

## Clinical Review: Management of Adult Kasabach-Merritt Syndrome Associated with Hemangiomas

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Received date: Nov 07, 2017; Accepted date: Dec 20, 2017; Published date: Dec 27, 2017

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### Abstract

Kasabach-Merritt syndrome (KMS) consists of a clinical triad of capillary hemangioma, thrombocytopenia and disseminated intravascular coagulation. KMS occurs most commonly in the pediatric population, and its occurrence in adults is rare. Specific guidelines or randomized clinical trials guiding clinical management of KMS in adult patients are lacking. This manuscript provides a comprehensive review of KMS and discusses recent advances in the medical management of KMS. We also propose a systematic therapeutic approach which would serve as a guide in the management of adult patients with KMS caused by hemangiomas.

**Keywords:** Kasabach-Merritt syndrome; Kasabach-Merritt syndrome in adult; Kasabach-Merritt syndrome management; Disseminated intravascular coagulation in hemangioma; Hemangioma management; Kasabach-Merritt syndrome pathophysiology; Advances in Kasabach-Merritt syndrome management

**Abbreviations:** KMS: Kasabach-Merritt syndrome; KHE: Kaposiform hemangioendothelioma; DIC: Disseminated intravascular coagulation; MRI: Magnetic resonance imaging

### Introduction

Kasabach-Merritt syndrome (KMS, also called as Kasabach-Merritt phenomenon (KMP) encompasses a triad of capillary hemangioma, thrombocytopenia, and consumptive coagulopathy [1]. KMS manifests as a secondary complication of a tufted angioma (TA), kaposiform hemangioendothelioma (KHE), hemangioma, angiosarcoma or even an aneurysm. Most of the available literature on KMS and its management stems from pediatric studies, with limited reporting on the management of KMS in the adult population. KMS is a rare presentation in adults, and its exact incidence is unknown. In terms of pediatric literature, TA and KHE are rare, with incidence of KHE estimated at 0.07/1000, 000 children per year [2,3]. The incidence of KMS in patients with KHE and TA are 70% and 10% respectively [4,5]. TA and KHE share several histopathologic similarities, while TA is a benign tumor characterized by tufts of capillaries within the dermis, [3,4] KHE tends to be locally aggressive tumor that may involve superficial or deep soft tissues [4,6]. In the adult population, KMS is seen most often as a complication from hemangiomas [7], hemangiomas [4] or angiosarcoma [8].

Hemangiomas are benign mesenchymal tumors, usually involving the liver or spleen. They are well-circumscribed lesions surrounded by thin capsule and their size can range from few millimeters to few centimeters (cm). Histologically, the tumor is composed of cavernous vascular spaces lined by a single layer of endothelium and these vascular compartments contain thin fibrous septae which may develop collagenous scar which in turn may initiate thrombosis. The term giant

hemangioma usually refers to a hemangioma whose size is more than 5 cm [9]. It is not clear if there is any linear relation to the size of the hemangioma and the initiation of KMS, but most of the KMS cases are reported in giant hemangiomas. Whether a specific organ system (or site) which harbors the hemangioma confers increased predilection towards initiating KMS is also unclear.

In contrast to hemangiomas, angiosarcomas are uncommon malignant neoplasms characterized by rapidly proliferating, extensively infiltrating anaplastic cells derived from endothelium. These tumors tend to be more aggressive, recur locally, spread widely, and have a high rate of lymph node and systemic metastases. Common sites of angiosarcoma include liver, breast, spleen, bone and heart. Histologically, low-grade lesions have vascular spaces lined by large endothelial cells that penetrate the stroma and papillary fronds of cells that project into the lumen. Higher-grade lesions are more cellular, with atypical cells and abnormal mitoses. Immuno- histochemical studies show CD31 and Factor VIII positivity in these malignant cells.

### Clinical case

A 35-year-old African American woman sustained a sub trochanteric fracture of the left femur after a minor fall from standing height. She had no significant past medical history apart from gradually progressing discomfort in her left upper thigh for duration of one year. Pertinent surgical and family history was negative. Initial magnetic resonance imaging (MRI) of the left thigh, with and without contrast, revealed a large 15 × 9 cm peripherally enhancing soft tissue mass (Figures 1A and 1B). The initial patient's hematological and coagulation parameters were within normal range. Surgical biopsy of the left femur mass was consistent with hemangioma with a secondary aneurysmal bone cyst (Figure 2A).

Immuno-histochemical studies revealed CD31 positive vascular lining (Figure 2B). Feeding artery (left deep femoral) embolization was performed, along with tumor debulking, open reduction and internal fixation with intramedullary nailing. A follow-up MRI performed 3 months later revealed a recurrent larger vascular lesion, which measured 16 × 11 cm (Figure 1C). The patient again underwent partial

embolization of the deep femoral artery, which was unsuccessful. Repeat MRI scan showed an enlarging mass (Figure 1D), measuring  $17 \times 12$  centimeters). The patient was referred to the hematology and oncology clinic for further management. Both swelling and pain over the left upper thigh continued to increase, with development of skin bruising, gingival bleeding and worsening hemorrhoid bleeding. A complete blood picture revealed hemoglobin at 12.1 g/dL, white blood cell count of  $9 \times 10^3/\mu\text{L}$  and platelet count of  $10^8 \times 10^3/\mu\text{L}$ . The platelet counts immediately trended to  $36 \times 10^3/\mu\text{L}$ . The coagulation profile revealed D-dimer  $>20 \mu\text{g/mL}$ , fibrinogen 62 mg/dL, prothrombin time (PT) 18.6 seconds, international normalized ratio (INR) 1.5 and partial thromboplastin time (PTT) 39.1 seconds, which was consistent with disseminated intravascular coagulation (DIC). MRI revealed further increase in the size of the hemangioma (Figure 1E).

In the context of thrombocytopenia, coagulopathy and left femur hemangioma, the patient was diagnosed with Kasabach-Merritt syndrome. On admission, she was started on prednisone (1 mg/kg), fresh frozen plasma (FFP) and cryoprecipitate with a goal to keep fibrinogen above 100 mg/dL. Aminocaproic acid was added as an adjunct to control bleeding diathesis. Repeated attempts of embolization were unsuccessful, and surgical management was deferred secondary to coagulopathy.

Worsening coagulopathy (patient required 160 units of cryoprecipitate), despite all of the above treatments, led to initiation of intravenous vincristine (1.4 mg/m<sup>2</sup> every 2 weeks, total of 4 doses) with concurrent radiation therapy (4,500 cGy in 25 fractions), along with continuation of daily oral prednisone (1 mg/kg). After completion of chemoradiotherapy, the prednisone was slowly tapered off over 2 months. At the end of this therapy, the lesion had regressed to  $13 \times 10$  cm (Figure 1F) with complete normalization of the coagulation profile. Her disease has been in control for the past 44 months.

### Pathophysiology

The pathogenesis of KMS is complicated and poorly understood. The proposed mechanism of KMS involves both primary and secondary hemostatic mechanisms, leading to platelet trapping, platelet activation/aggregation, and platelet consumption, along with activation of coagulation cascade within the abnormal vascular structure [10]. The site of platelet destruction has been a subject of controversy. Even though Indium-111 platelet scintigraphy studies demonstrate platelet trapping in the vascular lesion, the degree of thrombocytopenia is poorly correlative to the size of lesion.

In fact, other studies involving platelets labeled with Technetium-99m demonstrated lower level of platelet sequestration in vascular lesion compared to the spleen. The phenomenon of platelets destruction in spleen and not in vascular lesion could be explained by acquired platelet defects occurring in the vascular lesions, leading to their subsequent destruction in spleen [11]. It is also controversial as to why only a fraction of these vascular lesions lead to KMS. The most important structure which is at the epicenter of KMS initiation is endothelium. Kraling et al. [12] and Dosanjh et al. [13] demonstrated that hemangioma-derived endothelial cells showed increased expression of E-selection, a cell adhesion molecule and diffuse distribution of CD31 and von Willebrand factor (vWF), demonstrating an immature phenotype of the endothelium.

Endothelial damage also has been shown in bacterial [9,14,15] and multiple viral infections (measles virus, rubella virus, herpes simplex

virus, cytomegalovirus, human immunodeficiency virus, and other viruses) [16].

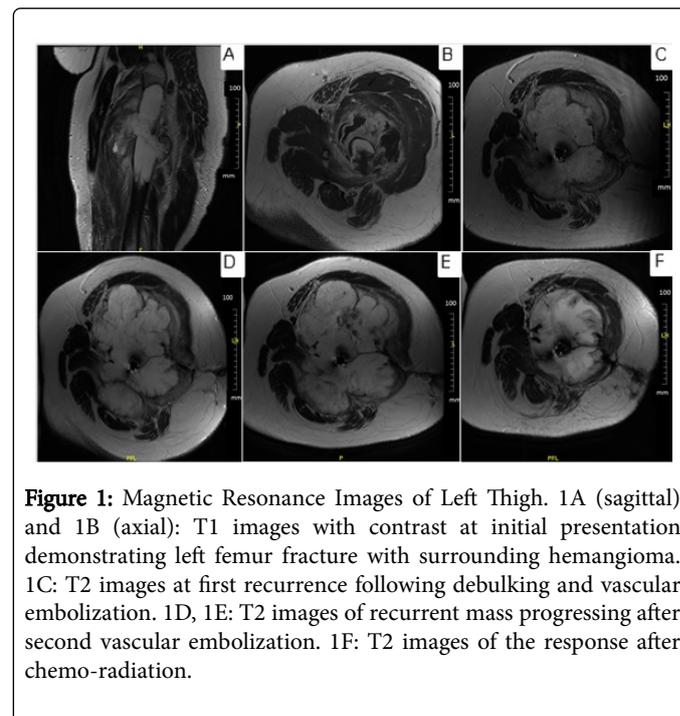
Regardless of the initiating factors, exposure of sub-endothelial collagen and tissue factor in rapidly changing endothelial cells leads to platelet binding via glycoprotein (GP)-Ib-V-IX and vWF, and subsequent activation of platelets. All these processes culminate in localized intravascular coagulopathy and can ultimately lead to life-threatening disseminated intravascular coagulopathy [16].

Platelet trapping leading to thrombocytopenia, hypofibrinogenemia, and increased fibrinolysis can potentially cause intra-lesional bleeding and tumor enlargement [2,17,18]. Micro-angiopathic hemolytic anemia can be also seen in these patients. Vascular endothelial growth factor- alpha (VEGFA) also seems to play an important role in tumor enlargement. VEGFA is secreted by tumor cells, tumor stroma and by platelets [2].

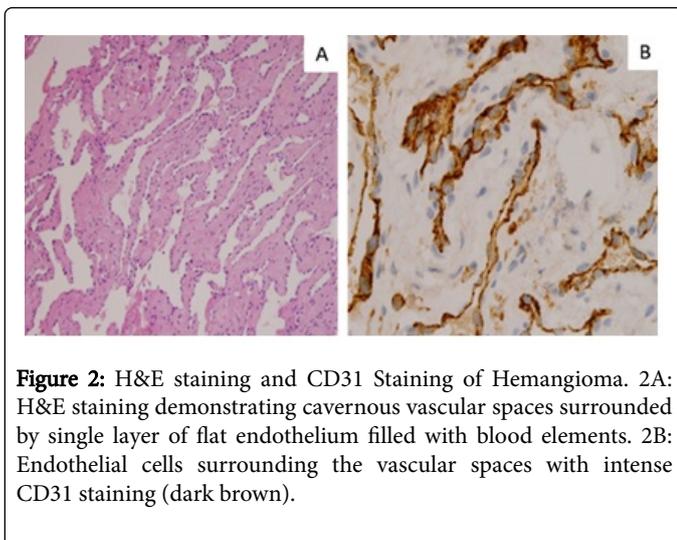
### Clinical presentation

Table 1 provides various presentations, treatments and outcomes of adult patients with KMS reported in the literature. As shown in the Table 1, KMS is more common in young adults and its incidence decreases steadily with age. The most common site involved includes liver and the extremities. Patients with KMS may present with rapidly enlarging painful mass, ecchymosis, overt bleeding symptoms or fractures.

High-output cardiac failure has been reported in the pediatric population, but this seems to be exceedingly rare in adults, with only two cases described in the literature [19]. The outcome in terms of morbidity and mortality is in a large part related to location, disease burden and severity of presentation. The degree of coagulopathy, accessibility of mass and side effects of treatment like drugs and surgical complications also affect the clinical outcomes.



**Figure 1:** Magnetic Resonance Images of Left Thigh. 1A (sagittal) and 1B (axial): T1 images with contrast at initial presentation demonstrating left femur fracture with surrounding hemangioma. 1C: T2 images at first recurrence following debulking and vascular embolization. 1D, 1E: T2 images of recurrent mass progressing after second vascular embolization. 1F: T2 images of the response after chemo-radiation.



## Diagnosis

KMS is rare and high index of suspicion is required for timely diagnosis. In a patient with suspicion for KMS based on above clinical features, histopathologic diagnosis by biopsy is recommended. This is especially important if suspicion of angiosarcoma is high. Performing biopsy sometimes is complicated by the very vascular nature of the tumor itself and, coexisting coagulopathy, hence correction of coagulopathy is recommended prior to attempting any biopsy.

The imaging studies with magnetic resonance imaging (MRI) can delineate the extent of involvement and also help document the response to treatment. T1-weighted images with contrast show diffuse enhancement of mass and T2-images show a diffuse increased signal with stranding in the subcutaneous fat [20,21]. As shown in images (Figures 1A-1F), we used MRI for initial diagnosis and subsequent follow-up after various treatments. Doppler flow studies may help differentiate a solid mass from a vascular lesion.

Radionuclide imaging using Chromium-51 labeled platelets, Indium-111 labeled platelets (or) Iodine-131 labeled fibrinogen studies are probably more sensitive than computed tomography (CT) scans or MRIs for delineating the size and number of vascular lesions [22]. There have been reports of using radio nucleotide imaging to find hemangiomas in children. However, the use of radio nucleotide imaging is limited, as MRI and clinical findings are usually sufficient for diagnosis. There is no available literature to support the use of positron emission tomography (PET) scan in KMS.

## Management

Because of the rarity of this manifestation and the absence of any randomized controlled trials, there are no clinical guidelines aiding in the management of KMS. The literature suggests use of multiple modalities for management of KMS.

Rather than concurrent treatment, more number of authors of published literature suggests use of sequential approach with various modalities for KMS [23,24]. The general approach is to manage coagulopathy effectively with supportive care and medical

management [23-30] before proceeding with surgical or interventional treatments [31-35].

Management of KMS can be divided into the following overlapping categories:

1. Management of coagulopathy and aggressive supportive care
2. Systemic treatment
3. Corticosteroids
4. Systemic chemotherapy: vincristine, cyclophosphamide, actinomycin-D
5. mTOR inhibitors: Sirolimus
6. Antifibrinolytics: aminocaproic acid / tranexamic acid.
7. Antiplatelet therapy: aspirin, ticlopidine, dipyridamole and pentoxifylline.
8. Anticoagulants: heparin / low molecular weight heparin.
9. Immunomodulators and anti-angiogenic agents: bevacizumab
10. Other agents: propranolol.
11. Surgical management
12. Embolization
13. Radiation therapy
14. Liver transplantation in liver hemangiomas or hemangiomas
15. Surveillance and follow up of treated patients.

## Management of coagulopathy

The ultimate management of coagulopathy is treatment of vascular lesion, but the supportive care can be used as below.

### Platelets

The authors recommend judicious use of platelet transfusion and restrict its use cases of active bleeding or prior to performing surgical procedures. Platelet counts in KMS can be alarmingly low, but life-threatening hemorrhages are rarely seen [3]. The half-life of platelets is very short due to intra-lesion trapping and destruction, leading to its ineffectiveness. The platelets transfusion can be harmful in that it can accumulate in the lesions leading to increase in size [36]. The transfused platelets can release pro- angiogenic growth factors which can further worsen the symptoms [37].

### Reversal of coagulopathy

Similar to platelets, use of cryoprecipitate and fresh frozen plasma for the correction of hypofibrinogenemia and coagulopathy should be given sparingly, and their use should be limited to: active bleeding, before surgical procedures, platelet count <10,000/ $\mu$ L or fibrinogen < 1 g/dL [3,38]. Recombinant factor VIIa can be used in active and uncontrolled bleeding [39]. The use of antifibrinolytics, like aminocaproic acid [40] and tranexamic acid [19,41-44] is limited to uncontrolled bleeding with low fibrinogen, elevated fibrin degradation products, and D-dimers. Transfusion of packed red blood cells should be considered when patient is symptomatic from anemia.

### Systemic therapy

Pharmacologic systemic therapy is a significant part of multi-modality treatment for KMS. When used as monotherapy only, the duration of response might be short lived [3,23, 24,45-47].

Study	Age/ Sex	Presentation	Location of Lesion	Tumor type	Treatment	Outcome/ Follow up months
Rodriguez et al. [2]	70/F	Abd. Pain	Liver	Angiosarcoma	Surgical Resection	Resolved / 8
Moussa et al. [9]	55/F	Breast Enlargement	Breast	Angiosarcoma	Steroids	Death / NA
Salameh et al. [19]	69/M	Skin Lesion Bleed	Scalp,Lung,GI tract	Angiosarcoma	ACA,Steroids, Adriamycin,Vinc.	Death / NA
Watzke et al. [40]	35/F	Abd Pain + DIC.	Liver	Hemangioma	Heparin,FFP,Surgery	Resolved / 6
Wang et al. [43]	26/F	Uterine Bleeding	Spleen	Hemangiomas	Tranexamic acid,FFP,Splenectomy	Resolved / NA
Giráldez et al. [51]	37/M	Lower GI bleed	Meso-colon	Hemangioma	Vinc.,Cyclophosphamide,Steroids	NA
Chen et al. [52]	20/F	Femur Fracture, DIC	Liver,Spleen,LE, Vulva	Hemangioma	Cryo,FFP,Steroids, XRT,TAE	Resolved / <1
Fernandez et al. [60]	52/M	Mass Head and Neck	Face,Neck,Ches t	TA within a PWS	Steroids,Vinc.,Cyclophosphamide,Imatinib,XRT,Bevacizumab	Improved / 26
Dufau et al. [98]	72/M	Pleural Effusion	Spleen	Hemangiomas	Splenectomy	Death/ 2
Mahmoud et al. [99]	39/M	Lower GI Bleed	Rectum,Liver,Sp leen	Hemangioma	Surgical Resection	Resolved / 48
Tani et al. [100]	67/F	Abd. Swelling	Liver	Hemangioma	Surgical Resection	Resolved / 2
Malagari et al. [102]	52/F	Abd. Swelling	Liver	Hemangioma	TAE with Gelatin	Resolved/ 24
Malagari et al. [102]	74/F	Melena + DIC	Liver	Hemangioma	TAE with Gelatin and Coils	Resolved / 24
Hochwald et al. [112]	51/F	Abd. Swelling + DIC	Liver	Hemangioma	XRT,Enucleation	Resolved/ NA
Biswal et al. [113]	24/M	LE Weakness	Thoracic Vertebra	Hemangiomas	XRT (30 Gy in 15 fractions)	Resolved/NA
Habringer et al. [123]	87/M	Thrombocytopenia	Liver	Angiosarcoma	None (Advanced age)	Death / NA
Imafuku et al. [124]	67/M	Scalp Ulcer	Scalp	Angiosarcoma	XRT,Heparin	Resolved /1
Bernathova et al. [125]	28/F	Breast Enlargement	Breast	Angiosarcoma	Chemotherapy,Surgery	NA
Phillippe et al. [126]	30/F	PPH	Face,Neck,Ches t,LE	Hemangioma	Cryo,FFP,ACA,Heparin	Resolved / 2
Ontachi et al. [127]	39/F	Abd. Swelling	Liver	Hemangioma	Danaparoid,Tranexamic Acid,XRT	Resolved/ NA
Mewes et al. [128]	62/F	Abd. Swelling	Liver	Hemangioma	Heparin and Surgical resection	NA
Longeville et al. [129]	47/M	Abd swelling + DIC	Liver	Hemangioma	Liver Transplant	Resolved / 12
Kumashiro et al. [130]	48/F	Abd. Swelling	Liver	Hemangioma	Liver Transplant	Resolved /NA
Warrell et al. [131]	45/F	Chest Mass + DIC	Bone,Soft tissue	Hemangioma	ACA,Cryo	Resolved
Menendez et al. [132]	46/F	Femur Fracture	Bone,LE	Hemangioma	Platelets,Cryo	Resolved
Shoji et al. [133]	62/F	Hematuria + DIC	UE,LE	Hemangioma	Heparin,Steroids	Resolved / NA
Singh et al. [134]	20/F	CHF and PPH	Face,Abd. Wall,LE	Hemangiomas	Blood Products	Resolved / NA
Singh et al. [134]	21/F	CHF and PPH	Face,Abd. Wall,LE	Hemangiomas	Blood Products	Resolved/NA
Klompaker et al. [135]	27/M	Abd. Swelling + DIC	Liver	Hemangiomas	Resection and Liver Transplant	Resolved / 36
Courcousakis et al. [136]	41/F	Breast Mass	Breast	Hemangiomas	NA	NA

Lee et al. [137]	69/F	Mass Head and Neck	Face	Merkel cell cancer	TAE	Resolved / 1
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Abd: Abdominal, ACA: Aminocaproic acid, CHF: Congestive Heart Failure, Cryo: Cryoprecipitate, DIC: Disseminated intravascular coagulation, Ext: Extremities, F: Female, FFP: Fresh Frozen Plasma, GI: Gastrointestinal tract, LE: lower extremities, M: Male, NA: Not available, PPH: Post-partum hemorrhage, PWS: port-wine stains, TAE: Transarterial Embolization, UE: Upper extremities, Vinc: Vincristine, XRT: Radiotherapy

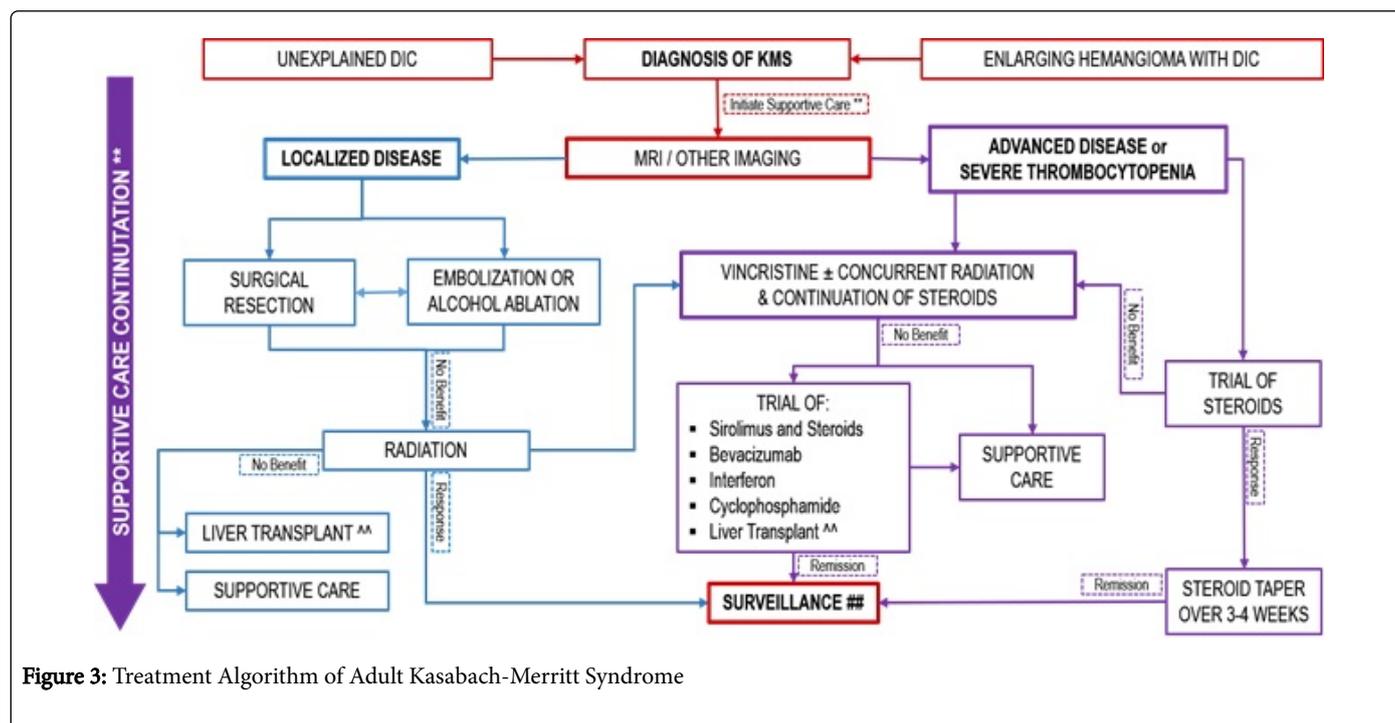
**Table 1:** Overview of different presentations, treatments and outcomes of adult patients with KMS.

### Corticosteroids

Greenberger et al. [65] in their studies on infantile hemangioma derived stem cells demonstrated that corticosteroids lead to suppression of vascular endothelial growth factor, monocyte chemoattractant protein-1, urokinase plasminogen activator receptor, and interleukin-6. All these factors are known targets of nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells (NF- $\kappa$ B) [3]. Clinical effectiveness of corticosteroids in management of KMS has been validated in multiple clinical trials [3,9,19,48-51]. The initial dosing and the type of corticosteroids used in KMS vary based on the case series or case reports published. In general the choices can be: intravenous prednisolone (2 mg/kg/day) or methylprednisolone (1.6 mg/kg/day) or bolus doses of methylprednisolone (30 mg/kg per day for three days) [3,23,52-57]. Due to long-term side effects of steroids, weaning should be attempted over 4-8 weeks.

### Vincristine

Vincristine, a microtubule inhibitor is the most studied systemic agent used in second line for KMS. Being a vesicant, it is recommended to be given intravenously via central venous line at 1-2 mg/m<sup>2</sup> per week [19,29,30,53,58-60]. In one case series, the average time for platelet recovery was two months, and the average time for hemangioma regression was four months [31]. The duration of the intended therapy is 20-24 weeks. Vincristine can be combined with other chemotherapy or antiplatelet drugs. Some studies have combined it with Adriamycin [33] or cyclophosphamide [61,62]. In a case series involving 11 patients, vincristine in combination with aspirin and ticlopidine [19,51,60] demonstrated excellent clinical response, and this response was quicker than vincristine alone [63]. The response rate of vincristine when used with steroids approaches 78% [30]. In 2013, an expert panel recommended steroids and vincristine as first-line treatment for KMS [64].



**Figure 3:** Treatment Algorithm of Adult Kasabach-Merritt Syndrome

### Other systemic chemotherapy agents

Although there is not much experience in adult patients, both cyclophosphamide [64] and actinomycin D [65] have shown some activity in the management of hemangiomatosis and KHE causing KMS in the pediatric population. Liposomal doxorubicin and paclitaxel has been used in adults with angiosarcoma [66].

### Role of mTOR Inhibitors

Mammalian target of rapamycin (mTOR) is a member of the serine/threonine kinase protein family which is involved in various cellular processes like cell metabolism, angiogenesis and growth. mTOR is regulated by phosphoinositide-3-kinase (PI3K) [67]. The mTOR inhibitor sirolimus has been shown to inhibit lymphangiogenesis, and it has been successfully used as a treatment option for vascular anomalies in children [28,68-70]. Advantages of sirolimus include oral administration without the need for a central line and more rapid

resolution of coagulopathy compared with a combination of vincristine and steroids. Some recent case reports have shown a rapid response of KHE and KMP to sirolimus [71-73]. In a case series reported by Kai et al., sirolimus was shown to be effective in children with refractory KHE with KMS. The response rates were 100%, with significant improvement in signs and symptoms. The average time of response was only 5.3 days (ranging from 4 to 7 days), and the average platelet stabilization time was only 15.1 days (ranging from 5 to 28 days), which indicated the rapid efficacy of sirolimus in the treatment. The average time for sirolimus treatment in patients with KHE is 20.5 months (range, 13 to 26 months). Another study showed that Sirolimus is a well-tolerated. The common grade three side effects bone marrow toxicity in 27%, gastrointestinal toxicity in 3% and metabolic toxicity in 3% [74,75].

### Antiplatelet therapy

As previously mentioned, platelet activation and release of proangiogenic mediators is a major driver of the pathogenic process in KMS and this forms rationale for using antiplatelet agents. The antiplatelet agents that have been used in KMS include: Aspirin, Ticlopidine, Dipyridamole and Pentoxifylline. Review of available literature does not support an increased risk of bleeding with use of antiplatelet agents in KMS, especially when there is no active bleeding. Although the data is controversial, the combination of aspirin and Ticlopidine appears to be the safest and most effective option [76-80]. Enjolras et al. reported that this combination was effective in 32% of patients in one series and 29% in another series [63,81,82].

### Immunomodulators

Use of interferon-alpha is reported in pediatric literature but there is a lack of any data in adults. Although some success with interferon-alpha has been reported, the failure rates are also high [81,83,84].

### Anti-Angiogenic Agents

As mentioned earlier, VEGF-A is involved in pathogenesis of KMS and Bevacizumab is a recombinant humanized monoclonal antibody against VEGF-A. Bevacizumab's use is currently being explored in a variety of vascular malformations and vascular tumors [85-87]. Bevacizumab has been successfully used in combination with steroids and radiation [88,89].

### Propranolol

Published literature shows variable efficacy of use of propranolol in KMS. In a small case series of 11 patients, improvement was noted in only four cases [90]. Potential explanations of the therapeutic effect included vasoconstriction, decreased expression of VEGF and the triggering of apoptosis of capillary endothelial cells. Despite initial success in KMS [60], a larger series of patients reported poor results with only one-third of patients responding [91,92].

### Surgical Management

Surgery is a feasible option for small, localized and accessible tumors or tumors whose size has been reduced by previous pharmacologic therapy. In patients who have failed medical treatment and, in life-threatening tumors surgery may serve as an important salvage option [92-94]. Wide local excision when possible and feasible is recommended [95]. Resolution of KMS has been reported in cases when complete resection is achieved [40,66,96-99].

### Others

#### Embolization

In patients who are at high risk of bleeding, in addition to supportive care and medical management, trans arterial embolization (TAE) can provide a minimally invasive and non-radical treatment option [100]. In large tumors, TAE can be a useful bridge before surgery is attempted or until the systemic treatment becomes effective [43,101,102]. There are also multiple case reports of successful treated KMS with endovascular approaches [103-106]. As mentioned in Table 1, KMS secondary to liver hemangiomas [107] and Merkel cell cancer involving the face [108] has been successfully treated with TAE. Intralesional injection of absolute alcohol [97] and steroids [102] have also been reported as management strategies.

#### Radiation

Procedural therapies other than surgical resection and TAE have included radiotherapy [52,109-112]. Historically, radiation therapy has been associated with multiple long-term side effects when used in pediatric population [60,100,113-116] its use in adults has been more liberal. In a series of 28 patients, concurrent radiation and steroids demonstrated a 75% response rate, with no radiation-induced side effects over a median follow-up of more than 6 years [117]. With new advancements in radiotherapy, there is minimal radiation delivered to uninvolved organs and this can lead to more liberal use for adult population.

#### Pneumatic compression

Pediatric literature suggests a role for intermittent pneumatic compression in the management of vascular lesion [34]. It can be considered when the vascular lesion is located on an extremity. In some selected cases, it could be considered as an intermediate step before other treatments are pursued.

#### Liver transplantation

Hemangiomas involving the liver can be treated with enucleation. The procedure is generally curative [23,118,119]. Successful cases of liver transplantation have been performed in patients with hemangioma of the liver [120-122].

#### Surveillance and follow up

After the therapy is completed, remission pattern needs to be confirmed by close serial monitoring of platelets, hemoglobin, PTT, PT, INR and fibrinogen. Although how often and how long should labs be checked is arbitrary, authors recommend clinical evaluation along with lab monitoring every week for 4 weeks followed by monthly for 3-4 months and then serially every 3 months or as clinically required. Radiological assessments can be performed based on clinical indication. Worsening localized pain symptoms, new onset of thrombocytopenia or new onset coagulopathy should alert the physician to suspect relapse and treat accordingly.

#### Our approach

Once the diagnosis of KMS is established, authors recommend close monitoring of complete blood profile and coagulation parameters. Judicious and appropriate use of blood products like cryoprecipitate, fresh frozen plasma, platelets and packed red cells is advised. The need

for adequate control of pain symptoms in symptomatic patients cannot be understated. MRI is recommended to accurately estimate the size and extent of the lesions. In absence of specific clinical guidelines and randomized trials, choice of therapy should be individualized after discussion with the patient and the family. Surgery is considered in patients with small and resettable lesions. In patients where initial surgery is not an option, we recommend high dose corticosteroids as an initial therapy, and if response is not achieved within a week, we recommend adding vincristine. Vincristine along with steroids alone or, with concurrent radiation should be considered. Vincristine is typically administered for 20 to 24 weeks, based upon the tumor response to treatment and acceptable therapy-related toxicity. In a very symptomatic patient or in cases associated with severe thrombocytopenia combined vincristine and radiation therapy along with supportive care may be an effective initial approach. Tumor embolization should be considered as a parallel strategy throughout this process. In a refractory setting, sirolimus with steroids, cyclophosphamide, interferon, bevacizumab, antiplatelet agents, propranolol, and mTOR inhibitors can be attempted. Once a remission pattern is obtained on steroids, we recommend a slow taper of corticosteroids over 3-4 weeks, before surveillance and follow up is started.

## Source of funding

None

## Conflict of Interest

All authors confirm no conflict of interest.

## Acknowledgements

The authors wish to acknowledge the authors of previous studies and case reports on KMS as mentioned in references.

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