Case report

rare tumors

Rare Tumors
Volume 10: 1–5

DOI: 10.1177/2036361318776185
journals.sagepub.com/home/rtu
SAGE

Impact of sirolimus treatment for refractory kaposiform hemangioendothelioma with exacerbation of the disease 10 years after initial diagnosis

Naoki Sakata[1], So-ichi Suenobu[2], Munehiro Okano[1], Satoshi Ueda[1], Masatomo Kimura[3] and Tsukasa Takemura[1]

Abstract

We describe our experience with a 12 year-old girl with kaposiform hemangioendothelioma accompanied by Kasabach–Merritt phenomenon with exacerbation of the disease 10 years after the initial diagnosis. Kaposiform hemangioendothelioma infiltrated into the subcutaneous tissue of the facial skin with deterioration of coagulopathy despite conventional therapies including corticosteroid, vincristine, and propranolol. Sirolimus, a mammalian target of rapamycin inhibitor, produced rapid and dramatic improvement of the Kasabach–Merritt phenomenon and kaposiform hemangioendothelioma shrinkage. Eventually, multifocal lesions of kaposiform hemangioendothelioma disappeared on the images of magnetic resonance imaging and have remained in remission for 27 months after sirolimus cessation. We demonstrated that the AKT/mammalian target of rapamycin signaling pathway played a pivotal role in the kaposiform hemangioendothelioma growth. Sirolimus must be a strong candidate for molecular therapy targeting kaposiform hemangioendothelioma.

Keywords

Sirolimus, mammalian target of rapamycin, kaposiform hemangioendothelioma, Kasabach–Merritt phenomenon, molecular targeting drug

Date received: 26 February 2018; accepted: 9 April 2018

Introduction

Kaposiform hemangioendothelioma (KHE) is a rare, aggressive, and infiltrative vascular tumor that usually develops within the first year of life. Classically, KHE presents on the skin, affecting deeper tissues by infiltrative growth, including bone, mediastinum, and retroperitoneum; very rarely, KHE develops at multiple sites.[1]

KHE may cause a coagulopathy, Kasabach–Merritt phenomenon (KMP), which involves platelet trapping in KHE, resulting in thrombocytopenia and consumptive coagulopathy. The mortality rate of KHE is high (20%–37%) and KMP is considered responsible for the significant morbidity and mortality.[1]

Regarding therapies for KHE, arterial embolization or surgical therapy is suitable for some patients. Several pharmacotherapies, including prednisolone, interferon-α, vincristine, and propranolol, have been used; however, none has been uniformly effective and a promising therapy

[1]Department of Pediatrics, Kinki University Faculty of Medicine, Osaka-Sayama, Japan
[2]Division of General Pediatrics and Emergency Medicine, Department of Pediatrics, Oita University Faculty of Medicine, Oita, Japan
[3]Department of Pathology, Kinki University Faculty of Medicine, Osaka-Sayama, Japan

Corresponding author:
Naoki Sakata, Department of Pediatrics, Kinki University Faculty of Medicine, 377-2, Ohno-Higashi, Osaka-Sayama 589-8511, Osaka, Japan.
Email: nsakata@med.kindai.ac.jp

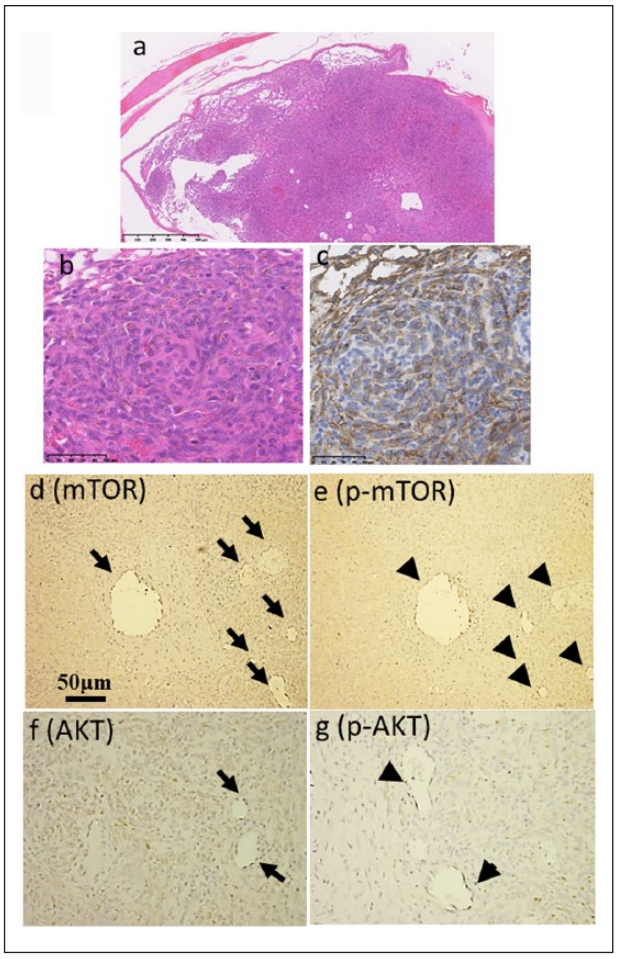

Figure 1. Pathologic findings and immunohistochemical staining for the mTOR pathway using paraffin embedded sections of the patient's tumor tissue. (a) Diffusely proliferating spindle neoplastic cells are merging with sporadical glomeruloid structures. Dilated lymphatic channels are in the periphery of the tumor nodule beneath the epidermis. (b) Neoplastic cells are forming compressed vessels with brown stippled hemosiderin. (c) D2-40 is identified in the neoplastic cells sparing central area of a glomeruloid structure. D2-40 is densely expressed in the surrounding lymphatic channels. The sections have also been stained for primary antibodies to (d) mTOR, (e) phospho-mTOR, (f) AKT1, and (g) phospho-AKT. The endothelial cells of stromal vessels in the KHE tissue (black arrows) expressed AKT and mTOR proteins that are also positive when probed with anti-phosphoprotein AKT (p-AKT), and anti-phosphoprotein mTOR (p-mTOR) antibodies.

has not yet been identified so far.[2] Recently, sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, usually used as an immunosuppressant after renal transplantation, has appeared effective even in patients refractory to conventional therapies.[3–8]

Here, we describe the clinical course of a 12-year-old girl with KHE accompanied by KMP. Despite conventional therapies including corticosteroid, vincristine, and propranolol, 10 years after the initial diagnosis, she had exacerbation of the disease with infiltration of subcutaneous tissues of the facial skin as well as deterioration of coagulopathy. We treated her with sirolimus and further discuss the clinical significance of the use of mTOR inhibitors in the treatment of KHE.

Case report

The initial diagnosis was made after the patient presented with an expanding mass in the right external auditory canal at 4 years of age. Computed tomography (CT) revealed that the tumor was located in the anterior wall of the right external auditory canal and was associated with osteolysis. A whole body examination using systemic CT demonstrated multiple low-density lesions in the spleen and osteolysis in multiple sites, including the long bones of the extremities and the thoracic and lumbar vertebrae, suggesting Langerhans histiocytosis. However, examination of a punch biopsy sample of the right external auditory canal revealed a tumor nodule beneath the epidermis. Surgically resected tissues were fixed with 10% buffered formalin and embedded in paraffin. Tissues were sliced in 4-μm sections and then stained with hematoxylin and eosin (Figure 1(a), ×7 and (b), ×40). It comprised diffuse proliferation of spindle cells and hematovascular channels with finely granular hemosiderin deposition. Glomeruloid structures were seen sporadically merging with diffuse zones. Thin-walled lymphatic channels surrounded the tumor nodule. Immunohistochemical analysis revealed that the neoplastic cells were positive for CD31, CD34, and D2-40 (Figure 1(c)). From these pathological findings, the patient was diagnosed with KHE. Moreover, the platelet count was $33 \times 10^3/\mu L$ and the serum levels of fibrinogen and fibrin-degraded protein (FDP) were 76 mg/dL and 30.7 ng/mL, respectively, indicating that the patient had accompanying coagulopathy with the KHE (KMP). She received prednisolone (initial dose, 2 mg/kg/day) to manage the coagulopathy and the dose of prednisolone was tapered. Next, interferon-α therapy was started; however, this was ineffective, evidenced by no shrinkage of the KHE and no resolution of KMP. She continued to receive prednisolone to manage the coagulopathy. Five years after the initial diagnosis, the patient received vincristine therapy (1.5 mg/m^2/week) for 3 months and, eventually, prednisolone was discontinued; however, deterioration in KMP was observed and prednisolone was restarted. Because propranolol is reportedly efficacious in severe hemangioma in infancy,[9] the patient was administered propranolol (2 mg/kg) for 6 months. Unfortunately, there were no effects on the KHE with KMP. Therefore, low-dose prednisolone administration (0.3 mg/kg/day) was necessary to manage the coagulopathy due to KHE. Ten years after the initial diagnosis, the patient presented with painful facial ecchymosis with subcutaneous induration (Figure 2). Her blood tests showed that the red blood cell (RBC) count was $216 \times 10^9/L$, the level of hemoglobin was 6.8 g/dL, and the platelet count was $15 \times 10^3/\mu L$. Serum levels of fibrinogen and FDP were

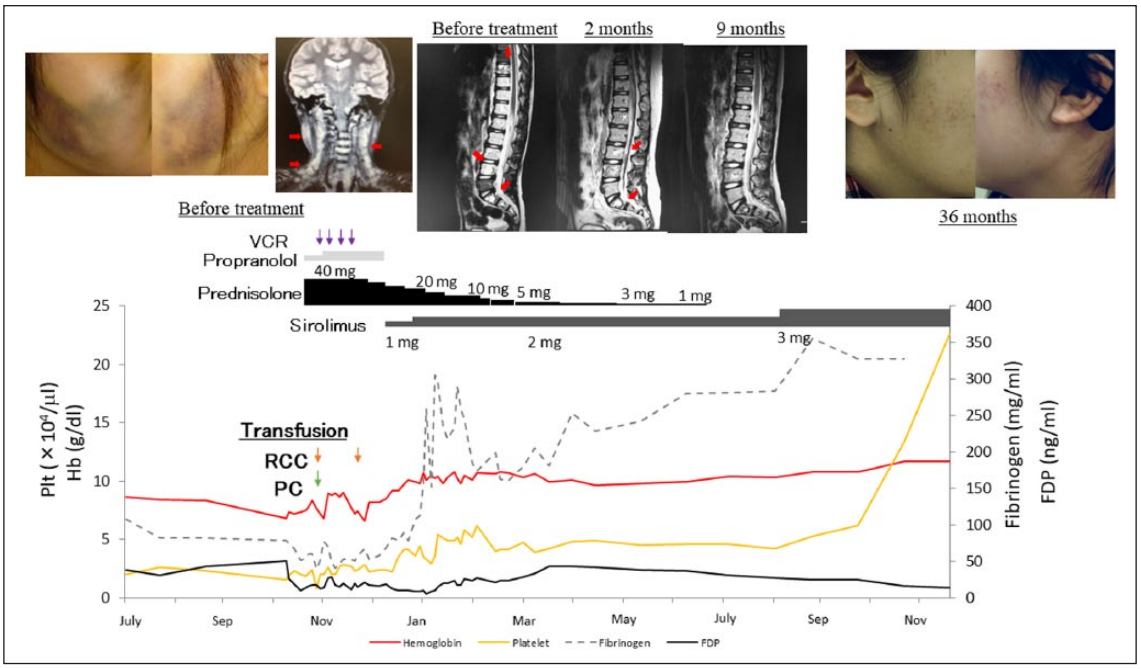

Figure 2. Clinical course.
VCR: vincristine; RCC: red cell concentrates; PC: platelet concentrates.

78 mg/dL and 49.8 ng/mL, respectively. Magnetic resonance imaging (MRI) revealed that the KHE infiltrated the subcutaneous tissue with deterioration of KMP (Figure 2). Therefore, she was treated with prednisolone (1.5 mg/kg/day) in addition to propranolol (2 mg/kg/day) and weekly vincristine (1.5 mg/m^2/week) therapy. However, even during the combination therapy, the ecchymoses on her face expanded, and blood transfusion of RBCs and concentrated platelets was required to stop nasal bleeding caused by the deteriorated KMP. Finally, we decided to use sirolimus to rescue the patient from the life-threatening status. Pertaining to the use of sirolimus, informed consent was obtained. The initial dosage was 0.8 mg/m^2 per dose administered twice daily (2 mg/body/day), approximately every 12 h, according to the dosing schedule reported by Adams et al.[10] The administration of vincristine and propranolol was ceased; however, prednisolone was continued with sirolimus. Two weeks after the patient was started on sirolimus, the hemoglobin level had increased from 8.5 to 10.1 g/dL, and after 3 weeks, the platelet count had increased from 24×10^3/μL to 44×10^3/μL (Figure 2). The platelet counts recovered up to 5×10^3/μL after 1 month, and the coagulopathy resolved. The patient was discharged from the hospital and continued to receive sirolimus as an outpatient. After 2 months, MRI showed marked shrinkage of the vertebral KHE lesions demonstrated as high-intensity areas on T2-weighted imaging (Figure 2). In addition, the patient's facial ecchymosis with subcutaneous induration shrank gradually. She had no adverse effects with use of sirolimus; therefore, we increased the dose of sirolimus to 3 mg/body/day (0.1 mg/kg) at 6 months because of plateauing of the platelet counts at approximately 50×10^3/μL. Prednisolone was gradually reduced and finally discontinued 8 months after the initiation of sirolimus. The patient was then treated with sirolimus alone for 23 months and further improvements were identified on blood tests, MRI (at 9 months), and physical examination (at 36 months) without side effects (Figure 2). No recurrence of the disease has occurred at 27 months after the cessation of sirolimus.

To examine whether the mTOR signaling pathway was actually activated in the KHE tissue, we performed immunohistochemical staining for the mTOR pathway, including AKT and mTOR, using paraffin embedded sections of the patient's tumor tissue. AKT and mTOR proteins were positive in the cytoplasm of endothelial cells that lined stromal vessels in KHE tumor tissue and these cells were also positive when probed with anti-phosphoprotein AKT (p-AKT) and mTOR (p-mTOR) antibodies (Figure 1(d)–(g)), indicating constitutive activation of the AKT/mTOR signaling pathway in the KHE.

Discussion

We present an unusual case of KHE diagnosed at 4 years of age. KHE is typically seen in infancy; additionally, in this case, the disease had spread to multiple sites in the bone and spleen tissue other than the skin, suggesting that the disease in the presented case had similar clinical characteristics to kaposiform lymphangiomatosis (KLA), a recently described entity.[11] Because KHE and KLA have very similar histopathologic characteristics,[11] we reviewed the pathologic findings of the biopsied specimens obtained at

diagnosis to confirm the pathologic diagnosis. As a result, histology of the present tumor was consistent with KHE. Furthermore, all patients with KLA had mediastinal involvement and the most common presentations were respiratory symptoms;[11] however, our patient exhibited no respiratory symptoms during the clinical course. Taken together, we believed that the diagnosis of the case was KHE with a unique clinical picture and course, with the exacerbation despite conventional therapies 10 years after the initial diagnosis.

According to the summary of the National Institutes of Health (NIH) consensus working group,[2] pharmacological treatment of KHE, although not always curative, aims to suppress tumor growth activity and control coagulopathy. Corticosteroids, considered first-line therapy, have never been prospectively investigated. Furthermore, a positive response may not be long-lasting. A promising therapy for infantile hemangioma, propranolol, has been reported to have limited efficacy in KHE.[12] Interferon-α and vincristine have also been widely used with some reported success,[13,14] but they caused unacceptable side effects in some patients. In our case, vincristine administration induced pancytopenia and resulted in the worsening of the KMP.

Interaction between vascular endothelial growth factor (VEGF) and VEGF receptors on the endothelial cells of hemangioma activates several signaling pathways essential for proliferation of hemangioma.[15] Moreover, the major signaling pathway involved in hemangioma growth is the AKT/mTOR signaling pathway.[16] We showed the constitutive activation of the AKT/mTOR signaling pathway in the endothelial cells of vessel-like structures in the KHE tumor tissue. Although the precious mechanisms remain undermined, blocking of mTOR activity by sirolimus resulted in the rapid and dramatic improvement of coagulopathy and shrinkage of KHE without side effects. Furthermore, it is notable that the efficacy has been lasting for 27 months after the cessation of sirolimus. From these observations, sirolimus is considered a strong candidate for a molecular targeting of drug in the treatment of KHE.

This is the first case report of a girl with KHE with constitutive activation of the AKT/mTOR signaling pathway in the tumor tissue. Our experience and findings described in this article lead us to believe that sirolimus is superior to conventional treatments and should be incorporated into the first therapeutic regimen in KHE with KMP. Clinical trials will be needed to clarify the promising efficacy of sirolimus in the treatment of KHE.

Acknowledgements

N.S. wrote the manuscript. S.S. performed the experiments to analyze the expression of AKT/mTOR using immunohistochemical analysis. N.S., M.O., and S.U. contributed to the patient's therapy. M.K. reviewed the pathologic diagnosis. T.T. revised the manuscript.

Ethical approval

Kindai University Faculty of Medicine does not require ethical approval for reporting individual cases or case series.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymised information and image to be published in this article.

References

1. 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: 142–147.
2. Drolet BA, Trenor CC 3rd, Brandao LR, et al. Consensus-derived practice standards plan for complicated kaposiform hemangioendothelioma. *J Pediatr* 2013; 163: 285–291.
3. Blatt J, Stavas J, Moats-Staats B, et al. Treatment of childhood kaposiform hemangioendothelioma with sirolimus. *Pediatr Blood Cancer* 2010; 55: 1396–1398.
4. Hammill AM, Wentzel M, Gupta A, et al. Sirolimus for the treatment of complicated vascular anomalies in children. *Pediatr Blood Cancer* 2011; 57: 1018–1024.
5. Kai L, Wang Z, Yao W, et al. Sirolimus, a promising treatment for refractory kaposiform hemangioendothelioma. *J Cancer Res Clin Oncol* 2014; 140: 471–476.
6. Schroeder U, Lauten M, Stichtenoth G, et al. Laryngomalacia and complicated, life-threatening mTOR-positive kaposiform hemangioendothelioma cured by Supraglottoplasty and sirolimus. *Klin Padiatr* 2014; 226: 362–368.
7. Uno T, Ito S, Nakazawa A, et al. Successful treatment of kaposiform hemangioendothelioma with everolimus. *Pediatr Blood Cancer* 2015; 62: 536–538.
8. Wang Z, Li K, Yao W, et al. Successful treatment of kaposiform lymphangiomatosis with sirolimus. *Pediatr Blood Cancer* 2015; 62: 1291–1293.
9. Leaute-Labreze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *N Engl J Med* 2008; 358: 2649–2651.
10. Adams DM, Trenor CC, Hammill AM, et al. Efficacy and safety of sirolimus in the treatment of complicated vascular anomalies. *Pediatrics* 2016; 137: e20153257.
11. Croteau SE, Kozakewich HP, Perez-Atayde AR, et al. Kaposiform lymphangiomatosis: a distinct aggressive lymphatic anomaly. *J Pediatr* 2014; 164: 383–388.
12. Wang Z, Li K, Dong K, et al. Variable response to propranolol treatment of kaposiform hemangioendothelioma, tufted angioma, and Kasabach-Merritt phenomenon. *Pediatr Blood Cancer* 2014; 61: 1518–1519.

13. Wu HW, Wang X, Zhang L, et al. Interferon-alpha therapy for refractory kaposiform hemangioendothelioma: a single-center experience. *Sci Rep* 2016; 6: 36261.
14. Wang Z, Li K, Yao W, et al. 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.
15. Jinnin M, Medici D, Park L, et al. Suppressed NFAT-dependent VEGFR1 expression and constitutive VEGFR2 signaling in infantile hemangioma. *Nat Med* 2008; 14: 1236–1246.
16. Medici D and Olsen BR. Rapamycin inhibits proliferation of hemangioma endothelial cells by reducing HIF-1-dependent expression of VEGF. *PLoS ONE* 2012; 7: e42913.