Archives de Pédiatrie 26 (2019) 365–369

Available online at ScienceDirect www.sciencedirect.com

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Short communication

A not so harmless mass: Kaposiform hemangioendothelioma complicated by a Kasabach–Merritt phenomenon

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ARTICLE INFO

Article history:
Received 15 November 2018
Received in revised form 25 April 2019
Accepted 18 June 2019
Available online 25 July 2019

Keywords:
Kaposiform hemangioendothelioma
Kasabach–Merritt phenomenon
Thrombocytopenia
Sirolimus
Cervical mass

ABSTRACT

A vascular mass localized in the face and the neck was displayed by ultrasonography in a 38-week-old male fetus. At birth, the mass was bulky and purplish. The newborn breathed spontaneously but with severe desaturation. During laryngoscopy, we observed an obstruction of the larynx with a left-shift caused by the hemorrhagic mass. Blood analysis revealed anemia, severe thrombocytopenia, and coagulation disorders. The diagnosis of kaposiform hemangioendothelioma (KHE) complicated by a Kasabach–Merritt phenomenon (KMP) was put forward and treatment with propranolol, corticoids, and vincristine was initiated. Platelets were transfused daily for 8 days but did not resolve the thrombocytopenia. At day 8, we added sirolimus to the treatment and noted a rapid response with the normalization of the platelet count within 1 week and a significant regression of the mass. In this paper, we review the clinical and biological features of hemangioendothelioma associated with KMP and discuss its current and future treatment. Sirolimus seems to be very promising.

1. Introduction

Kasabach–Merritt phenomenon (KMP) is a rare but life-threatening complication of kaposiform hemangioendothelioma (KHE).

We report the case of a newborn with a prenatal diagnosis of a vascular tumor invading the upper airway complicated at birth by KMP. The usual treatment (vincristine and corticosteroid) were ineffective and life was compromised. Sirolimus, a mTOR inhibitor, was administered with a fast and impressive response. In this paper, we review treatment strategies for KHE complicated by KMP.

2. Observation

After an initially normal follow-up of the pregnancy, a mass was discovered in a male fetus at 38 weeks of gestation. The fast-growing vascular tumor was located in the right side of the neck and the face, and seemed to be noncompressive (Fig. 1). A C-section was performed 3 days later to optimize neonatal care. At birth, the neck mass was purplish and compatible with a hemangioma. The newborn was breathing spontaneously but presented severe hypoxemia. Direct laryngoscopy revealed a shift to the left of the upper airway, secondary to the invasion of the laryngeal structures by the hemorrhagic mass. A laryngeal mask was placed in order to ensure adequate ventilation until intubation was performed under fibroscopic guidance. Skin petechiae and heavy bleeding around the umbilical venous catheter appeared quickly. Platelets and red blood cells were urgently transfused. Blood tests revealed moderate anemia (hemoglobin 10.4 g/dL), profound thrombocytopenia (platelets 11,000/mm^3), and coagulation disorders (hypofibrinogenemia 0.7 g/dL; D-dimer level $>$ 4000 ng/mL).

In regard of the association of an infiltrative vascular tumor in the head and neck area, thrombocytopenia and coagulation disorders, the diagnosis of KHE complicated by a KMP was put forward. Propranolol (2 mg/kg/day), methylprednisolone (5 mg/kg/day) and vincristine (1 mg/m^2/week) were the first-line treatment initiated on day 1. We completed this treatment with

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https://doi.org/10.1016/j.arcped.2019.06.003
0929-693X/

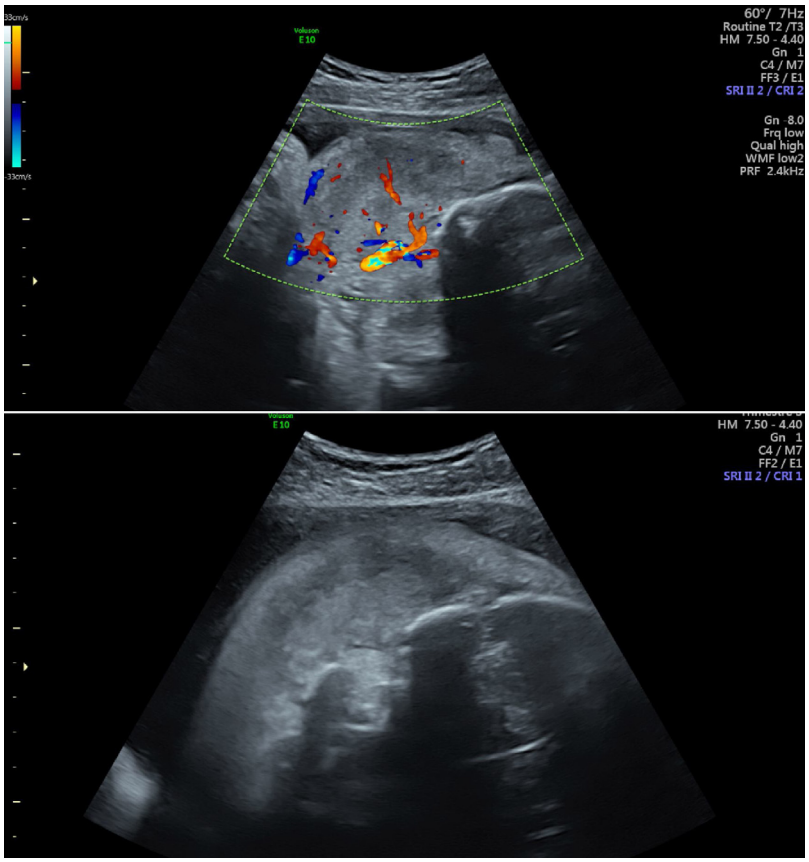

Fig. 1. Prenatal ultrasound of the vascular tumor.

tranexamic acid (15 mg/kg/day), gastric protection, and infectious prophylaxis with trimethoprim.

Platelet transfusions were given daily because the platelet count remained below the threshold of 20,000/mm^3 (and because of the need for invasive respiratory support and the amount of initial bleeding) until the 8th day of life. We did not note any increase in blood platelet counts, probably due to their immediate intratumoral consumption.

Sirolimus (dosage, 0.05 mg/kg twice a day, then adjusted according to blood monitoring targeting 10–15 μg/L) was added during the 2nd week of life and seemed rapidly effective, with normal platelet count obtained within 1 week and visible tumor involution (Fig. 2).

MRI revealed a vascular tumor consistent with the diagnosis of a hemangioendothelioma, invading parapharyngeal and laryngeal spaces, with a shift to the left of the oropharynx and the larynx. Hepatic infantile hemangioma was shown on ultrasonography. No biopsy was done.

Extubation was performed after fibroscopic guidance during the 5th week of life. Propranolol, vincristine, and methylprednisolone were progressively discontinued and the lesion continued to regress. Sirolimus was stopped at 9 months of age, without relapse of the tumor growth.

At 1 year of age, this child's neuromotor development and growth were normal for his age. Ultrasound showed the persistence of abnormal tissue at the initial site of the tumor, without Doppler activity inside.

3. Discussion

KHE is a benign tumor with locally aggressive characteristics. It derives from vascular endothelial cells [1–4]. Clinically, this tumor is bulky (> 5 cm), solitary, purplish, painful, indurated, and poorly defined. It is typically located in the head and neck area, the axillae, the groin, the extremities, the trunk and the retroperitoneum [1–3,5,6]. There is no ethnic or gender prevalence [3].

The age of presentation is variable, but this tumor often appears in the first 6 months of age. It can sometimes be diagnosed in utero as is the case for our patient. This diagnosis may be associated with increased severity [5–7].

Differential diagnosis with infantile hemangioma is important and can be made with clinical, radiological, and histological features (Table 1).

KHE shares several histopathologic and clinical features with tufted angioma (TA), belonging to the same neoplastic spectrum.

3.1. KMP

Platelet aggregation in the tumor can occur in 50–70% cases of KHE or tufted angioma and can lead to a KMP, which is observed in fewer than 1/100,000 children [6–10]. Biologically, severe thrombocytopenia (< 50,000/mm^3) is associated with hypofibrogenemia, increased levels of D-dimers, and normal prothrombin and activated cephalin times [1–3]. Other clinical findings can be hematoma, epistaxis, hematuria, or bleeding at the puncture site [11].

Physiological pathways have not yet been identified. Some authors have proposed that platelet aggregation and activation could be induced by the interaction of the podoplanin (D2-40), a transmembrane glycoprotein expressed by lymphatic endothelioma, with the CLEC-2 (C-type lectin receptor) of platelets. This would result in platelet sequestration in the lesion [12,13].

The risk factors of KMP in KHE are the location of the lesion (more frequent in retroperitoneum, mediastinum, or head and

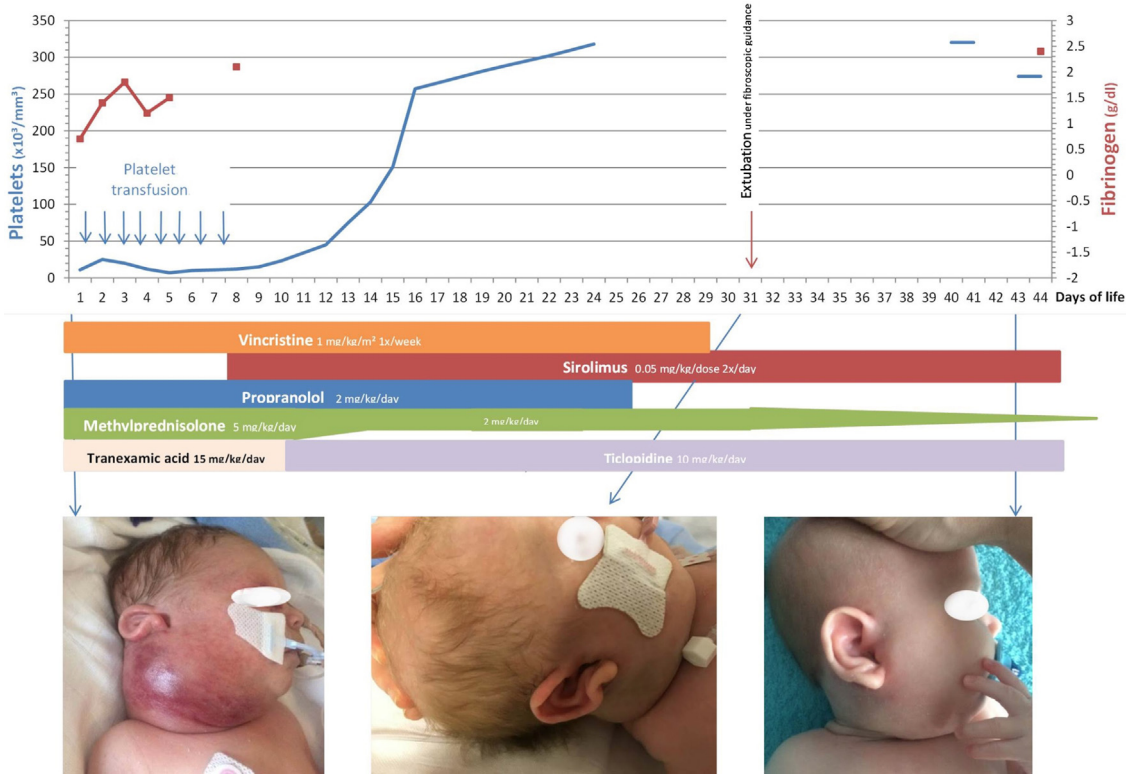

Fig. 2. Clinical and biological progression of the patient with treatment.

neck area), deep infiltration in the fascia or the muscle, a tumor diameter greater than 5–8 cm, and the young age of the child [4–7].

Early diagnosis is essential to prevent hemorrhagic complications and to establish the treatment plan. It is based on clinical features and blood analyses, and it can be helped by MRI [13]. Conventional radiology and CT are not helpful (5). When in doubt, histologic analyses can be done [1–3].

No histological sample was taken in our patient, because of the life-threating conditions (upper airway invasion and severe thrombocytopenia).

Table 1
Clinical, radiologic and histologic features of hemangioma and kaposiform hemangioendothelioma (KHE) used for differential diagnosis.

	Infantile hemangioma	Kaposiform hemangioendothelioma
Epidemiology	Female predominance	No sex ratio
	Appears during the 1st weeks after birth	Congenital (50%) or developing rapidly after birth
Clinical	Rapid growth during the 1st month	Rapid growth
	Soft mass in relief, reddish	Indurated, purplish, and edematous mass
	2/3 located in the head and neck area	Predominance in the trunk, extremities, and retroperitoneal area (rarely head and neck area)
	Multiple lesions in 20% of cases	Single lesion
Imaging (MRI)	Well-defined mass of soft tissues	Poorly defined mass invading several tissue layers
	Marked T2-hyperintense lesions	Heterogeneous regions of isointensity or mild hyperintensity on T2WI
	Homogeneous enhancement	Heterogeneous post-gadolinium enhancement
	No overt destruction of adjacent bone	Destruction/remodeling of adjacent bone
	High-velocity vessels in and around the tumor	Multicompartment involvement
		Adjacent fat stranding
	Size of irrigating and draining vessels proportional to tumor volume	Irrigating and draining vessels dilated but small in comparison with tumor volume
	Never bone involvement	Possible association with osteolysis or bone remodeling
Histology	Proliferation of endothelial cells and pericytes grouped in lobules with large vessels	Infiltrative growth pattern
		Spindled endothelial cells
		Microthrombi
		Hemosiderin deposits
		Lymphatic abnormalities
	Benign tumor	Intermediate malignity with invasive characteristics
	GLUT-1 positive	Focal immunopositivity for lymphatic endothelial markers (D2-40), CD31, CD34, and FLT1
		Immune negativity for GLUT-1
Prognosis	No mortality	High morbidity and mortality (30%)
	Never KMP	Complicated by KMP in 50–70% of the cases
		Skin sequelae divided into three types: wine stains, telangiectasia, subcutaneous infiltrate

KMP: Kasabach–Merritt phenomenon; MRI: magnetic resonance imaging.

3.2. Treatment of vascular tumors complicated by KMP

No standard guidelines exist but a clinical consensus is well established (Table 2) [5]. A multidisciplinary approach is essential to optimize medical care.

Surgical excision is the gold standard if it can be done in healthy margins and with no deterioration, but is rarely possible due to the infiltrative feature of the tumor [5,11]. A partial resection would be associated with a high risk of hemorrhage and local recurrence [4,5].

Pharmacological treatment does not always lead to complete healing, but its targets are the reduction of the tumor bulk and thus coagulopathy correction.

In the 1980s, corticosteroids were considered as the first-line treatment, often associated with vincristine [4,5,7,13]. Interferon-alpha 2a (3 billion U/m^2/day for 1 month) is not yet used because of its liver toxicity and its risk of spastic diplegia in children under 8 months [13]. Anti-fibrinolytic treatment (tranexamic acid, etc.) and antiplatelet agents are often added, with variable results [5]. Aspirin will be more particularly used to treat late inflammatory manifestations [7]. Heparin is contraindicated because it increases tumor growth and angiogenesis [3,5]. Radiation therapy is efficient but should not be used because of its adverse effects. Embolization is possible but rarely applicable [5].

All these treatments were replaced by sirolimus, an inhibitor of the mammalian target of rapamycin, which has shown promising effects on vascular malformations such as KHE [14]. By inhibiting the PI3 K/AKT pathway, sirolimus acts on the lymphatic component of KHE (inhibition of cellular proliferation and metabolism and lymphangiogenesis). The recommended initial dose is 0.1 mg/kg/day divided into two doses, which should be adjusted according to the monthly blood test (target level, 10–15 ng/mL) [12,15–18]. This agent induces a quick response (4 days to 6 weeks) both on platelet count and tumor volume [3,17], as illustrated in our case report.

Its adverse effects are mucositis, peripheral edema, arterial hypertension, hypertriglyceridemia, hypercholesterolemia [7,10,12,15–18], and microcytic anemia. Immunosuppression-related infections are prevented by cotrimoxazole administration and can justify the weaning of sirolimus [13,16].

A recent clinical study [19] confirmed the remarkable efficacy of sirolimus, even in patients resistant to conventional drugs, and more importantly, highlighted the constancy of its effects. In this study, cases complicated by functional deformities or severe life-threatening conditions and non-respondent to sirolimus alone were treated with a combination of prednisolone and sirolimus over the short term and showed successful results. It is suggested that these two drugs have potential or synergistic effects in the treatment of KMP. In contrast, a long-term combination therapy has no benefit but more adverse effects. The authors proposed to wean progressively from prednisolone within 4–6 weeks when a satisfactory clinical and biological response is obtained.

The duration of the treatment should be prolonged but has not yet been defined [17].

The oral administration of sirolimus, its great tolerance, and its low toxicity make this drug an advantageous alternative in the treatment of KHE, most particularly in severe cases complicated by KMP [17].

Propranolol, a nonselective beta-adrenergic antagonist used to treat infantile hemangioma, was tried in our patient without success. Some studies confirm this inefficacy [15,20,21]. This highlights that KHEs are different from classic infantile hemangioma.

Platelet transfusions are to be avoided as much as possible. Their capacity to correct the coagulopathy in cases of KMP is very transient, because it is consumed into the mass. Moreover, they may exacerbate this phenomenon and lead to a painful tumor engorgement [3,6,22,23]. They should be reserved for cases of active bleeding or when invasive interventions are urgently required [3,4,6,11].

Administration of fresh frozen plasma is recommended in case of bleeding [5].

3.3. Prognosis and complications

The mortality rate of KHE complicated by KMP ranges from 10 to 40%, predominantly resulting from rapid tumor growth and infiltration, compression or destruction of vital structures, hemorrhagic complications, and hemodynamic instability [4,7,19]. KHE is a long-term disease, which can remain unsymptomatic for several years after normalization of the platelet count.

Table 2
Consensus-derived practice standards plan [5].

	Posology	Adverse effects
Complete surgery if possible in healthy margins		
First-intention chemotherapy (in dual therapy)		
Vincristine	0.05 mg/kg 1 ×/week (for 20–24 weeks)	Neurotoxicity Nausea and vomiting, constipation Alopecia
Corticosteroids		Arterial hypertension
Prednisolone (oral)	2–5 mg/kg/day	Hyperglycemia Immunosuppression
Methylprednisolone (iv)	1.6 mg/kg/day	Growth cessation
New drug		
Sirolimus	0.1 mg/kg/day (2 × day). Then adjust with blood monitoring (target: 10–15 ng/mL)	Mucositis Arterial hypertension Hypertriglyceridemia Hypercholesterolemia Immunosuppression Microcytic anemia
Propranolol	To evaluate	
Other		
Interferon-alfa 2a	3,000,000 U/m^2/day (1 month)	Hepatotoxicity Spastic diplegia
Embolization, radiotherapy, or antifibrinolytic agent		
Platelet transfusion (only for active bleeding or emergency invasive surgery!)		

It can generate esthetic, muscular, or orthopedic sequelae and also limit mobility and cause joint pain or severe scoliosis [2,7].

The time before improvement of the aspect of the lesion cannot yet be predicted. However, progression in color (from purple to pink) and softening are the first signs of the treatment response. In most cases, the tumor size will decrease slowly, even after stopping the treatment [2].

In contrast to infantile hemangioma, KHE will not involute spontaneously. All patients retain cutaneous side effects, which are divided into three types: cutaneous red stain, telangiectatic streaks, and swelling or subcutaneous mass [2,6]. Inflammatory manifestations such as erythema, tumefaction, or pain are possible in this residual lesion [7].

There is no consensus on the medical follow-up of these patients, but it is suggested that it be extended at least until the child is 6 years old, due to the persistence of the risk of KMP. If the tumor is located near a joint, the follow-up will be pursued until puberty (risk of excessive growth due to the hypervascularization of the joint).

According to some authors, there is a risk of metastases in the regional lymph nodes. A case of distant metastases has also been reported [20], but this remains controversial.

Children should benefit from long medical follow-up to prevent and identify adverse effects of chemotherapy.

4. Conclusion

The KMP is a rare complication of KHE. The differential diagnosis with infantile hemangioma is important because of its rapid growth and high mortality rate. This diagnosis is possible when an indurated and infiltrative vascular tumor is associated with anemia, thrombocytopenia, and consumptive coagulopathy.

A few years ago standard clinical guidelines recommended the association of vincristine and corticosteroids when complete resection is not possible. These treatments were replaced by sirolimus, which seems very promising in terms of efficiency as well as ease and safety of use. As observed in this case report, it led to a fast and impressive response, whereas the usual treatments had shown little effectiveness in this severe case (in utero diagnosis, head and neck location, invasion of the upper airway). The short-term association with prednisolone is still under study.

Platelet transfusions should only be given in case of active bleeding or surgery.

Funding

None.

Disclosure of interest

The authors declare that they have no competing interest.

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