Multidisciplinary management of a neonate with kaposiform hemangioendothelioma with extensive cranial fossa destruction

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Abstract
Kaposiform hemangioendothelioma is a rare, benign, locally destructive vascular tumor. Kasabach–Merritt phenomenon, a consumptive coagulopathy, is a life-threatening complication associated with kaposiform hemangioendothelioma. We describe a case of kaposiform hemangioendothelioma complicated by Kasabach–Merritt phenomenon in a neonate born with a large facial mass with deep extension toward the cranium and airway. The mass was not identified prenatally. The patient was a 37-week gestation age female neonate born via spontaneous vaginal delivery and noted to have a large left-sided facial mass that was not noted on the most recent prenatal ultrasound at 22 weeks gestation age. At birth, the patient was in respiratory distress and required continuous positive airway pressure support. Imaging revealed a large highly vascularized soft tissue mass adjacent to the airway with intracranial extension and bony destruction. Fine needle aspiration confirmed kaposiform hemangioendothelioma. On day of life 6, the patient was noted to have thrombocytopenia, elevated d-dimer, anemia, and hypofibrinogenemia, consistent with Kasabach–Merritt phenomenon, which resolved at day of life 12. Given the location and extent of the mass, medical therapy with single agent oral sirolimus was chosen over surgery. At 13-month follow-up, the infant is well on sirolimus therapy, and the mass has decreased in size, both clinically and on imaging. This case highlights the importance of prompt diagnosis and management of kaposiform hemangioendothelioma with extensive craniofacial and bony involvement with Kasabach–Merritt phenomenon with single oral therapy of sirolimus. Fibrinogen concentrate may be considered in the Kasabach–Merritt phenomenon refractory to cryoprecipitate.

Keywords
Kaposiform hemangioendothelioma, Kasabach–Merritt phenomenon, multidisciplinary approach, delivery, obstetric, infant, newborn

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Introduction
Kaposiform hemangioendothelioma (KHE) is a rare, benign vascular tumor that presents at birth or early infancy and has an incidence and prevalence of 0.071 and 0.91/100,000 children per year, respectively. Most cases of KHE involve the trunk or limbs and are known to infiltrate adjacent soft tissues. Bone destruction is uncommon even in severe, extensive cases. A life-threatening complication of KHE is Kasabach–Merritt phenomenon (KMP), a consumptive coagulopathy characterized by thrombocytopenia, hypofibrinogenemia, elevated fibrin split products, and tumor growth.

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We describe a case of KHE complicated by KMP and extensive bony destruction in a neonate who presented with a large facial mass with deep cranial extension and extension toward the airway, with response to oral sirolimus monotherapy. This case highlights the importance of prompt diagnosis and management of KHE and the value of a multidisciplinary approach.

**Case**

A 37-week gestation 2.37-kg female born to a 35-year-old G2P2 mother via spontaneous vaginal delivery was found to have a left-sided facial mass that extended from the inferior orbit to the left auricle and past the mandible into the superior neck (Figure 1). The pregnancy was uncomplicated, and the mother had received regular prenatal care. The mass was not identified prenatally, and no antenatal imaging was taken. At birth, the infant received positive pressure ventilation for poor respiratory effort, followed by continuous positive airway pressure before transfer to the neonatal intensive care unit (NICU). Apgar scores were 1 and 7 at 1 and 5 min, respectively. On examination, in addition to the mass, the left auricle was noted to be displaced and she was unable to close the left eye. Otherwise, no midline shifts, deformities, or skin changes were appreciated.

Initial laboratory values on day of life (DOL) 1 revealed mild anemia with hemoglobin 12.8 g/dL, but were otherwise within normal limits. Pediatric surgery and otolaryngology were consulted shortly after admission, and bedside nasal scope exam revealed left-sided upper airway compression obstructing visualization of the left glottis. Multidisciplinary discussions were held among neonatology, pediatric surgery, otolaryngology, and oncology services to plan for imaging and biopsy to determine the extent and nature of the mass. Given the consideration of a vascular lesion and plan for biopsy, management included avoidance of intubation that could cause trauma and evaluation for the risk for bleeding.

Ultrasound of the affected area on DOL 2 revealed a large mixed solid and cystic mass in the left cheek and neck that abutted the airway and adjacent vessels (Figure 2). Magnetic resonance imaging (MRI), performed on DOL 3, demonstrated a large vascular craniofacial soft tissue mass measuring \( 5.8 \times 5.5 \times 6.1 \) cm\(^3\) (cranio-caudal, AP, transverse) centered in the left parapharyngeal, masticator, and parotid spaces with superior extension into the left cavernous sinus, left temporal bone, left occipital bone, extradural left middle and posterior cranial fossa, medial extension into the retropharyngeal space, posterior extension into the left cervical posterior triangle, and inferior extension into the left sub-mandibular space (Figure 3). The differential included congenital/infantile fibrosarcoma, teratoma, or KHE. Computed tomography (CT) confirmed a large, solid mass with increased blood flow extending to the infratemporal fossa and into the intracranial compartment below the left temporal lobe with additional extension into the cavernous sinus and into the posterior fossa. The tumor measured \( 5.5 \times 5.2 \times 5.3 \) cm\(^3\) (cranio-caudal, AP, transverse) and was described as moderately dense suggesting a cellular mass.

Figure 1. Photographs of infant demonstrating shrinkage of mass over time.
Given the intracranial extension, neurosurgery was consulted to assist with evaluation and management. On DOL 6, in preparation for the planned procedure of fine needle aspiration biopsy for tissue diagnosis, coagulation studies were done and found to be consistent with KMP (Table 1). The infant was treated initially with 39 mL (~15 mL/kg) of cryoprecipitate, however, serum fibrinogen remained low at 76 mg/dL the following morning. Laboratory values normalized following administration of 77.2 mg/kg of human fibrinogen concentrate (RiaSTAP®), with fibrinogen level improving from 76 to 252 mg/dL after administration.

The patient was taken to the operating room for direct laryngoscopy by an otolaryngologist and fine needle aspiration by an interventional radiologist. Laryngoscopy revealed a normal larynx and a large left-sided pulsating bulging mass in the parapharyngeal space. Despite the concern for bleeding and largely vascular nature of the tumor, there was minimal blood loss during the biopsy. On DOL 10, the infant had a brief episode of hemoptysis of nearly 5 mL of fresh blood; bedside scope revealed patchy mucosal ulcerations of the adenoid bed in the pharynx without active bleeding. Thrombocytopenia, anemia, hypofibrinogenemia, and elevated D-dimer improved.

Figure 2. Gray scale and color doppler transverse ultrasound images of the left facial mass demonstrate a solid mass with increased blood flow.

Figure 3. Coronal and axial T2W MR images demonstrate a hypertense solid mass centered in the left masticator, parapharyngeal and parotid spaces. There is superior extension into the left middle cranial fossa, cavernous sinus, temporal bone, occipital bone, and posterior fossa; inferior extension into the submandibular space; medial extension into the nasopharynx and oropharynx resulting in severe airway narrowing; posterior extension into the left posterior triangle of the neck. Large internal flow voids representing vessels are noted in the mass resulting in high vascularity as seen on ultrasound.
The patient fed orally with gavage of the remainder of the feeding during her inpatient stay and experienced no complications. After initiation of sirolimus on DOL 13, she had no further episodes of bleeding, KMP did not recur, and the baby was discharged home at 4 weeks of life on sirolimus therapy. CT head at 4 months of life demonstrated an interval decrease in size of the soft tissue mass in the left skull base with minimal residual tumor in the floor of the middle cranial fossa, and improvement of airway compromise. The infant displayed no side effect during the newborn period, but, at a few months of life, developed oral sores that were managed conservatively, intermittent self-resolving elevation of triglycerides, and minimal self-resolving elevation of transaminases. At 13 months of life, she is growing and developing normally, and the mass is barely palpable; she remains on sirolimus monotherapy.

over the first 2 weeks of life (Table 1 and Figure 4). The imaging characteristics and associated KMP placed KHE highest on the differential. Following multidisciplinary discussions, medical therapy was initiated while waiting for the histologic confirmation given the extensive destructive nature, location of the tumor, and coagulopathy. The standard of care for KHE includes either intravenous vincristine or oral sirolimus in addition to steroids if KMP is not responding rapidly. Vincristine is a chemotherapeutic agent, requires a central line for administration, and has multiple potential side effects. Per oncology recommendations, the infant was treated with daily oral sirolimus therapy and *Pneumocystis jiroveci* pneumonia prophylaxis with sulfamethoxazole-trimethoprim (twice daily 2 days per week per guidelines). Pathology confirmed the diagnosis of KHE on DOL 14.

### Table 1. Laboratory values.

| Lab         | Initial (DOL 1) | Initial (DOL 6) | Start of sirolimus (DOL 13) | Last follow-up (DOL 275) | Metric | Normal range  |
|-------------|-----------------|-----------------|-----------------------------|--------------------------|--------|---------------|
| Hemoglobin  | 12.8            | 12.4            | 9.3                         | 9.8                      | G/DL   | 15.0–22.0     |
| Hematocrit  | 38.1            | 35.2            | 27.5                        | 31.8                     | %      | 44.0–70.0     |
| Platelets   | 221             | 72              | 299                         | 446                      | 10^3/UL | 150–450       |
| Protime     | 15.1            | 12.1            | s                           |                          | s      | 10.5–15.7     |
| INR         | 1.2             | 0.9             | s                           |                          | s      | 0.8–1.2       |
| PTT         | 39.1            | 33              | s                           |                          | s      | 25.2–33.2     |
| Fibrinogen  | 76              | 440             |                             |                          | MG/DL  | 220–440       |
| D-dimer     | 19.69           | 7.09            | 0.53                        |                          | UG/ML FEU     | < 0.4         |

**Figure 4.** Trend of platelet count and fibrinogen concentration.
Discussion

Early diagnosis and treatment of KHE is important for improving patient outcomes.6 Given the potential complication of KMP, characterized by activation of the coagulation cascade and platelet trapping,4 it can be difficult for providers to plan the logistics and ideal timing of the invasive procedure needed for tissue diagnosis. Moreover, KHE presenting as a facial mass with mass effect on the airway can pose further challenges for procedural planning.

While previous reports in the literature discuss different potential therapeutic options after diagnosis,7–10 this case highlights the importance of timely anticipatory airway and hematologic management in the inpatient setting while awaiting diagnosis. Multidisciplinary discussions and planning are vital to ensure optimal outcome. Otolaryngology, pediatric surgery, neurosurgery, anesthesiology, hematology/oncology, and transfusion medicine are all subspecialties that should be consulted, as needed, early in the patient’s course so that preoperative concerns can be addressed, discussed, and planned for. Screening for platelet consumption and coagulopathy during this period can identify and prevent serious complications related to delayed diagnosis of KMP and is of crucial importance prior to invasive diagnostic procedures and to prevent spontaneous bleeding events.

Serial monitoring of the platelet count, serum fibrinogen, and D-dimer levels are most important in identifying KMP. Furthermore, closely following the hemoglobin is important in these patients who are at high risk for bleeding. Of significance, prothrombin (PT) and partial thromboplastin times (PTT) may be normal in KMP despite coagulopathy and screening should include fibrinogen levels.3,11 Platelet transfusions should be avoided if possible in cases of suspected KMP, due to the risk of further platelet trapping and enlargement of the mass.4 In general, it is recommended that cryoprecipitate be considered for fibrinogen levels <100 mg/dL.12 In this patient, cryoprecipitate was administered initially for low fibrinogen levels in the setting of KMP; however, no increase in fibrinogen level was observed. After administration of fibrinogen concentrate (RiaSTAP), fibrinogen levels rose promptly. When compared with cryoprecipitate, RiaSTAP has the potential to improve fibrinogen levels with the advantage of more precisely targeting minimum desired levels.13,14 RiaSTAP has been used in neonates undergoing cardiac surgery with predictable and quantifiable changes in rotational thromboelastometry values following administration.15 In neonates where fluid restriction may be necessary, use of a fibrinogen concentrate might prove beneficial. In our case, the patient was able to proceed with the plan for tissue biopsy the same day and had no major bleeding complications.

Given the rarity of KHE, there is a paucity of well-designed clinical trials to guide treatment decisions, and management is typically based on expert opinion and clinical experience of the practitioners.16,17 While surgical resection may offer the most definitive cure for small, localized tumors,12 it is not advisable for large, infiltrative craniofacial tumors in proximity of the airway as in our case. Standard of care medical therapy is still vincristine and steroids, but over the past decade, there have been many reports of the efficacy of sirolimus as a first-line therapy for KHE.7,16,18,19 Our patient was treated with oral sirolimus therapy with clinical improvement and resolution of KMP. During the newborn period, we typically use sirolimus (0.4 mg/m2/dose either Q12h or daily depending on other comorbidities) administered orally in the buccal mucosa or via gavage tube with 10 mL water flush. Trough levels of sirolimus are checked at 3 and 7 days, and the dose and interval adjusted to reach a level of 10–15 ng/mL for KHE management. In contrast to our use of sirolimus monotherapy, in a recent randomized clinical trial, Ji et al.20 found that sirolimus plus prednisolone was more effective in achieving a durable platelet response and fibrinogen stabilization with fewer blood transfusions and lower total incidence of disease sequelae than monotherapy alone. Similar cases at other institutions globally may be treated using monotherapy or multimodal therapies with steroids, vincristine, interferon-alfa, antiplatelet agents, propranolol, and sirolimus with varying outcomes.12 Treatment regimens with vincristine/prednisolone require the use of a central line and have much higher toxicity and potential side effects, including profound immunosuppression, neuropathy, high blood pressure, hyperglycemia, adrenal insufficiency, and a Cushingoid habitus.12

Conclusion

While current literature focuses on identification and optimal long-term treatment of KHE in children, this case highlights the importance of early surveillance for coagulopathy, the challenge of management in cases of neonatal KHE involving the cranium and adjacent to the airway, and the benefits of multidisciplinary management. Fibrinogen concentrate may be considered in KMP refractory to cryoprecipitate.

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.
Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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