Efficiency of an *mTOR* Inhibitor in Kasabach-Merritt Phenomenon with Indolent Tufted Angioma: A Case Report

Charlée NARDIN[1], Olivia BOCCARA[2], Catherine ESCHARD[3], Michael BAYARAM[4], Thibaud DABUDYK[5], François AUBIN[1] and Eve PUZENAT[1]*

*Departments of Dermatology, [1]Centre Hospitalier University Hospital, 3 boulevard Alexandre Fleming, FR-25000 Besançon, [2]Hôpital Necker-Enfants malades, Paris and [3]Centre Hospitalier Universitaire, [4]Department of Pathology, Centre Hospitalier Universitaire, Reims, and [5]Department of Pediatry, Centre Hospitalier Universitaire Minjoz, Besançon, France. *E-mail: eve.puzenat@chu-besancon.fr*

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Kasabach-Merritt phenomenon (KMP) is a life-threatening condition characterized by thrombocytopaenia and disseminated intravascular coagulation (DIC), associated with kaposiform hemangioendothelioma (KHE) or tufted angioma (TA) (1). TA is a rare, benign vascular tumour, appearing as an infiltrative and erythematous skin plaque that grows and becomes inflammatory when complicated by KMP. The diagnosis is established by histopathology. Treatment of KMP remains challenging. However, mammalian target of rapamycin (mTOR) inhibitors have shown efficacy in this condition. We report here a case of KMP arising from TA successfully treated with sirolimus.

CASE REPORT

A 1-month-old boy presented to our clinic with epilepsy after a fall. Since birth, he had had an unresectable subcutaneous vascular abdominal tumour with 2 skin patches, diagnosed as TA on a skin biopsy. Histopathology showed a proliferation of endothelial cells aggregated in vascular lobules scattered in the dermis, with the typical "cannonball" appearance. Some blood cells were seen trapped in the ducts formed by tumour endothelial cells. Immunohistochemistry analysis was positive for endothelial markers, CD31 and CD34, for the lymphatic marker, D2-40 and negative for GLUT1. The patient was first treated by oral prednisolone, 10 mg/kg/day, and acetylsalicylic acid, 30 mg/day. When he was brought to the emergency room, he had drug-resistant epilepsy with intracranial hypertension and a palpable subcutaneous abdominal mass.

The abdominal tumour has been stable since birth, with a size of 15-cm, height and 30-cm width, extended from the abdomen to the right side of the back and associated with 2 red-bluish skin patches 3 cm in diameter (**Fig. 1** a, b). Admission laboratory testing indicated a severe drop in platelet count (5×10^9/l, normal range 147–386 $\times 10^9$/l), decreased fibrinogen (0.5 g/l, normal range 2–4 g/l), elevated D-Dimer (16,532 µg/l, normal range 0–500 µg/l), elevated fibrin degradation products (25,000 µg/ml, normal range < 5 µg/ml) and anaemia with haemoglobin down to 7 g/dl (normal range 11.8–14.7 g/dl). Abdominal magnetic resonance imaging (MRI) demonstrated a stable vascular tumour of the subcutaneous tissue extending from the anterior wall to the posterior abdominal wall without intra-abdominal involvement (Fig. 1 c, d). Furthermore, a left subdural haematoma and subarachnoid haemorrhage associated with acute left cortical, subcortical and external caspule ischaemic lesions were identified by cerebral MRI. In the intensive care unit, initial treatments consisted of platelet transfusions, management of epilepsy and interruption of acetylsalicylic acid. Based on the association of TA and disseminated intravascular coagulation (DIC), a diagnosis of KMP was made and platelet transfusions were interrupted, whereas intravenous corticosteroids were increased. After 24 h, brain haemorrhage stopped, but DIC remained active. Thus, prednisolone was switched to sirolimus (1.6 mg/m^2/day in 2 divided oral doses per day; dosage adjusted every week based on the serum drug level; target dose 5–10 ng/ml). Response was achieved within one week on platelet counts and DIC. Platelets increased to 0.25×10^9/l at day 1, 102×10^9/l at day 10, and reached 267×10^9/l after one month of treatment. Likewise, DIC progressively regressed and disappeared after 2 weeks, with the exception of D-dimers, which levelled off at approximately 700 µg/l. At the same time, the abdominal tumour decreased slowly. At last follow-up visit (6 months), the patient was still being treated with sirolimus without complication, with a diminished abdominal tumour and no recurrence of DIC.

DISCUSSION

The patient had indolent TA at KMP presentation, whereas thrombocytopaenia was worsening and DIC detected. Cutaneous KHE can lack cutaneous findings, but patients with KMP usually have inflammatory symptoms, such as enlarging lesion and increased firming with a change in cutaneous colour (2). Cases of retroperitoneal and mediastinal KHE with KMP without skin change have been reported (2).

Since there is no gold-standard treatment, KMP management widely varies (3). Steroids have long been considered as a first-line treatment (4) even if monotherapy is often ineffective or insufficient, as found in this case (5). Vincristine has a good efficacy (62% response rate), but is currently used as a second-line treatment because of the delay of response around 6 weeks, the need for intravenous access, and neurological toxicity (5, 6). Recent reports have demonstrated a good safety profile and efficacy of mTOR inhibitors in multiple vascular

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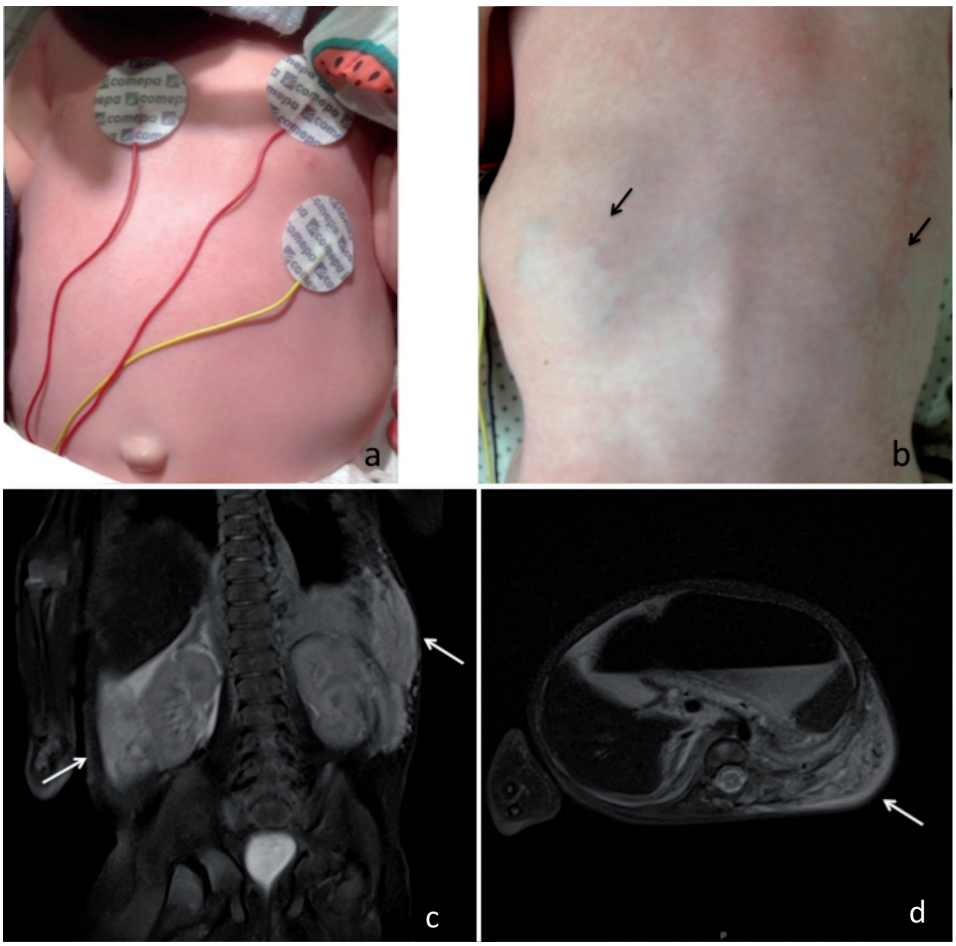

Fig. 1. Subcutaneous tufted angioma. (a) Abdominal mass. (b) Tufted angioma appearing as red-blue patches on the infant's back (*arrows*). (c, d) Abdominal magnetic resonance imaging (MRI), showing subcutaneous tufted angioma of the abdominal wall (*white arrows*).

proliferations (7–9). mTOR is a multifunctional kinase complex that plays a pivotal role in cell growth and metabolism. mTOR inhibitors, such as sirolimus, inhibit the PI3K/Akt/mTOR signalling pathway and by then angiogenesis, tumour growth and lymphangiogenesis (7). Sirolimus has been used on refractory KMP associated with KHE. It appeared safe and showed a rapid respond within 2 weeks, as found in our patient (7, 10, 11).

In conclusion, the usefulness of sirolimus in KHE also holds true in tufted angioma. mTOR inhibitors may be recommended as an early treatment of severe KMP instead of steroids or vincristine.

The authors declare no conflicts of interest.

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