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Unique Cobb syndrome with Kaposi hemangioendothelioma/tufted angioma as dominant phenotype: a case report

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Cobb syndrome, a neurocutaneous disease that is not widely recognized, is characterized by vascular anomalies involving the skin and spinal cord at the same metamere.[1 2] Cobb syndrome can be accompanied by various clinical phenotypes of vascular anomalies, of which spinal arteriovenous malformations (AVMs) are the most widely mentioned in previous studies.[3–5] Due to its rarity, the clear diagnostic criteria, incidence, and pathogenesis of Cobb syndrome are still unclear. A unique Cobb syndrome characterized by a Kaposi hemangioendothelioma (KHE)/tufted angioma (TA) phenotype was diagnosed for the first time in this study. Histopathological consistency for spinal and cutaneous lesions was also confirmed. The patient was successfully treated with sirolimus, a mammalian target of rapamycin (mTOR) targeted therapy. We propose that Cobb syndrome should be classified based on its dominant phenotypes to further guide clinical treatment strategies, and potential molecular targeted therapies will provide viable treatment options for different phenotypes of Cobb syndrome.

A 4-year-old girl with erythema on the left waist came to our clinic with her parents. The erythema was flat, with irregular borders, 2×3 cm in size, and was initially noticed on the waist 2 years after birth. According to the medical history reported by her parents, she received surgical resection, and postoperative pathological examination revealed that there were nested vascular tissues in the dermis, which confirmed the diagnosis of TA (figure 1A). For further diagnosis, deep puncture biopsy of the paravertebral mass was performed in our clinic, and pathological analysis confirmed the diagnosis of KHE (figure 1B–D). However, 4 months after surgery, the patient presented with multiple, scattered masses with blue-to-purple color surrounding the surgical incision, and the erythema became progressively larger and darker (figure 2A). Family history was unremarkable.

Magnetic resonance imaging (MRI) showed multiple abnormal signals in the left iliac, left pedicle, transverse process and vertebral body of the L2-S3 spine, as well as hyperplasia masses involving the left lower abdomen, soft tissue surrounding the left psoas major muscle and left lumbosacral vertebral body (figure 2B). She was additionally found to develop complications secondary to KHE, including pseudoscoliosis and progressive claudication (figure 3A–C). Based on MRI results of segmental involvement of the spine, soft tissue, and skin at the same metamere and pathologically confirmed KHE/TA features, the patient was eventually diagnosed with unique Cobb syndrome with KHE/TA as the dominant phenotype. Conservative

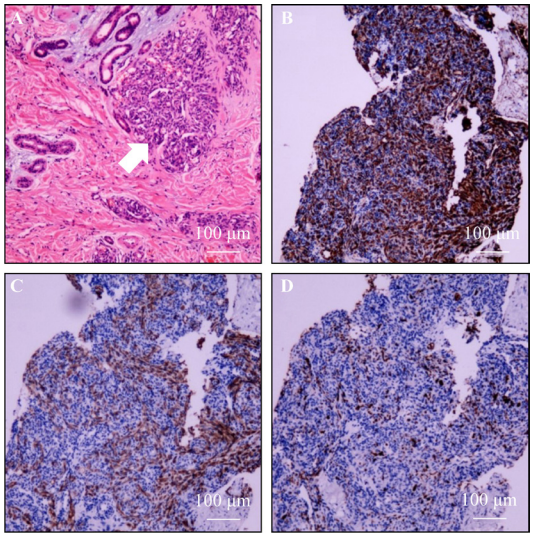

Figure 1 Postoperative pathological results. (A) Hematoxylin–Eosin staining showed nested vascular tissue in the dermis (indicated by white arrow), confirming the diagnosis of TA. (B-D) Deep puncture biopsy of the paravertebral mass confirmed the diagnosis of KHE (B: CD34 (+), C: D2-40 (+), D: Glut-1 (-)). KHE,Kaposi hemangioendothelioma; TA, tufted angioma.

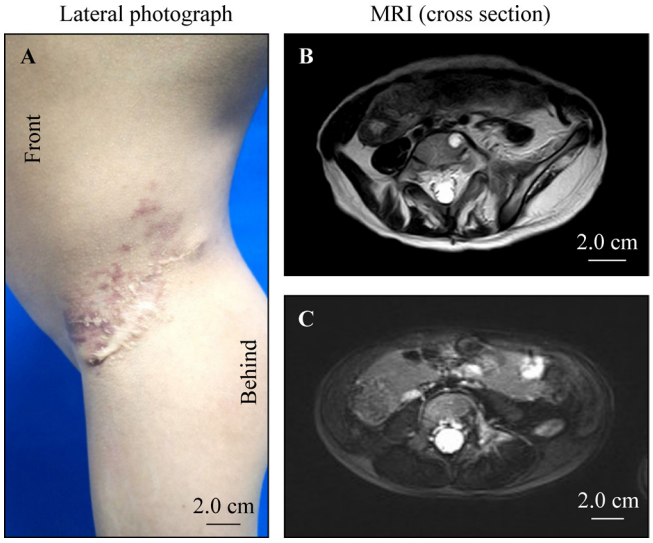

Figure 2 Case presentation of Cobb syndrome with Kaposi hemangioendothelioma/tufted angioma (KHE/TA). (A) patient presented with erythema surrounding the surgical incision on the left waist. (B) Preoperative MRI showed multiple abnormal signals in the left iliac, the left pedicle, transverse process and vertebral body of L2-S3 spine, as well as hyperplasia masses involving the left lower abdomen, soft tissue surrounding the left psoas major muscle and the left lumbosacral vertebral body. (C) Repeat MRI was performed 6 months into sirolimus therapy and revealed dramatic decreased of the dermis and near resolution of muscular invasion. KHE,Kaposi hemangioendothelioma; MRI, Magnetic resonance imaging; TA, tufted angioma.

management, including rehabilitation and functional exercise for 3 months, did not alleviate the patient's symptoms.

As an inhibitor of mTOR pathway, sirolimus has been widely used in immunotherapy after renal transplantation,[6] and later it was found to have a good effect

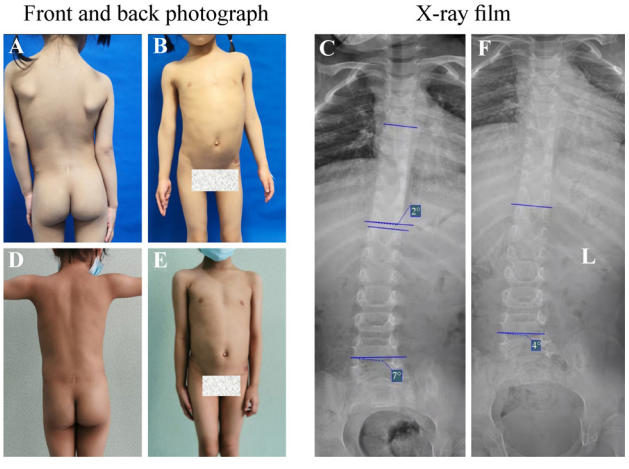

Figure 3 The remission of pseudoscoliosis symptoms in patients. (A-C)The patient was additionally found to develop pseudoscoliosis and progressive claudication. (D-F) The patient had great improvement of pseudoscoliosis and claudication after treatment with sirolimus therapy for 6 months.

on vascular malformations with low flow rate.[7] Given previous report of successful treatment of KHE with sirolimus, limited conservative options, difficulty and challenge of surgery, and potential progression of the spinal component, the patient was treated with sirolimus, an oral mTOR inhibitor, at a daily dose of 0.7 mg two times per day. The patient received regular blood drug concentration tests, and the blood drug concentration of sirolimus was maintained at 8 ng/mL. Repeat MRI after 6 months of treatment showed that dermis was decreased dramatically and muscular invasion was nearly resolved (figure 2C). By this time, her pseudoscoliosis and claudication had also greatly improved (figure 3D–F).

In this study, we reported one unique Cobb syndrome with KHE/TA as dominant phenotype. We diagnosed the child with KHE/TA-phenotypic Cobb syndrome based on the physical examination of erythema, MRI results of vascular lesions at the same metamere, and pathologically confirmed KHE/TA features. Similar to previous report that multiple cavernous angiomas were identified in both the spine and skin,[8] we further confirmed histopathological consistency for spinal and cutaneous lesions. KHEs and TAs are similar in clinicopathology, share common epigenetic pattern, and may form a spectrum of one entity. This finding suggests that minimally invasive skin biopsies can be used as an alternative option for spinal biopsies that are challenging and damaging for histological examination or potential genetic analysis to further define phenotype and guide targeted therapy.

Our patient was successfully treated with sirolimus, an mTOR inhibitor, which resulted in dramatic reduction of the lesions and rapid and continuous resolution of the patient's lifelong scoliosis and secondary claudication. The usual dose of sirolimus is to maintain a blood concentration of 8–12 ng/mL, which has been used to treat patients with KM syndrome (the patient's pathological findings were consistent with KM syndrome, and the same low-flow vascular malformation). We chose to maintain a low concentration of 8 ng/mL, and the child had few secondary infections during the 3 years of treatment. His re-examination of biochemical indicators showed that there was no significant abnormality in blood lipid (abnormal lipid metabolism is also one of the common side effects of sirolimus); however, the pathological features from TA to KHE raised further concern about platelet fluctuations. Up to now, the child has taken medication and has been closely followed up for 3 years. Now, the child's growth and development are similar to children of the same age, and his muscle strength and exercise performance have been greatly improved. In addition, no secondary tumor growth was observed (possibly due to the short follow-up time).

We suggest that although the majority of Cobb syndromes are associated with spinal AVM as the clinical phenotype, other types, such as hemangioma and low-flow vascular anomalies, cannot be ignored. We propose that Cobb syndrome should be classified in detail according to its dominant phenotypes as to further guide clinical treatment

strategies: spinal high-flow type (such as AVM, AVF), spinal low-flow type (such as CA), and spinal angioma type (such as KHE/TA described in this report). Over the past two decades, disease-causing genetic mutations have been identified, and most types of pathophysiological pathways have begun to be elucidated. Chemotherapy, such as sirolimus, an inhibitor of the PI3K/AKT/mTOR pathway, was proven to be effective and safe for a variety of vascular anomalies, venous/lymphatic malformations and KHE that can offset the progression of the malformations.[9] We hypothesize that different molecular targeted therapies will provide new treatment options for Cobb syndrome with different phenotypes.

The pathological results of Cobb syndrome suggest that it is the same as KM syndrome on the microscopic level. The difference is that Cobb syndrome is usually accompanied by deep paraspinal or even intraspinal lesions in the same segment in addition to the surface lesions, which causes pain, scoliosis and decreased motor ability on the affected side. We consider that this clinical manifestation may be caused by the muscle strength imbalance caused by the involvement of muscles, fascia and soft tissue on the side of the lesion. Therefore, when the lesion was improved by sirolimus, the muscle strength of both sides gradually balanced, which eventually led to the improvement of scoliosis and the motor ability of the affected side.

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