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Case Report

Thrombocytopenia and Giant Hemangioma: Know How to Evoke and Treat the Kasabach-Merritt Syndrome. A Case Report and Literature Review

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Abstract

Introduction: Kasabach-Merritt syndrome is a rare form of vascular tumor that are often misdiagnosed, which is complicated by intra-tumor coagulopathy and requiring urgent management.

Objective: This review highlights the clinical presentation, histopathology, management, and treatment of Kasabach-Merritt syndrome. A clinical case compiled in the pediatric department of the university Hospital Center of Oran Algeria, is described to illustrate the presentation and our management of a patient with Kasabach-Merritt syndrome.

Observation: A female infant was admitted, on the thirtieth day of life, for a purplish red swelling of the left hemiface. He had hemolytic anemia, profound thrombocytopenia and consumptive coagulopathy. It was successfully managed with a combination of high dose of oral corticosteroids and vincristine.

Conclusion: Vincristine and oral corticosteroids were useful for our patient and may be considered an option for first-line therapy of Kasabach-Merritt syndrome. The absence of a codified therapeutic protocol makes the management of this tumor a real challenge.

Keywords: *Kasabach-Merritt Syndrome; Thrombocytopenia; Hemangiomas; Coagulopathy; Vascular Tumor; Kaposiform Hemangioendothelioma*

Abbreviations

CS: Corticosteroids; CT: Computed Tomography; IH: Infantile Hemangioma; ISVVA: International Society for the Study of Vascular Anomalies; KHE: Kaposiform Hemangioendothelioma; MRI: Magnetic Resonance Imaging; PT: Prothrombin Time; PTT: Activated Partial Thromboplastin Time; TA: Tufted Angiomas; VCR: Vincristine

Introduction

Soft tissue tumors account for approximately 25% of neonatal tumors and are most often benign. Vascular tumors are the most frequent benign tumors and infantile hemangioma (IH) accounts for 32% of these tumors, affecting 1 out of 200 children at birth [1].

The international society for the study of vascular anomalies (ISVVA) classifies vascular tumors as: the kaposiform hemangioendothelioma (KHE), the tufted angiomas (TA), IH, congenital hemangiomas and other rarer forms of tumors [2]. KHE is a rare vascular tumor with locally aggressive behavior (or borderline vascular tumors) [2]. However, recent studies support that more than half of KHE and up to 10% of patients with TA, not IH, are complicated by an intra-tumor coagulopathy responsible for Kasabach-Merritt syndrome (KMS) [3-5].

KMS, first described in 1940, is a rare but life-threatening coagulopathy of infancy which presents with thrombocytopenia, microangiopathic hemolytic anemia, and consumptive coagulopathy in the setting of a rapidly enlarging vascular tumor [6]. While the precise incidence of KHE and TA are not known, they are noted to be rare and estimated to be 0.07/100,000 in one article based on observed cases at a large center [9]. Tumors typically present in early infancy [7]. Rarely KHE may present in adulthood, and in adulthood is typically not associated with KMS [8].

The pathophysiology is believed to be consumption of platelets and fibrinogen by intralesional thrombosis [9]. The lesions are typically superficial and solitary, but may involve internal structures such as the liver. Cardiac failure may result from high-volume arteriovenous shunting. Shock, intracranial bleeding, or other internal hemorrhages may result in mortality rates as high as 30% [9]. Treatment includes supportive therapy and management of the underlying tumor [10].

A classic clinical case is described to illustrate the presentation and our management of a patient with KMS. The clinical presentation and laboratory findings, as well as the pathophysiology and the different therapeutic modalities of KMS are discussed.

Case Report

We report the case of a 4 weeks old Algerian female infant was admitted to pediatric department of the university Hospital Center of Oran, Algeria, for a large cutaneous lesion in the left hemi face.

She is descended from non-consanguineous parents. The mother was 24 years old, primi gravida, with Pregnancy hypertension treated with nicardipine and aspirin. The pregnancy was followed up. He was delivered at term by caesarean section. There were no complications at delivery. The apgar was normal at 5 minutes. The clinical examination at admission had found a newborn reactive, hemodynamically stable. The birth weight was at 3500g; the height at 50 cm and the cranial perimeter at 35 cm. No history of neonatal problems. No past or family history of significance. After birth, in the first week of life, a purplish mass was noted on the left cheek evoking a hemangioma of the face. The tumor lesion grew progressively after the second week of age.

On his arrival at the Marfan pediatric department of the Oran of the university Hospital Center: On routine physical examination, she was ill looking, pale, not cyanosed or jaundiced. She was keeping her neck in hyperextension posture, afebrile without respiratory distress and well hydrated. The skin of the left hemiface was indurated, with violet-red, swollen and firm vascular mass, without sharp margins which extended to the neck. The left eyelid was also edematous. Extensive unilateral left periorbital ecchymosis was documented with right subconjunctival hemorrhage with no discharge (Figure 1).

Within a couple of days after presentation, the mass enlarged very rapidly. The tumor enlarged significantly in size with a noticeable overlying purpuric plaque covering the left side of the face. The periorbital and periauricular edema on the affected side was prominent (Figure 2). She did not have purpuric rash, bruises or ecchymosis on her skin or mucus membranes. Her vital signs and oxygen saturation were normal. Examination of the chest, cardiovascular, abdomen and central nervous systems were normal. Malformative assessment was negative.

Ultrasound and computed tomography (CT) of brain and abdomen were normal. CT scan of the head show significant enhancement with dermal and subcutaneous thickening of the left hemiface measured at 8 mm.

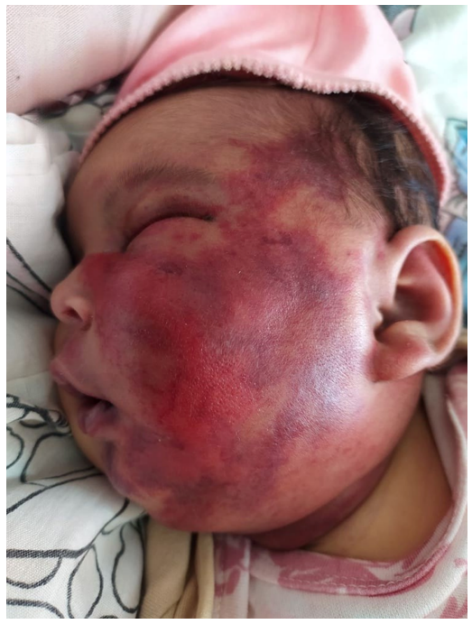

Figure 1: *Clinical case of KMS with KHE with diagnosed in a 31-days-old patient. Photos taken at the Oran pediatric department. A violet-red lesion in the left hemiface with irregular margins.*

Figure 2: *Extension of cutaneous lesion: extensive unilateral left periorbital ecchymosis with right subconjunctival hemorrhage.*

Laboratory tests showed normocytic normochromic anemia: hemoglobin at 8.6 g/dl and deep thrombocytopenia: platelet at 5000/mm^3 (150 - 450 × $10^3/mm^3$), and a normal peripheral blood film except for thrombocytopenia. The workup of jaundice revealed that the grouping of the baby and her mother was: O rhesus negative. Total bilirubin was at 120 mg/l; direct bilirubin at 12 mg/l and indirect bilirubin at 108 mg/l. C reactive protein test was normal.

An assessment of hemostasis was requested: Prothrombin time (PT) at 98%; INR = 1.1, activated partial thromboplastin time (PTT) at 29 seconds; hypofibrinogenemia with fibrinogen level of 0.21 g/l (2 - 3.9 g/l), and elevated D-Dimers > 10000 ng/ml (< 500 ng/ml).

The diagnosis of a hemangioma or extensive tumor complicated by disseminated intravascular coagulation became more likely: the diagnosis of KMS associated with KHE was made.

Our patient did not receive any platelet or blood transfusion. Then the patient was treated by oral high dose of corticosteroids (CS), prednisolone tablets (2 mg/kg/day) but the platelets count remained very low without affecting tumor size. For our patient, we chose Vincristine (VCR) and CS as therapy, as per institution preference and depending on the availability of drugs at the CHU of Oran. The dose of prednisolone was increased to 4 mg/kg/day, and weekly intravenous VCR injections at a dose of 0.05 mg/kg/day were started on the thirty eighth day of life, over a period of 20 weeks.

VCR in combination with CS resulted in resolution of coagulopathy and tumor regression. The KMS stabilized within a couple of days, and prior to completion of 4 days of therapy, thrombocytopenia, hemoglobin, and fibrinogen significantly improved. The patient's thrombocytopenia improved quickly, with the platelet count surpassing 50 × $10^3/mm^3$ on the fifty eighth day of life. The patient was stable while she was in hospital with no active bleeding from any site.

The patient was discharged at fifty eighth days of life with a platelet count of 50 × $10^3/mm^3$ and a plan for weekly intravenous VCR injections to be continued as an outpatient. She remained on 4 mg/kg/day of prednisolone. After 3 weeks of treatment, the cutaneous component improved significantly and a CS wean was initiated. This treatment has been associated with gradual normalization of hemostasis and hematologic abnormalities.

After discontinuation of CS, the KMS did not recur. Our patient has now completed 4 months of therapy and continues to receive VCR monotherapy every week. The cutaneous component of the patient's KHE has now resolved as well (Figure 3 and 4). The baby is currently five months old. The lesion has significantly decreased in size since the initial admission, and platelet, D-dimer, and fibrinogen levels, as well as the international normalized ratio. The patient never experienced any major bleeding complications or any adverse effects as a result of VCR or CS therapy.

Discussion

KMS is a rare vascular tumor of infancy that can easily be confused with IH, the most common benign vascular tumor in infants. KMS typically presents as a reddish or brownish discoloration of the skin progressing to an ecchymotic violaceous or pink bulging mass. They can be painful and infiltrate aggressively, with the potential for injury, infection, and obstruction of vital structures [11].

KMS typically has its onset early in infancy with a median age of onset of 5 weeks [12].

In approximately 50% of cases, KMS was associated with a vascular tumor diagnosed at birth with 90% of published cases diagnosed before 1 year of age. However, both genders and all ethnicities appear to be affected equally [7].

KMS was most often associated with a rapidly growing, large (> 5 cm) solitary tumor commonly involving extremities, trunk, or face and neck. Most of these tumors involved subcutaneous and deep structures and were locally invasive. Skin over the tumors was most often

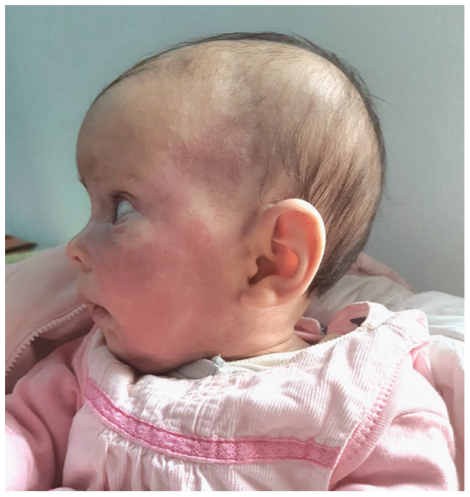

Figure 3 and 4: *Five months old. After 4 months of therapy with VCR and CS, almost complete resolution of the cutaneous component was achieved.*

described as deep red to purple in color with an advancing ecchymotic rim. The tumors were often warm and leathery to palpation with a nodular feel [13].

Widespread cutaneous petechiae were often seen in subjects with platelet counts less than 10,000. Signs and symptoms of bleeding were seen in more than 50% of children with KMS at presentation in one report [14]. Subjects with retroperitoneal or visceral lesions presented with abdominal distention, signs of organ dysfunction, or high-output heart failure often without cutaneous signs.

Diagnosis of KMS requires laboratory evaluation and identification of an underlying vascular tumor. Laboratory evaluation should include a complete blood count, coagulation panel and PTT [15]. All subjects with KMS had profound thrombocytopenia and hypofibrinogenemia with elevated fibrin split products (D-dimers), suggestive of an active consumptive coagulopathy. Platelet counts at the time of diagnosis ranged from 6000 to 98,000 with fibrinogen levels less than 100 mg/dL; whereas, D-dimers were always greater than 1. PT and

PTT were not routinely measured, but ranged from normal to significantly prolonged [15]. In one series, 80% of subjects presented with anemia at diagnosis [12]. Evidence of intravascular hemolysis, including red blood cell fragmentation, elevated LDH, and hyperbilirubinemia, was a common finding [14,16].

When identifying the underlying, cutaneous lesion, physical examination may be sufficient. If a visceral tumor is suspected, further imaging such as MRI may be useful in establishing both the presence of the tumor and its local extent. MRI may show significant gadolinium enhancement with dermal and subcutaneous thickening. Superficial draining vessels were often dilated, but vessels in the tumor were small and infrequent. Signal voids consistent with hemosiderin deposits were often noted on MRI [13,17].

Biopsy of the suspected underlying lesion should be considered to establish the identity of the underlying lesion but is typically not possible if KMS is already present due to the risk of bleeding [18].

Seminal studies in the 1990s challenged the long-held belief that KMS was a complication of IH and definitely showed the association of KMS with KHE and TA [3,11,13]. None had histology or clinical features consistent with IH. Since then, biopsies of most lesions associated with KMS have shared the same histopathologic features [3,11-13]. Indeed, the original case described by Kasabach and Merritt of a 2-month-old child with a capillary hemangioma with purpura was likely a KHE [6].

Why KMS develops exclusively in the setting of KHE or TA is currently unknown. Lyons and colleagues [19] have speculated that it is the unique architectural or endothelial composition found in KHE and TA that promote platelet trapping and a consumptive coagulopathy. In contrast to the ordered treelike vasculature of IH, convoluted capillaries arise directly off large vessels in KHE and TA resulting in turbulent flow-promoting platelet activation and aggregation. Furthermore, unique characteristics of the endothelial tumor cells within KHE and TA may promote platelet adhesion and activation. However, only a percentage of patients diagnosed with TA or KHE have an associated consumptive coagulopathy, arguing that other features, such as tumor size, may be an important determinant. The observation that most patients diagnosed with KMS are a few weeks or months of age could possibly be explained by proportionately larger tumors in this age group, or suggest other important developmental differences in platelet or endothelial function that may result in an increased susceptibility for development of KMS in young patients with KHE or TA [19].

KHE and TA arise from capillary and lymphatic endothelium. KHE is an infiltrative tumor, typically involving the dermis, subcutaneous fat, and muscles. Histologically, KHE is marked by irregular sheets of spindle-shaped endothelial cells and characteristic slit-like vascular channels, with positive immunohistochemical staining for lymphatic markers, D2-40, LYVE1, and Prox-1,8 and negative for GLUT-1, the marker for IH [11,20]. Immunohistochemical stains are also positive for vascular markers CD31 and CD34. TA is characterized by irregularly sized nodules or tufts of capillaries in a "cannonball" pattern [20]. Similar to KHE, TA shares an identical immunophenotype and stains positive for Prox-1, D2-40, LYVE1, CD31, and CD34 [20,21].

KMS is associated with significant morbidity and mortality. Mortality has ranged between 10% to 30% in most series [12,15,22]. Death usually occurs from life-threatening hemorrhage, cardiac failure, or invasion/compression of the underlying vascular lesion into local structures. Retroperitoneal lesions are associated with increased mortality, potentially due to delay in diagnosis [14].

No definitive management strategy has been developed for the treatment of KMS associated with KHE. The principle of treatment for KMS has been to shrink or remove the causative lesion, leading to the restoration of normal coagulation parameters. This must be accompanied by supportive therapies, including transfusion of blood products when absolutely necessary [17].

The principle of management of coagulopathy in KMS is to treat patients not numbers [23]. Despite marked thrombocytopenia at presentation, platelet transfusions should be reserved for active bleeding or in preparation for surgery or procedures. Infused platelets have a short circulatory time and have been noted to rapidly increase the size of the tumor and even exacerbate KMS in some cases, presumably

through increased platelet trapping within the lesion [23,24]. The use of aminocaproic acid and local measures may be helpful to reduce the need for platelet transfusions in these patients [25]. Antiplatelet agents, such as acetylsalicylic acid and dipyridamole, have been used in an attempt to reduce platelet aggregation within the body of the tumor [26,27].

Treatment of hypofibrinogenemia with cryoprecipitate and prolonged PT or PTT with fresh frozen plasma should also be a clinical decision rather than correction of a laboratory result. Symptomatic anemia should be treated with red blood cell transfusions [28].

Successful treatment of the underlying malignancy is critical to the correction of KMS and to the overall survival of patients. Several therapies have been reported for KHE/TA, but none have been uniformly effective. Although surgical removal of the tumor has been associated with immediate normalization of hemostasis and hematologic abnormalities, it is rarely attempted because of the large size and infiltrating nature of KHE/TA associated with KMS [29]. Tumor embolization has been used with some success in combination with medical and surgical therapies [28,29].

Multiple medical therapies have demonstrated promise in the treatment of KMS. Historically CS are typically first-line treatment. For patients who respond, clinical response is usually seen within 2 weeks, after which CS should be tapered slowly [15,29]. Traditionally, CS have been used as first-line therapy in patients with KMS in whom surgical excision of the tumor is not possible. However, one-third of patients may be refractory to treatment with CS, as was the case for our patient [30].

If regression cannot be achieved, alpha interferon (IFN), VCR and mTOR inhibitors such as sirolimus, antiplatelet agents, propranolol and other chemotherapy agents may be used with variable outcomes and long-term side effects [31-35].

Firstline therapy with CS at dosages ranging from 2 to 30 mg/kg/day resulted in improved hematological parameters in 10% to 30% of subjects within days of starting therapy without affecting tumor size [29,30]. IFN alone or in combination with CS resulted in resolution of coagulopathy and tumor regression in approximately 40% of subjects.4 However, the significant risk of irreversible neurotoxicity (spastic diplegia) in young infants treated with IFN has tempered its use [36,37].

VCR is emerging as a safe and effective treatment for KMS. In one series all 15 subjects treated with VCR as frontline therapy, either alone or in combination with other agents, experienced improved coagulation and hematologic parameters. 13 of these patients showed significant reductions in tumor size in response to VCR therapy [38].

Despite cure of KMS, most patients remain with a large residual tumor after medical or surgical therapies. These quiescent tumors can progress, often resulting in pain, functional impairment, and in rare instances, a late relapse of KMS [39]. Significant late effects in this population highlight the need for long-term follow-up and a better understanding of the unique biology of KHE to facilitate the development of new (targeted) therapies resulting in more complete resolution of the underlying malignancy [5].

Recent studies of mTOR inhibitors show promise in treating tumors such as KHE [40]. mTOR acts as a control protein for many cellular processes, including angiogenesis and cellular anabolism and is a rational target for inhibition in heavily vascular tumors. Multiple case reports, small studies, and a phase II prospective clinical trial support the use of m-TOR inhibitors in vascular anomalies based on the concept that patients have activation of the phosphatidylinositol 3-kinase/AKT signaling pathway, controlled by mTOR. Accordingly, overexpression of AKT/protein kinase B, TIE2 receptor-activating mutations, and the loss of function mutations in the PTEN tumor suppressor gene have all been associated with the development of vascular anomalies in patients and laboratory models [41-43]. In our patient, addition of sirolimus appeared to be the factor that improved his clinical status.

This is consistent with other literature that has shown effectiveness of mTOR inhibition in patients with KHE refractory to standard or alternative treatment modalities [40]. In a multicenter retrospective analysis, patients who received sirolimus as part of treatment tended to have improvement in clinical symptoms and tumor size, suggesting that sirolimus therapy should be considered [44].

Conclusion

The KMS remains an enigmatic disorder that requires an early diagnosis because of the high risk of bleeding and massive blood loss. It is associated with the vascular tumors KHE and TA and occurs most commonly in young infants. Treatment of KMS and the underlying malignancy requires a multidisciplinary team that can provide coordinated care over many years.

Deep or complicated forms of KMS are associated with an unfavorable prognosis. VCR and oral high-dose of CS were useful for our patient. The CS were weaned after the KMS resolved and the patient continues to tolerate VCR with complete resolution of KMS and KHE. VCR and CS may be considered an option for first-line therapy of KMS in KHE.

The absence of a codified therapeutic protocol makes the management of this tumor a real challenge. Improvement in outcome will only be achieved through consensus on treatment guidelines and an improved understanding of the unique biology of this rare entity and life-threatening syndrome.

Conflicts of Interest

The authors have declared no competing interest.

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