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CLINICAL REPORT

# Kaposiform Haemangioendothelioma-spectrum Lesions with Kasabach-Merritt Phenomenon: Retrospective Analysis and Long-term Outcome

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**Kasabach-Merritt phenomenon (KMP) is a rare life-threatening vascular condition of infancy. Prognosis factors and long-term follow-up data are lacking. We retrospectively analysed the records of 24 infants (10 females, 14 males) treated for KMP in the Department of Dermatology of Necker-Enfants Malades Hospital, Paris, France, from 1984 to 2012. Mean duration of thrombocytopaenia (2,000−38,000 platelets/mm$^3$, mean 10,500/µl) was 8.8 months (range 3 days−84 months), which correlated with tumour infiltration depth on imaging. D-dimer levels were always elevated, even before KMP onset. Each patient received a mean of 4.8 different treatments (range 1−10). Median follow-up was 6.5 years (range 2 months−22 years). All infants had residual cutaneous lesions, and some also had inflammatory manifestations ($n$=9), elevated D-dimer ($n$=5) and orthopaedic sequelae ($n$=5). The permanent coagulopathy (elevated D-dimer) even after resolution of KMP suggests the presence of chronic low-grade platelet trapping, with possible sudden worsening, and raises the possibility of prophylactic anti-platelet therapy. *Key words: vascular tumour; thrombocytopaenia; Kasabach-Merritt phenomenon; tufted angioma, kaposiform haemangioendothelioma; infant.***

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Kasabach-Merritt phenomenon (KMP) is a rare and life-threatening condition, defined as the combination of a large vascular tumour and thrombocytopaenia in an infant. The tumour is either congenital or develops rapidly after birth. Originally described as a "capillary haemangioma" (1), the tumour comprises histopathological features of kaposiform haemangioendothelioma (KHE) and tufted angioma (TA), which are very similar tumours (2, 3). Thrombocytopaenia, resulting from platelet trapping within the tumour, is always severe and is accompanied by various degrees of decreased fibrinogen and elevated levels of D-dimer. Those particular biological features of KMP must be differentiated from the clotting disorder associated with extensive superficial or visceral venous or lymphatico-venous malformations (4). The gold standard of care and management are still under discussion (5, 6). For many authors systemic corticosteroids remain the first-line treatment (7). However, new treatments, such as sirolimus, appear to be promising (8−10).

We report here on our 26 years' experience of KMP multidisciplinary management, describing the long-term outcome and overall good prognosis, the particular features that may be useful prognosis factors, and the management we have developed for this condition.

## MATERIALS AND METHODS

All infants with KMP followed since the creation of the Department of Dermatology, Necker-Enfants Malades Hospital, Paris, France, were included in this study. The diagnosis criteria were the presence of a vascular tumour in an infant, combined with profound thrombocytopaenia (< 50,000/mm$^3$). The following items were analysed: age, sex, date of diagnosis, clinical manifestations, follow-up and laboratory tests. The available histopathological and imaging data were reviewed by the same pathologist (SF) and the same radiologist (FB), respectively. Informed consent was obtained to publish patients' photographs.

A diagnosis of TA was retained if histological analysis showed tightly packed capillaries in a cannonball pattern located in the mid-to-deep dermis, surrounded by a crescent-shaped channel. A diagnosis of KHE was retained if the lobules were poorly circumscribed and invasive, located in haemorrhagic connective tissue, and showed solid aggregations of poorly-canalized, slit-like capillaries lined with spindle cells. Lesions were classified as "pure TA", "pure KHE", or "mixed TA-KHE". When possible, immunostaining with GLUT-1 (polyclonal, Diagosmix, Santa-Barbara, USA) and D 2-40 (monoclonal anti-podoplanin Dako, Glostrup, Denmark) antibodies was performed.

The efficacy of different therapeutic lines was assessed for each patient as persistent improvement in platelet count and tumour mass reduction after treatment introduction.

Sequelae were analysed on the basis of the clinical features encountered at the last follow-up visit. Residual lesions were classified according to the system of Enjolras et al. (11). Type I corresponds to red stain more or less fibrotic, type

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II to telangiectatic streaks and swelling, and type III to firm subcutaneous mass.

## RESULTS

Twenty-four patients (14 males, 10 females) with KMP were identified since 1984 (Table SI[1]).The vascular tumour was present at birth in 15/24 cases or appeared before 6 months of age for the remainder. The tumour was located on the trunk ($n=11$), limbs ($n=13$) and head and neck ($n=4$); in 4 cases it extended to adjacent regions; 1 patient presented with bifocal lesion; the tumours were located deep within the trunk with no cutaneous involvement in 2 children. Typical clinical features, i.e. a painful, purple, tense, inflammatory tumour, were reported in 19 patients (Fig. 1A and C); the tumour was bluish with superficial ectatic veins in 2 patients (Fig. 1B). Tumour sweating was noted in 1 patient. The tumours were hairy in 4 cases.

Platelet count ranged from 2,000 to 38,000/mm$^3$ (normal 175,000–500,000/mm$^3$) (mean lowest count = 10,500/mm$^3$), with a mean duration of 8.8 months (3 days–84 months), and 2.5 months (7 days–8 months, data available for 10 patients) since efficient treatment was introduced.

Both thrombocytopaenia and clinical modifications occurred simultaneously in 16 of the available 19 patient's data. In the remainder, thrombocytopaenia developed progressively over several days or weeks, leading to treatment initiation before platelets had decreased to less than 20,000/mm$^3$. This was also the case for patients 1 and 2, whose platelet counts were never lower than 38,000/mm$^3$ and 37,000/mm$^3$, respectively. Two patients presented with 1 (patient 22) and 2 (patient 19) relapses within the first year, consisting of clinical worsening (tumour swelling, warmth and pain exacerbation) along with profound thrombocytopaenia.

Coagulation anomalies always accompanied thrombocytopaenia. When laboratory test results were available, fibrinogen levels were always low (< 0.5 g/l; normal 1.5–3 g/l); D-dimer level had always risen from 4–8 µg/ml to 64–128 µg/ml (normal < 1 µg/ml), and remained elevated after the platelet count had returned to normal ($n=9/9$). When measured (patients 4 and 7), D-dimer level was elevated before the onset of severe thrombocytopaenia. Haemorrhagic complications occurred in 5 children: cerebral bleeding leading to death

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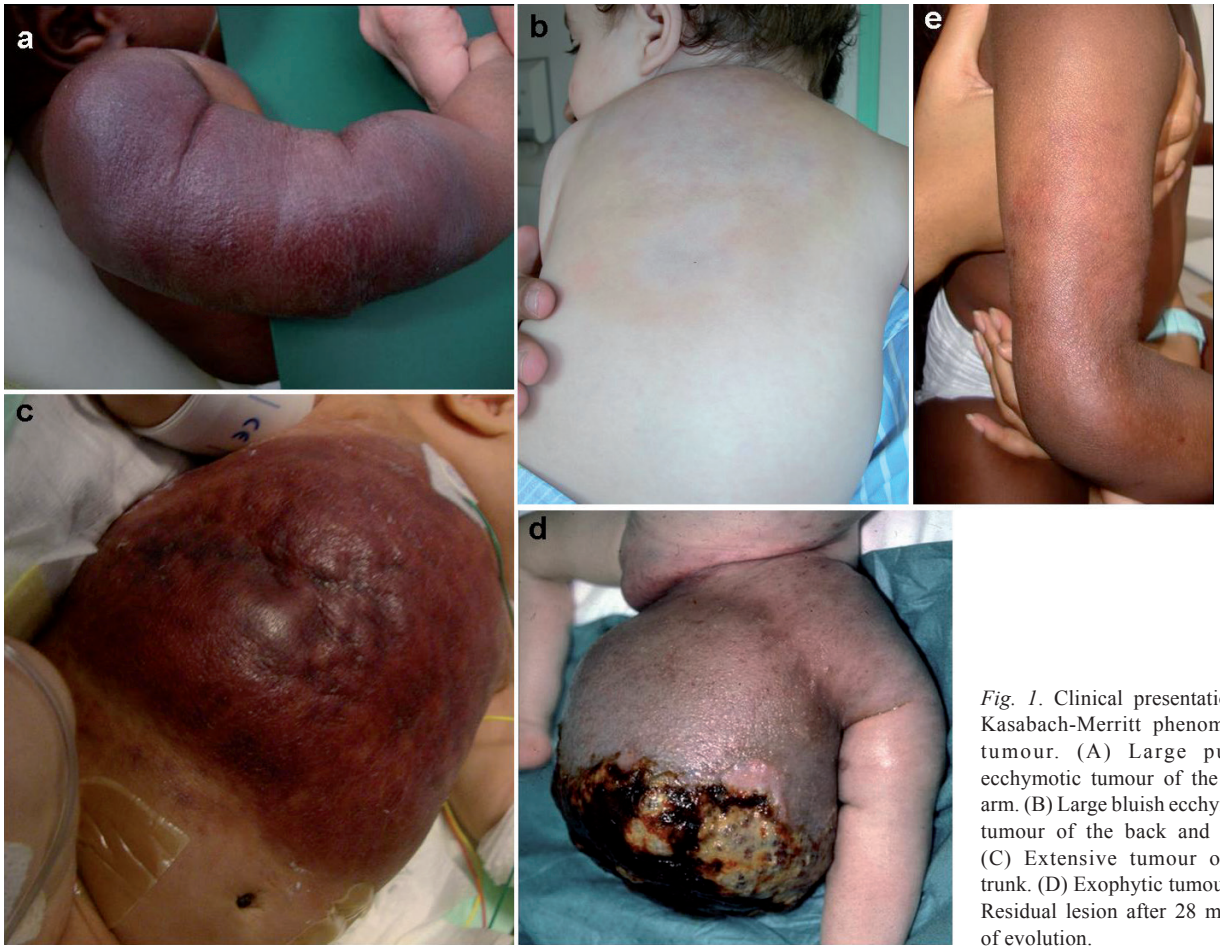


*Fig. 1.* Clinical presentation of Kasabach-Merritt phenomenon tumour. (A) Large purple ecchymotic tumour of the right arm. (B) Large bluish ecchymotic tumour of the back and neck. (C) Extensive tumour of the trunk. (D) Exophytic tumour. (E) Residual lesion after 28 months of evolution.

(patient 10), bleeding at the tumour site (patients 8 and 12), or during catheter removal (patient 13), and haemothorax with hypotension during catheter insertion (patient 18).

Radiological data were available for 15 cases. Tumour infiltration ranged from subcutaneous tissue to visceral organs. Muscle infiltration was common ($n=12$). Two children (Nos. 12 and 21) had exophytic, and then very thick tumours (Fig. 1D).

A total of 16 biopsies were obtained from 13 children. Two further patients underwent surgical excision for diagnosis and therapeutic reasons, respectively. For 11 patients, the material was obtained during KMP, for 3 patients (2, 6, 11) after KMP resolution and for patient 20 before KMP onset. In patient 11, the biopsy was performed 7 years after KMP resolution. Patient 8 experienced a large necrosis of the buttock with dramatically exacerbated laboratory tests (platelet count and disseminated intravascular coagulation (DIC)) one month after the skin biopsy. No complications were observed after skin biopsies for the other patients.

There was no histological material available for review for patients 7 and 9, who were classified as TA and KHE, respectively, at the time of diagnosis. The reviewed lesions were classified as "pure TA"($n=5$; Fig. 2B), "pure KHE" ($n=4$; Fig. 2A) or mixed TA-KHE ($n=3$; Fig. 2C). The samples of the bifocal tumour of patient 3 showed "pure KHE" on the leg tumour and mixed TA-KHE on the trunk. In patient 11, the lesion did not fit into any of these categories, showing dilated, medium-to-large and variably-shaped capillaries in a fibrotic background.

Immunohistological analysis was available for 12 patients, showing GLUT-1-negative staining for all patients, and D2-40-positive staining in all patients but

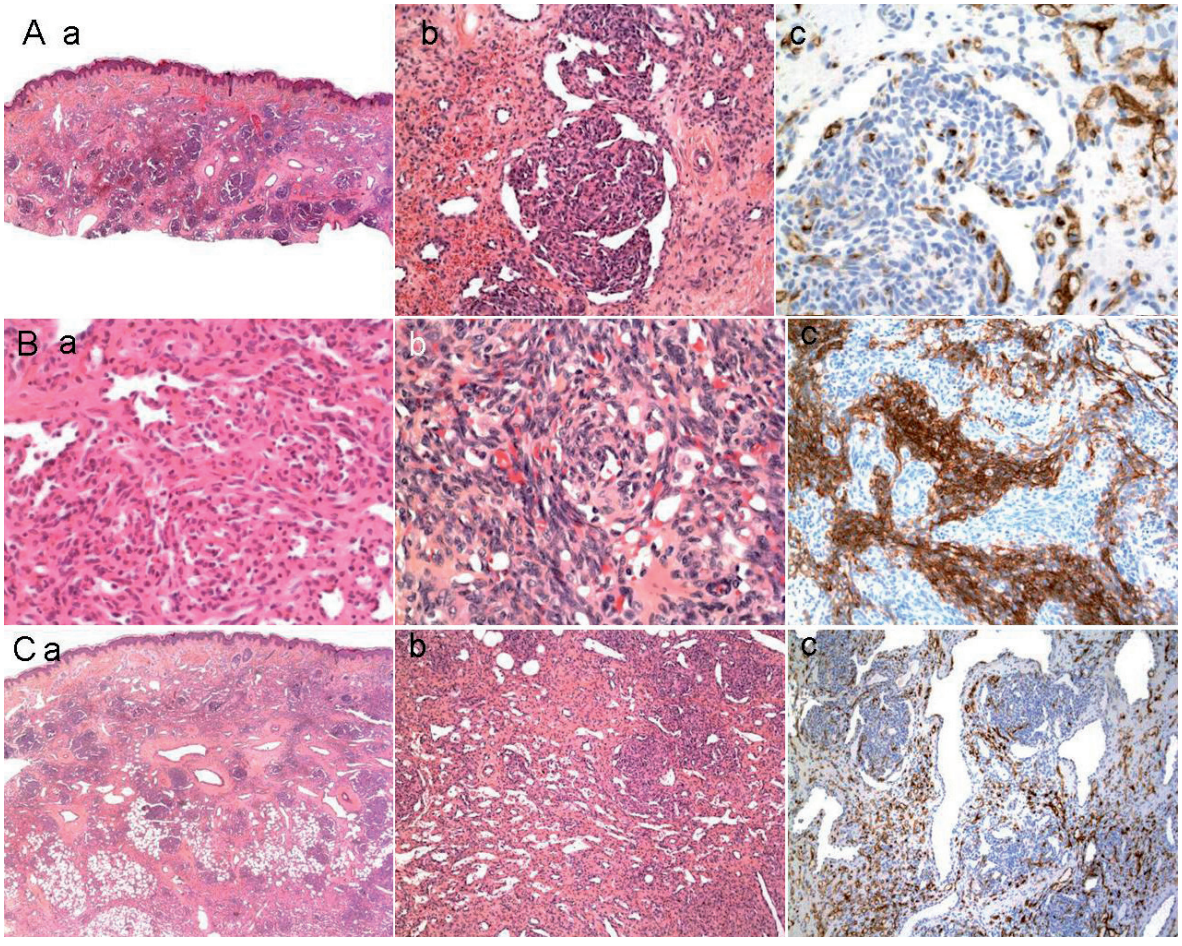


*Fig. 2*. Histopathological characteristics. (A) Tufted angioma (TA): (a) multiple small well-circumscribed nodules throughout the dermis (Haematoxylin eosin safron (HES) ×16); (b) typical "cannonball" nodule with packed small capillaries surrounded by crescent-shaped larger capillaries (HES×100); (c) podoplanin is mostly expressed by the vessels located outside the nodules and by some small round vessels inside it. Crescent-shaped vessels are negative (immunohistochemistry with D240 antibody, ×100). (B) Kaposiform haemangioendothelioma (KHE): (a, b) solid aggregations of poorly canalized slit-like capillaries lined with spindle cells and containing blood red cells (HES×100 and ×250); (c) podoplanin is mostly expressed by the fusiform cells located into the nodules and by some small round vessels. Interestingly, some areas made up of fusiform cells are totally negative (immunohistochemistry with D240 antibody, ×100). (C) Mixed TA and KHE: (a) co-existence of well-circumscribed small nodules, mostly located in the dermis and less-circumscribed invasive nodules in the subcutis (HES×25); (b) slit-like, irregular, dissecting capillary proliferation (HES×100); (c) podoplanin is mostly expressed by the spindle-shaped and round cells located in the nodules. However, some nodules are almost unstained. Interestingly, large and empty capillaries are not stained (immunohistochemistry with D240 antibody, ×100).

1 (patient 20). Treatments are summarized in Table SII[1]. Patients received 1–10 treatments or procedures (mean 4.8). Treatment was effective in 15 cases. In 9 cases, the role of treatment in clinical healing and platelet count normalization is not clear. The 2 KMP relapses were treated with the previous efficient treatment.

Vincristine had the best efficacy rate (62%). Systemic corticosteroids were efficient in 13% of cases. The antiplatelet drug combination (ticlopidine + aspirin) was efficient in 27% of cases. Physical compression alone was not associated with significant clinical improvement. However, it was associated with efficient treatment in 10 patients.

Median follow-up (Table SII[1]) was 6.5 years (range 2 months−22 years). All patients presented with cutaneous residual of variable intensity (Fig. 1E). Type I was observed in 13 cases (minor = 11; severe = 2), type II in 3 cases, and type III in 5. A total of 9/24 (37.5%) children had clinical inflammatory manifestations, consisting of erythema, swelling and pain, located on the residual lesion (type I = 5, type II = 2, type III = 3), with elevated serum D-dimer levels in 5 patients for whom laboratory test results were available. Patient 11 continues to experience painful inflammation on her leg, leading to functional impairment whenever antiplatelet therapy is discontinued, and therefore has ongoing treatment with aspirin. Patient 19 took antiplatelet therapy for 4 years, because each time it was stopped, he experienced pain and a feeling of warmth in the lesion, along with D-dimer level elevation, which has not recurred since. Orthopaedic sequelae were leg-length discrepancy (in 2 patients) and limited joint mobility or muscle retraction (in 5 patients) with no consequence on everyday life.

## DISCUSSION

This case series is characterized by a low mortality rate, contrasting with the 10–40% rate classically reported, which probably reflects the increase in multidisciplinary care and improvements in understanding of the disorder (11, 12). However, KMP is a long-lasting disorder that may remain symptomatic several years after resolution of deep thrombocytopaenia and may leave orthopaedic sequelae. Painful inflammatory manifestations were observed on tumour sites, along with D-dimer elevation, before onset of deep thrombocytopaenia and despite platelet count normalization, for which anti-platelet therapy was efficient. Such manifestations are consistent with the idea of a "low-grade" KMP that may worsen suddenly.

In a series of KHE, Croteau et al. (13) observed that tumours infiltrating to muscle, and/or large enough to involve more than one anatomical region, were more likely to manifest KMP than were superficial lesions. In fact, muscle infiltration was detected in most of our patients; 2 patients presented with deep infiltrative tumours involving 2 anatomical regions and a specially protracted deep thrombocytopaenia; conversely, 2 other patients presented with superficial tumours (superficial muscle involvement, and subcutaneous involvement respectively) and transient, moderate thrombocytopaenia. The intensity of platelet trapping and related thrombocytopaenia and coagulopathy seem to be related to the extent and depth of tumour infiltration; those 2 characteristics may be considered as prognostic factors (13). Indeed, tumour shrinkage always occurs in parallel with the increase in platelet count, followed by a gradual local clinical improvement, always leaving a residual lesion.

KHE and TA are histopathologically very close (2, 3, 6).The occurrence in the same patient of TA and KHE, cases of mixed TA-KHE, and the homogenous distribution of histological types in our series, confirm that KHE and TA are part of the same spectrum. In one patient, for whom the biopsy was performed several years after platelet count normalization, histological analysis could not conclude KHE or TA; however, lymphatic vessels were still detectable, which may correspond to residual structures of an involuting KHE-spectrum lesion.

Due to the retrospective nature of our work, we could not specify the platelet count threshold, or the specific clinical criteria that defined therapeutic efficiency; thus, treatment efficacy estimation was based on clinical assessment of the treating physician, which is at least partly subjective.

The low success rate of corticosteroids contrasted with their continuing use as first-line therapy (5, 7). Considering their well-known adverse effects, our team now prefer not to prescribe high-dose corticosteroids as first-line treatment. Vincristine is now utilized for approximately 15 years in KMP, and had the highest efficacy rate in our series. However, it is given intravenously, with frequent difficulties in administration in this age-group (14).While aspirin was efficient for the treatment of the late inflammatory manifestations, antiplatelet therapy was often ineffective during the acute phase (73%). This suggests that antiplatelet therapy could control a mild phenomenon, with a potential prophylactic interest for asymptomatic tumours combined with elevated D-dimer, in order to avoid the development of severe thrombocytopaenia. Moreover, a few cases of TA involution have been described with low-dose aspirin treatment (15).

Surgery and embolization are possible, but rarely realizable. Few patients responded to interferon-α or pentoxyphylline (16, 17). Interferon-α is responsible for spastic diplegia in infants, and has to be avoided whenever possible in this age-group, particularly as the data supporting its efficacy are insufficient; its use would be considered only in case of failure of previous treatments. Radiation therapy was inefficient, and should no longer be employed because of its potential side-effects.

We were unable to identify an effective treatment in 9 patients, suggesting that KMP may resolve sponta-

neously with suitable supportive care alone. Despite the lack of evidence of efficacy of physical compression, we believe that it can be useful, particularly for the limbs, as it reduces the tumour volume, which dictates the tumour's ability to trap platelets. Propranolol failed in 2 patients, which is consistent with literature data (18). Since the end of this study, a further patient with KMP was given sirolimus, which has recently been described as effective in vascular anomalies with a lymphatic component, including TA and KHE (8−10). In this patient, the platelet count started to improve within less than 3 weeks and was normal after 7 weeks of treatment, with no subsequent relapse.

In conclusion, KMP is a clinico-biological phenomenon of variable intensity depending on tumour volume. With a multidisciplinary approach, the final outcome is mostly favourable. The recognition of minimal coagulopathy in a susceptible tumour may indicate the need for prophylactic antiplatelet drug treatment. In our experience, when deep thrombocytopaenia has settled, treatment with corticosteroids is disappointing. While vincristine appears to be the most efficient treatment, sirolimus is a promising molecule because of its anti-angiogenic properties, in particular on lymphatic vessels (19). Oral administration of sirolimus is also attractive, with an apparent good safety profile (8−10).

*The authors declare no conflicts of interest.*

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