

## CASE STUDY

# NEWBORNS WITH KASABACH–MERRITT PHENOMENON-ASSOCIATED KAPOSIFORM HEMANGIOENDOTHELIOMA: A REPORT OF 6 CASES

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## ABSTRACT

Combination of kaposiform hemangioendothelioma (KHE) and Kasabach-Merritt phenomenon (KMP) in newborn children is a life-threatening constellation. The purpose of the study is the choice of the diagnostic and treatment methods in these patients and evaluating the effectiveness of treatment using radiological methods of investigation. The study enrolled 6 newborn patients with KHE within a period 2013 - 2018. MRI (CT) performed to make the diagnosis and evaluate treatment response.

Hypervascular mass accompanied by reticular lymphedema, hyper intensive in T2 WI; isointensive in T1 WI, intense contrast enhancement, heterogeneous diffusion restriction were unique MRI characteristics of KHE. The sustained remission was achieved with treatment by propranolol (n=2), vincristine (n=1), and their combination (n=3).

**KEY WORDS:** kaposiform hemangioendothelioma, Kasabach-Merritt phenomenon, newborns, thrombocytopenia

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## INTRODUCTION

According to the updated ISSVA classification of vascular anomalies 2018 [1], kaposiform hemangioendothelioma (KHE) refers to a locally aggressive or borderline tumors, which are characterized by signs of malignant invasive growth but lack of metastases. In newborn period of life KHE may be misdiagnosed as infantile or congenital hemangioma, however, KHE is associated with more aggressive clinical course and worse prognosis [2]. KHE usually shows rapid increase in size with some stabilization over time but only without completely regressed despite therapy. Combination of KHE and Kasabach-Merritt phenomenon (KMP) in newborn children is a life-threatening constellation. The phenomenon carrying the names of the authors who first described it in 1940 [3] and is characterized by a consumptive coagulopathy (low fibrinogen level and elevated fibrin split products), and severe thrombocytopenia seen secondary to intralesional platelet entrapment [4]. Despite the high morbidity and mortality rate, there are no evidence-based standard diagnostic and treatment methods.

Severe thrombocytopenia, manifestations in early childhood period of life, high risk of complications, absence of the published large clinical groups and randomized trials determine the importance of documenting each case of KHE to better understand the pathophysiology of the disease and choose its optimal management and treatment.

## THE AIM

The aim of study is the choice of the diagnostic and treatment methods and evaluating the effectiveness of treatment in newborns with KHE associated with Kasabach–Merritt phenomenon using radiological methods of investigation.

## MATERIALS AND METHODS

The study was carried out in accordance with World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. It has been complied with the principle of privacy and respectfulness for the child's as an individual incapable of self-defense. The study was approved by the local Research Ethics Committee of our University and written informed consent was obtained from the parents of each patient.

## PATIENTS

Within a period from March 2013 to November 2019, 6 newborn patients with KHE underwent treatment in a single hospital, sex distribution 3 f / 3 m. The patients' characteristics are presented in Table 1.

Tumors locations were the following: entire upper extremity (n = 1), shoulder and shoulder girdle (n = 2), leg (n = 1), neck and mediastinum (n = 1), chest wall, retroperitoneal space, diaphragm (n = 1). No multifocal lesions were observed, however,

**Table 1.** Characteristics of 6 patients with KHE

Nº	Sex	Debut of the disease	Localization	Medications	Duration of treatment	Result of treatment
1.	female	Since birth	Upper extremity	Prednisolon, propranolol	12 months	Good
2.	female	28 days	Thoracic wall, retroperitoneal space, diaphragm	Prednisolon, propranolol, vincristine	15 months	Satisfactory
3.	male	Since birth	Shoulder, shoulder girdle	Prednisolon, propranolol	15 months	Good
4.	female	Prenatal	Shoulder, shoulder girdle	Prednisolon, propranolol, vincristine	14 months	Good
5.	male	Prenatal	Leg	Prednisolon, vincristine	6 months	Good
6.	male	Since birth	Neck, mediastinum	Prednisolon, propranolol vincristine	11 months	Good

in 5 patients' lesions occupied more than one anatomic area. Laboratory examinations included a total blood count, platelet count, coagulogram (APTT, D-dimers, and fibrinogen).

## VISUALISATION METHODS

Imaging was performed using ultrasound scanning and MRI, sometimes CT. MRI (CT) performed before the start of treatment, every 3 months during treatment and/or when changing therapeutic tactics, and 3 months after the end of treatment.

The ultrasound examination performed on «Philips» scanner with a 12-3 MHz linear transducer in the mode of GrayScale, and color Doppler scanning. Common ultrasounds signs of KHE were heterogeneous echogenicity, and hypervascular pattern.

CT examination was performed on Siemens Somatom Definition AS with tube voltage of 70-120 kV; as a contrast Iopamidol 755.2 mg was used at 1 ml/kg bodyweight.

MRI examination was performed on Siemens Aera 1.5 Tesla scanner; as a contrast agent was used gadoteric acid 279.32 mg at 0,2. ml/kg bodyweight.

## LIMITATIONS

Only a small number of cases were identified.

## CLINICAL CASES

There was no gender predominance in the group of newborns with KHE, the male to female ratio was 1:1. The first clinical symptoms of the disease in 5 patients were visible since birth, in one case debut of the disease was at the age of 22 days. Prenatal diagnosis of the tumor was established in two cases on routine ultrasound. KHE of extremities are present as expanding painful soft tissue masses and swollen erythematous or violaceous skin.

In the child with the neck and mediastinum KHE there were no visible skin changes, asymmetry of the face and neck was noted due to mass on the side of the lesion. Increasing symptoms of the upper airway compression led to the respiratory insufficiency and the need for intubation.

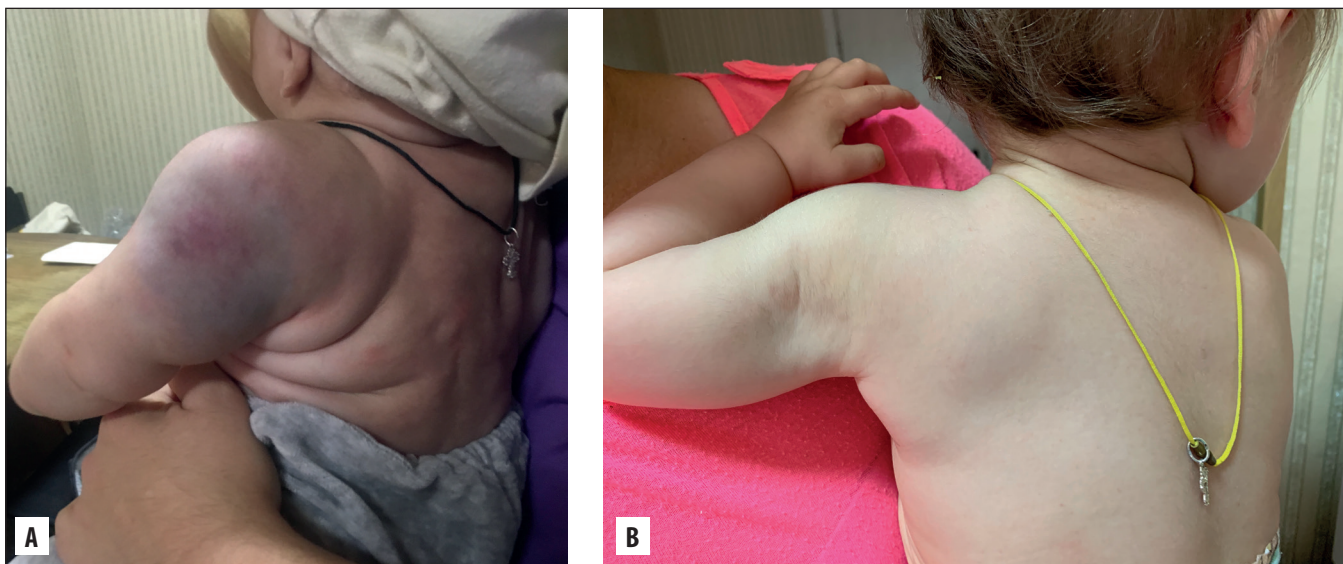
In the child with lesions of the retroperitoneal space, diaphragm, and chest wall, the first manifestations were erythematous spot with slight infiltration of the soft tissues of the chest wall and petechial hemorrhages on the skin around the lesion. CT and MRI demonstrate infiltrative lesion that involves various tissues types - skin, fat, muscle, pleura, and bone. In this patient the course of disease was complicated by haemothorax at age 1.5 month that required thoracocentesis, pleural drainage and blood transfusion.

Thrombocytopenia (Kasabach-Merritt phenomenon) was diagnosed in all newborns with KHE, the platelet count before treatment was  $8-20 \times 10^9/l$ . Despite severe thrombocytopenia, none of the patients presented hyperfibrinogenemia, fibrinogen ranged 1.8 - 3,2 g/l, D-dimer level usually was elevated (in a range of 1.2 – 5.6  $\mu L/ml$  with reference level of 0,5  $\mu L/ml$ ) in all patients both before treatment and after platelet count normalization. Among complications we observed upper airway compression which required prolonged (two weeks) intubation (n=1), haemothorax and posthemorrhagic anemia (n=1). A minor anemia sign was present at 3 patients (not counting moderate posthemorrhagic anemia in a patient with haemothorax).

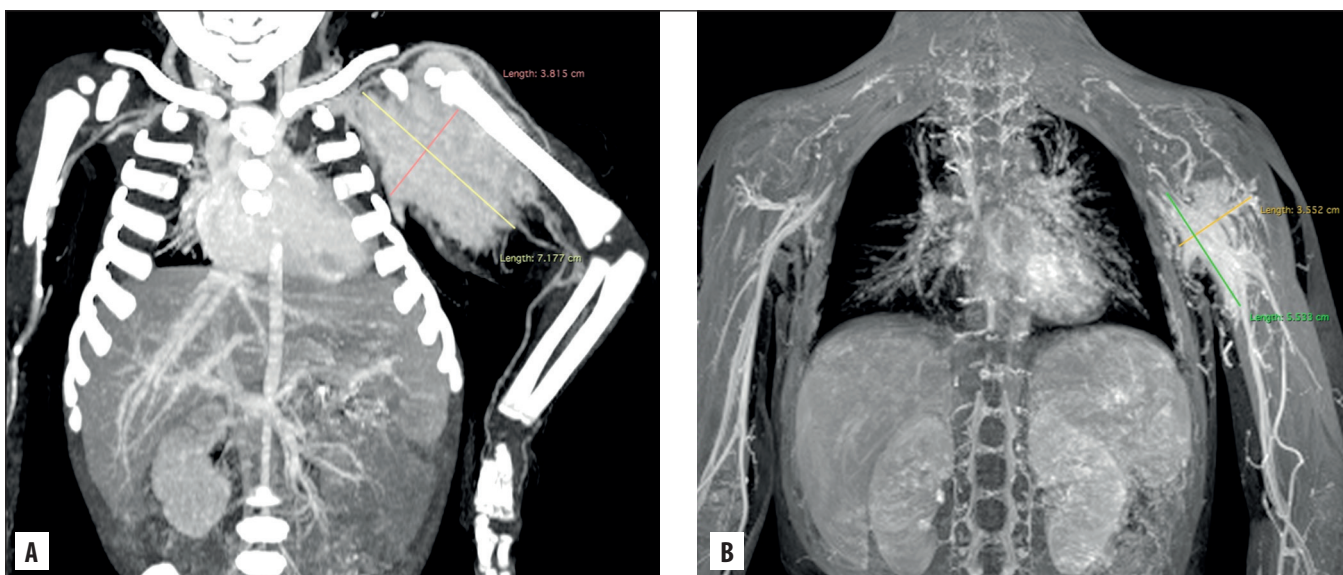
Ultrasound scan was used like screening imaging method in all patients. GrayScale imaging showed poorly demarcated heterogeneous mass, color Doppler showed intensive vascularization, high-flow vessels are oriented perpendicularly to skin surface.

Distinctive CT features of KHE were isodense relatively to muscles infiltrative mass with fuzzy, ill-defined contours, which intensively accumulates contrast, and early contrast enhancement.

MRI showed muscle infiltration in all patients, bone tissue (thoracic vertebrae and ribs) was affected in one



**Fig. 1.** Shoulder of the girl before and after treatment.  
 A. MRI before treatment. On T1 weighted imaging in the frontal plane isointensive muscle infiltrative lesions with fuzzy contours, reticular lymphedema (long arrow) and skin thickening (short arrow) are also observed.  
 B. Follow-up studies show a partial regression of the tumor after 10 months of treatment



**Fig. 2.** Scan of the boy's body.  
 A. Initial CT scan (maximal intensity projection of thick slab) in a 4-months-old patient. Post-contrast coronary image show infiltrative mass involving the shoulder muscles, capsule of the shoulder joint, the shoulder vascular-neural bundle is surrounded extrinsically by the mass, perifocal lymphedema is also shown.  
 B. MRI follow-up after 18 and 24 months on post-contrast T1 weighted images with suppression of the signal from fat and the reconstruction of the projection of maximum intensity, stable residual tumor is visible.

patient with retroperitoneal tumor. MRI characteristics of KHE are different degree of heterogeneity, hyperintense infiltrative lesion in T2 weighted images, possible nodal inclusions; predominantly isointensive lesions in T1 WI, in some cases visualization of hyperintense inclusions – hemorrhages, intense contrast enhancement, especially in the early stages, heterogeneous diffusion restriction. Common radiological signs of KHE were the hypervascular mass

accompanied by reticular lymphedema. Subject to careful analysis of the clinical course, laboratory parameters and radiological characteristics the diagnosis usually doesn't need the histological verification, which correlates with multicenter survey data [4].

Corticosteroids in dosage equivalent of 4-6 mg/kg/day of oral prednisone was a start therapy in all patients. Treatment duration was 3 - 8 weeks. Within corticosteroids



treatment we observed platelet count normalization in 7-15 days, but minimal signs of decreasing of tumor size. Moreover, after corticosteroid therapy there was a soft tissue mass enlargement with superficial ulcers in one patient.

After two weeks of corticosteroids therapy we prescribed propranolol in dosage of 2-2.5 mg/kg/day, divided into three intakes. Clinical and laboratory monitoring was performed for 2 months, and MRI scan in 3 months. A sustained clinical and laboratory remission was achieved in 2 patients after propranolol monotherapy. In other 3 patients a month after corticosteroids withdrawal we observed platelet count dropping to  $60 \times 10^9/l$  and less and increasing of tumor size. In all these cases vincristine was prescribed in a dosage of  $1.5 \text{ mg/m}^2$  once a week with following positive clinical outcome (Fig. 1).

In the patient who presented tumor growth within corticosteroid treatment we started vincristine therapy without prescribing propranolol. Vincristine treatment duration was 6 - 12 months. Within first two months it was administered once a week, the following two months - once in two weeks, and then - once in three weeks. In a patient with retroperitoneal space, chest wall and diaphragm involvement we observed the tumor growth after 6 months of vincristine treatment. He also presented petechial skin rash and low platelet count. The treatment was prolonged for 6 more months with vincristine administration once a month. Here vincristine treatment complications were presented by polyneuropathy and flaccid tetraparesis. The symptoms relieved after treatment termination, with B-complex vitamins prescription in aftercare period.

For treatment withdrawal we used clinical data (absence of tissue infiltration, motor recovery and airway patency recovery), laboratory data (normalization of platelet count), and MRI with no signs of tumor activity.

An outcome was considered to be good in 5 patients and as satisfactory in one child. No excellent outcome was observed as in all patients MRI showed a residual tumor mass in 6 months after treatment termination (Fig. 2). There were no fatal cases.

## DISCUSSION

Thrombocytopenia combined with large femoral hemangioma and petechial skin lesions was described first in 1940 by Kasabach HH and Merritt KK. Before 1993, when Zukerberg et al. was the first to identify KHE as particular tumor [5], it was described in medical literature as «giant hemangioma/angioma with Kasabach-Merritt phenomenon», «hemangioma with Kaposi's sarcoma feature» or «kaposilike infantile hemangioendothelioma». The percent of thrombocytopenia presentation ranged from 10 to 80. The dependence on tumor size and patient's age was revealed: KMP was diagnosed in 79% of children under 1-year-old, in 47% of children aged 1-5 years, in 43% of children from 3 to 12 years old and only in 10% of 13-21 years old patients. Natural increasing of KMP percentage is observed according to the tumor size, as the basic mechanism of its appearance is platelets destruction within tumor vessels [4],

median tumor size in patients without KMP is  $12 \text{ cm}^2$ , in patients with KMP it is  $49 \text{ cm}^2$  [6]. We usually use the term KMP to characterize the thrombocytopenia lower than  $100 \times 10^9/L$  [7], along with that in our study the platelet count was never higher than  $20 \times 10^9/L$ .

Numerous methods are described for KHE treatment. Tumor excision was possible only in 18% of patients. In cases of nonresectable tumors a vast variety of treatment methods were suggested. Embolization, sclerotherapy, abscission and radiotherapy are not widely used as their efficiency is lower than 30%, and some of these methods are potentially dangerous for children. Pharmacological therapy is most commonly used.

In meta-analysis published in 2015 by Liu X et al. [8] and by Yao W et al. in 2018 [9], vincristine is pointed out as the most effective KHE treatment. In recent years publications authors give priority to mTor inhibitors, such as sirolimus and everolimus, showing their advantages in being more effective in comparison to vincristine [10, 11]. Nevertheless, all articles provide small number of cases, and there is no credible data on these medications safe use in newborns.

Among side effects that occurred during the treatment dyslipidemia and immunosuppression must be mentioned. Dyslipidemia required treatment cancellation in a child under 1-year-old [12]. Immunosuppression presented mostly when treatment was combined with prednisone. In 2018 two fatal outcomes were registered officially for the first time ever. The two was caused by pneumocystis pneumonia within sirolimus treatment that followed after prednisone administration in children with KHE and KMP [13]. Both patients were of early age, the treatment started at the age of 1 month old and 5 month old. Infectious complications developed in 2 and 1 months respectively. Czechowicz et al [14] describes the outcome of sirolimus treatment in 6 newborns with median age of 14.8 days. There were two children with KHE in this cohort. Authors describe each clinical case, and KHE patients are those in whom sirolimus blood concentration is the highest after 6 doses (which were not observed in children with lymphatic malformations). One case was lethal. Considering the fact sirolimus showed mixed outcome as treatment for newborns, this method requires further research.

Considering all potential severe complications and prednisolone as a start-therapy in patients with KHE, we haven't used mTOR inhibitors in newborns.

Antiangiogenic effects of propranolol which were accidentally discovered and a dramatic response that infantile hemangiomas gave for treatment by it forced an attempt to use propranolol in other vascular tumors treatment. However, the outcome was less successful, being positive only in 36% of patients [15] that correlates with our research results; we achieved positive outcome in 2 of 6 patients (33.3%).

In KHE treatment we avoided prescribing platelet concentrate transfusions, as no defects in platelets were observed, and such a transfusion can provoke pain, tumor enlargement and worsening of thrombocytopenia. The

only exception was an episode of acute bleeding, which in our study was observed in a patient with hemothorax. Complete tumor regression is rare; usually imaging shows residual tissue changes [16].

## CONCLUSIONS

The results of our study reveal that MRI is informative method of diagnostic and evaluation of treatment effectiveness of KHE. Hypervascular mass accompanied by reticular lymphedema, intense contrast enhancement in the early stages, heterogeneous diffusion restriction were unique MRI characteristics of KHE. Short courses of corticosteroids are effective for thrombocytopenia relief in KHE patients, but they do not result into essential decreasing of tumor size. The sustained remission was achieved with treatment by propranolol (n=2), vincristine (n=1), and propranolol+vincristine combination (n=3). MRI showed residual signs of tumor in all KHE patients.

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## Conflict of interest:

*The Authors declare no conflict of interest.*

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