Kasabach-Merritt phenomenon in 107 referrals. *J Pediatr* 2013; 162(1):142-147.
5. Falk S, Stutte HJ, Frizzera G. Littoral cell angioma: a novel splenic vascular lesion demonstrating histiocytic differentiation. *Am J Surg Pathol* 1991; 15(11):1023-1033.
6. Kasabach HH, Merritt KK. Capillary hemangioma with extensive purpura: report of a case. *Am J Dis Child* 1940; 59:1063-1070.
7. Haque PD, Mahajan A, Chaudhary NK, et al. Kasabach-Merritt syndrome associated with a large cavernous splenic hemangioma treated with splenectomy: a surgeon's introspection of an uncommon, little read, and yet complex problem. *Indian J Surg* 2015; 77(1):166-169.
8. Louis TH, Sanders JM, Stephenson JS, et al. Splenic hemangiomatosis. *Proc Bayl Univ Med Cent* 2011; 24(4):356-358.
9. Enjolras O, Mulliken JB, Wassef M, et al. Residual lesions after Kasabach-Merritt phenomenon in 41 patients. *J Am Acad Dermatol* 2000; 42(2):225-235.
10. Taeguyn K, Mi Ryung R, Kee Yang C, et al. Kasabach-Merritt Syndrom arising from a tufted angioma successfully treated with systemic corticosteroid. *Ann Dermatol* 2010; 22(4):426-430.
11. Hall GW. Kasabach-Merritt syndrome: pathogenesis and management. *Br J Haematol* 2001; 112(4):851-862.
12. Mizutani K, Umaoka A, Tsuda K, et al. Successful combination therapy of propranolol and prednisolone for a case with congenital Kasabach-Merritt syndrome. *J Dermatol* 2017; doi: 10.1111/1346-8138.13984.
13. Wang Z, Li K, Dong K, et al. Variable response to propranolol treatment of kaposiform hemangioendothelioma, tufted angioma and Kasabach-Merritt syndrome. *Pediatr Blood Cancer* 2014; 61:1518-1519.
14. Wang Z, Li K, Dong K, et al. Refractory Kasabach-Merritt phenomenon successfully treated with sirolimus and a mini-review of the published work. *J Dermatol* 2015; 42(4):401-404.
15. Wang Z, Li K, Dong K, et al. Successful treatment of Kasabach-Merritt phenomenon arising from kaposiform hemangio-endotheliomas by sirolimus. *J Pediatr Hematol Oncol* 2015; 37(1):72-73.
16. Ji Y, Chen S, Xiang B, et al: Sirolimus for the treatment of progressive kaposiform hemangioendothelioma: a multicenter retrospective study. *Int J Cancer* 2017; 141(4):848-855.
17. Delgado M, Pérez-Ruiz E, Alcade J, et al. Anti-angiogenic treatment (Sunitinib) for disseminated malignant haemangiopericytoma: a case study and review of the literature. *Case Rep Oncol* 2011; 4(1):55-59.
18. Phillips WG, Marsden JR. Kasabach-Merritt syndrome exacerbated by platelet transfusion. *J R Soc Med* 1993; 86(4):231–232.
19. Tee M, Vos P, Wiseman S, et al. Incidental littoral cell angioma of the spleen. *World J Surg Oncol* 2008; 6:87.
20. Bisceglia M, Sickel JZ, Giangaspero F, et al. Littoral cell angioma of the spleen: an additional report of four cases with emphasis on the association with visceral organ cancers. *Tumori* 1998; 84(5):595-599.