Kaposiform hemangioendothelioma (KHE) is a rare vascular tumor that usually affects soft tissues of newborns and infants. Although histologically benign, KHE is locally aggressive because of its tendency to infiltrate surrounding tissues. Occasionally, it may be associated with Kasabach-Merritt syndrome (KMS), a severe consumptive coagulopathy caused by a platelet trapping syndrome (1,2). Mortality in newborns has been reported to be 24%, despite surgical or medical therapy, or both (1–4). Treatments with systemic steroids, antiplatelet drugs, and vincristine have been widely reported with varied results (1–5), but little attention has been given to embolization in newborns. Embolization has been scarcely reported despite its potential benefits in the acute setting to control both the local tumor and the coagulation disorder (3,6,7). We report two cases of newborns with prenatal diagnosis of lower limb KHE with life-threatening KMS, in which embolization combined with vincristine led to clinical remission and uneventful follow-up. Institutional review board approval was not required because of the retrospective nature of the cases reported.

**CASE 1**

A female fetus of 37 weeks’ gestational age with a prenatal ultrasound diagnosis of a right lower limb vascular tumor was delivered by cesarean section. Apgar score was 9/10 at birth, and the neonate weighed 2,700 g. The patient was referred to our hospital on day 1 of life. On arrival, physical examination showed an extensive soft tissue tumor affecting the right side of the vulva, gluteus, thigh, and knee, with purpuric changes in the skin extending from the pelvis to the foot. The tumor was purple colored and infiltrating with poorly defined edges (Fig 1a). Blood tests showed anemia, thrombocytopenia, and severe coagulopathy 12 hours after delivery: hematocrit 24% (normal 35%–45%), platelets $19 \times 10^9/L$ (normal $150–450 \times 10^9/L$), pro-
thrombin time (PT) 18 seconds (normal 10–13.5 seconds), and activated partial thromboplastin time (APTT) 31 seconds (normal 35–45 seconds).

At 2 days after birth, the infant developed congestive heart failure and severe decompensated coagulopathy, manifested by pulmonary and gastrointestinal bleeding. Additional blood tests revealed fibrinogen 1 g/L (normal 1.50–3.87 g/L) and elevated D-dimer > 2,000 ng/mL (normal < 500 ng/mL). The clinical and laboratory parameters were typical of KMS. The infant needed assisted mechanical ventilation and was treated with intravenous steroids (prednisone 2 mg/kg/d), diuretics, and digoxin; platelets; and cryoprecipitate transfusions. Despite the supportive measures and medical therapy, the clinical condition and the coagulopathy gradually worsened. When the infant became hemodynamically unstable on day 4, an emergency embolization of the vascular tumor was performed.

Under general anesthesia, a 4-F introducer was placed in the left femoral artery by percutaneous puncture. Right lower limb angiography, performed with a 4-F Cobra catheter (Glidecath; Terumo, Tokyo, Japan) by contralateral approach, showed an extensive hypervascular tumor in the thigh (Fig 1b). Selective partial embolization of the profunda femoris artery feeders supplying the tumor was performed using 300–500 microspheres (Embospheres; Merit Medical Systems, Inc, South Jordan, Utah). Angiography performed after embolization showed significant reduction of tumor vascularization (Fig 1c).

The clinical condition improved immediately after embolization. The hemorrhages ceased, and the infant became hemodynamically stable, although she still had mild residual congestive heart failure. The coagulation profile showed improvement: platelets 40 × 10^9/L, PT 15 seconds, APTT 35 seconds, and fibrinogen 1.40 g/L. However, D-dimer (> 2,000 ng/mL) remained elevated. Physical examination showed a reduction in volume and induration of the tumor, and the purpuric color of the skin resolved. Follow-up was uneventful until day 11, when both cardiac parameters and the coagulation profile worsened. A second emergency embolization was performed using the same endovascular approach previously described. Embolization of the remaining tumor was performed with 300–500 microspheres and an intratumoral pseudoaneurysm with n-butyl cyanoacrylate (Histoacryl; B. Braun Melsungen AG, Melsungen, Germany) mixed with lipiodol (Guerbet, Aulnay-sous-Bois, France) (Fig 1d). A substantial improvement in both clinical and clotting parameters was observed, with further reduction in size of the tumor (Fig 1e). The patient re-
mained stable, although D-dimer continued to be elevated, and platelets never exceeded $80 \times 10^9/L$.

A cutaneous biopsy performed 1 month after birth showed a proliferation of spindle-shaped endothelial cells forming vessels in a lobular pattern, confirming the diagnosis of KHE. A regimen with intravenous vincristine was started with a dose of 0.05 mg/kg in weekly pulses for 14 weeks. The tumor gradually decreased in size, and laboratory values eventually normalized. When the patient was 2 months old, she was discharged from the hospital, continuing her treatment (vincristine) as an outpatient until completion of 14 weeks. Corticosteroids were gradually tapered after discharge, until 2 months of treatment were completed.

KMS recurred 4 months later, and the patient was readmitted to the hospital. The soft tissues of the thigh had turned darker, purple colored, edematous, and painful. A significant decrease in platelet count ($10 \times 10^9/L$) and elevation of D-dimer ($>2,000$ ng/mL) were observed. Corticosteroids and vincristine treatment were reinstated, and embolization was performed again, with the same approach as previously discussed. Embolization of the remaining tumor was performed with 300–500 microspheres and 500–700 microspheres until near stasis. Excellent clinical improvement was rapidly seen in both laboratory parameters (platelets $100 \times 10^9/L$; D-dimer 1,500 ng/mL) and physical examination with softening of soft tissues and decreased edema. The patient was discharged 1 week after the embolization, and the steroid therapy was discontinued. Treatment with vincristine as an outpatient was continued until completion of a 4-week treatment. The tumor progressively shrank until its complete disappearance, leaving only a small scar. The patient remained symptom-free and tumor-free at 3-year follow-up (Fig 1f).

CASE 2

A female fetus of 39 weeks’ gestational age with a prenatal ultrasound diagnosis of a right lower limb vascular tumor was delivered by cesarean section. Apgar score was 8/10 at birth, and the neonate weighed 3,300 g. A large (10-cm) soft tissue tumor located in the right thigh was noted at birth. The tumor gradually increased in size in the following weeks. The concomitant appearance of hematuria and petechiae prompted referral to our service on day 26. After admission to our hospital, physical examination showed the tumor was indurated with purpuric changes and ecchymosis, better detected at the knee and posterior thigh (Fig 2a). Blood tests showed anemia, thrombocytopenia, and severe coagulopathy: hematocrit 22%, platelets $7 \times 10^9/L$, PT 18 seconds, APTT 30 seconds, fibrinogen 0.9 g/L, and D-dimer $>5,000$ ng/mL. The clinical and laboratory parameters were typical of KMS.

The neonate was treated with intravenous steroids (prednisone 2 mg/kg/d), platelets, and cryoprecipitate transfusions. Despite medical therapy, the coagulopathy did not improve, and embolization was performed. Under general anesthesia, a 4-F introducer was placed in the left femoral artery by percutaneous puncture. Right lower limb angiography, performed with a 4-F Cobra catheter (Glidecath) by a contralateral approach, showed an extensive hypervascular tumor in the thigh (Fig 2b). Selective partial embolization of the profunda femoris artery feeders supplying the tumor was performed using 300–500 microspheres (Embo-spheres). Angiography performed after embolization showed significant reduction of the tumor vascularization (Fig 2c). In the same session, a biopsy of the tumor was performed.

Hematuria ceased after embolization, hematocrit elevated to 33%, and the tumor showed reduction in both volume and induration. The coagulation profile improved markedly: platelets $44 \times 10^9/L$, PT 15 seconds, APTT 35 seconds, and fibrinogen 1.2 g/L. However, D-dimer ($>5,000$ ng/mL) remained elevated. Pathology showed proliferation of spindle-shaped endothelial cells forming vessels in a lobular pattern confirming the clinical suspicion of KHE (Fig 3). Vincristine treatment was started in weekly pulses with a dose of 0.05 mg/kg. After 2 weeks of treatment, blood tests showed further improvement: platelets $150 \times 10^9/L$, PT 15 seconds, APTT 40 seconds, fibrinogen 1.5 g/L, and D-dimer $>2,000$ ng/mL. The tumor reduced further in size, and the surrounding skin was pink. The patient was discharged and continued vincristine treatment as an outpatient for 14 weeks. The tumor gradually shrank leaving only a small purple area, with no pain or motor deficiencies. The patient remained symptom-free at 6-month follow-up (Fig 2d).

DISCUSSION

KHE is a rare, locally aggressive vascular tumor, commonly associated with KMS, a thrombocytopenic consumptive coagulopathy (1,2). It is congenital in about 60% of cases, but it may also affect infants or children and, less frequently, young adults (3,4). It is a serious clinical condition, with a reported mortality of 24% and even higher in patients < 6 months of age (4). Death most often results from expansive tumor growth and life-threatening hemorrhage (2,4).

KHE usually manifests as an infiltrating soft tissue tumor accompanied by edema and purple skin discoloration when associated with KMS. The diagnosis is suspected on clinical and laboratory grounds and may be confirmed by magnetic resonance (MR) imaging or pathology. On MR imaging, it is typically seen as a moderately intense, T2-weighted tumor with ill-defined borders infiltrating the surrounding fat tissue (1). Pathology shows a lobular architecture composed of endothelial cells forming vessels of variable size and peripheral spindle cells positive on D2-40 and negative on Glut 1 immunostaining (8).

KMS is a thrombocytopenic consumptive coagulopathy associated with a vascular tumor that was first described
in 1940 (9). Since then, the term has been most commonly used to describe thrombocytopenia associated with capillary hemangiomas, but it has also been used in cases of coagulopathies seen with other vascular malformations. However, more recent investigations have shown that the term KMS should be reserved for cases of clinically significant thrombocytopenia associated exclusively with either KHE or tufted angioma (1,2,4).

The patients in this report were considered to have KHE associated with KMS based on physical examination and associated severe thrombocytopenia. In both cases, the diagnosis was later confirmed by biopsy. MR imaging was not performed in case 1 because of the critical condition of the neonate. The differential diagnosis included congenital hemangioma, tufted angioma, hemangiopericytoma, and sarcoma. The clinical presentation was not typical of tufted angioma in either case, and the presence of KMS ruled out other possible tumors.

The treatment of KHE associated with KMS is challenging and controversial. In a stable patient with a well-localized tumor, surgical treatment is feasible if an acceptable morbidity is anticipated. Platelet transfusions, antifibrinolytic agents, antiplatelet drugs, corticosteroids, chemotherapy (vincristine), radiotherapy, and embolization have been reported, all with various adverse effects and varying clinical success (1–5,10,11).

Surgical resection was not considered in our cases because of severe coagulation disorders and the size of the tumors. Platelet transfusions and steroids were started immediately after the clinical onset but were unable to control

Figure 2. Case 2. (a) The right lower limb of a neonate at 26 days of life shows a vascular tumor. (b) Angiography shows the hypervascular tumor at the thigh. (c) Angiography after embolization shows marked reduction of the tumor vascular supply. (d) Clinical control at 6 months of age.
KMS or the local tumor growth. The hemorrhages continued, and the clinical condition of the newborns worsened in the acute setting despite medical treatment.

Transarterial embolization resulted in immediate improvement of the clinical condition in both neonates. The coagulation profile also improved, as shown by significant increase of the number of platelets and the normalization of fibrinogen and APPT parameters. In case 1, the hemorrhages ceased, the infant became hemodynamically stable, and the tumor decreased in both volume and induration. Although KMS recurred 1 week later and again 5 months after the initial endovascular procedure, repeat embolization controlled both the symptoms and the coagulation profile. In case 2, the hematuria ceased after embolization, and the tumor decreased in both volume and induration without recurrence.

Embolization has been used for decades to treat vascular tumors, but reports on indications and clinical success in newborns with KHE and KMS are scarce (3,12). Embolization has shown effectiveness in KMS control and in initiating tumor regression in emergency situations (5–7,13); however, it is technically challenging, and experience in pediatric endovascular interventions is mandatory to avoid complications (3,13). Transarterial embolization presents some distinctive issues when performed in newborns. The small size of femoral arteries requires the use of thin catheters to perform both angiography and embolization. The procedure should be performed as fast as possible to reduce the catheterization time. Femoral patency after intervention is essential if the need arises for staged embolization (as occurred in case 1) and for future normal growth of the accessed limb (14).

Contrast material is a limiting factor in infants weighing only a few kilograms because of the danger of volume overload. It has been reported that small amounts (4–6 mL/kg body weight) of low osmotic contrast material may be used with perfect tolerance and no worsening of the cardiac status (13,14). The general anesthesia necessary to perform the procedure constitutes another challenge. Assisted ventilation, pulse oximetry, continuous electrocardiogram monitoring, noninvasive automatic pressure monitoring, and body temperature control are mandatory. Some anesthetic medications (ie, curare, isoflurane, fentanyl) are potentially dangerous in patients being treated with digitalis and diuretics (14). Accurate hemodynamic balance needs to be carefully maintained during the procedure to avoid volume overload.

Despite the aforementioned limiting factors of embolization, if performed by a well-trained multidisciplinary team, it offers very low morbidity, few technical failures, and efficacy. The goal of embolization in newborns with KHE and KMS is to decrease the flow of the vascular tumor; it is not mandatory to achieve a complete occlusion (13). Beneficial changes in the coagulation profile and symptomatic relief rapidly follow partial embolization, as occurred in the cases reported here. Particulate embolic agents are well suited to achieve this goal (6,7); however, the use of embolic liquid agents has also been reported (5,15). Both types of embolic agents were used in our cases according to the specific angioarchitecture of the vascular

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**Figure 3.** Biopsy specimen of case 2 shows proliferation of spindle-shaped endothelial cells (arrows) forming vessels in a lobular pattern (original magnification 200×, hematoxylin and eosin).
tumors. Although fiber coils have been reported as embolic agents, their use should be discouraged because additional embolization procedures are common, as occurred in case 1 (5,6,12,13).

More recent reports consider intravenous chemotherapy with vincristine, an inhibitor of endothelial proliferation, as a first-line treatment option for KHE associated with KMS (10,11). Although it may have neurologic and hematologic toxicity, vincristine has shown excellent objective clinical and tumoral responses (1,11). As with any systemic medication, vincristine requires time to become therapeutically active; the average time to normalize the platelet count with vincristine has been reported to be about 5 weeks (10). Vincristine was administered in both patients reported here but only after biopsy confirmation of the tumor etiology. It was safe and successful for long-term tumor control, although delayed clinical recurrence was observed in case 1.

Because of the complex clinical behavior of newborns with KHE associated with KMS, interdisciplinary management is important to determine the appropriate therapy among all reported treatments. Arterial embolization may be life-saving in the acute setting of a critically ill newborn because it may rapidly reduce tumor volume and improve coagulation disorders. Combined treatment with systemic drugs, such as vincristine, is recommended to achieve long-term cure.

In conclusion, this brief report illustrates the role of successful interdisciplinary management and combined treatment in two newborns with KMS and a prenatal diagnosis of a rare, life-threatening vascular tumor. Arterial embolization, although challenging in neonates, has resulted in significant improvement of critical symptoms when used in the emergency setting until pharmacologic treatment becomes effective. Vincristine has been shown to be effective in for long-term control of both KMS and KHE.

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