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CASE REPORT AND MINI-REVIEW

FEATURES OF THE COMMUNITY–ACQUIRED PNEUMONIA IN A CHILD WITH KASABACH-MERRITT SYNDROME: CASE-REPORT AND MINI-REVIEW

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Abstract

Introduction. The Kasabach-Merritt syndrome is a rare and severe disease that occurs in children in the presence of a large-sized hemangioma, accompanied by coagulation disorders. This disease complicates the course of many somatic diseases in children, including community-acquired pneumonia, due to the clotting disorder.
Case presentation. A case of a 4.5-month-old child with a combination of capillary hemangioma of the dextral chest surface, complicated by Kasabach-Merritt syndrome, and community-acquired right-sided focal pneumonia is presented. The possible effect of the Kasabach-Merritt syndrome on the course of community-acquired pneumonia has been analyzed. Additionally, the drugs' effect on the coagulation disorder, the state of hemangioma, and the course of community-acquired pneumonia in children have been investigated.
Conclusions. Severe coagulation disorders may occur in patients with Kasabach-Merritt syndrome and community-acquired pneumonia. Constant monitoring is

Résumé

Caractéristiques de l'évolution de la pneumonie acquise communautaire chez un enfant atteint du syndrome de Kasabach-Merritt

Introduction. Le syndrome de Kasabach-Merritt est un processus pathologique rare et grave qui survient chez l'enfant en présence d'hémangiomes de grande taille et accompagné de troubles de la coagulation. Cette pathologie est souvent compliquée par le développement de saignements sévères, de thromboses locales, d'anémie et de dysfonctionnements des organes vitaux. Il est logique que cet état pathologique puisse compliquer l'évolution de nombreuses maladies somatiques chez l'enfant, y compris la pneumonie extra-hospitalière, principalement en raison de troubles du caillement sanguin.
Rapport du cas. L'objet de notre étude était un enfant de 4,5 mois souffrant d'une combinaison de maladies comme l'hémangiome capillaire du côté droit de la poitrine, compliqué par le développement du syndrome de Kasabach-Merritt et la pneumonie

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essential during hospitalization. Such combination of diseases should be treated considering the ability of the drugs to influence both the hemostasis system and the progression of hemangioma's growth.

Keywords: Kasabach-Merritt syndrome, hemangioma, community-acquired pneumonia, children, clotting disorder.

extra-hospitalière. Le rapport clinique présenté analyse les mécanismes possibles de l'effet du syndrome de Kasabach-Merritt sur le cours de la pneumonie extra-hospitalière par l'exemple du dossier clinique de l'enfant que nous avons traité. Nous avons analysé les particularités du traitement du point de vue de l'effet des médicaments sur les troubles de la coagulation, l'état des hémangiomes et le déroulement de la pneumonie extra-hospitalière chez l'enfant.

Conclusions. Quant le syndrome de Kasabach-Merritt est associé à une pneumonie d'origine communautaire, il est nécessaire de considérer le développement possible de complications hémorragiques graves. Pendant le séjour des patients à l'hôpital, une surveillance constante du système sanguin congestif est nécessaire. Le traitement de cette association de maladies doit être effectué en tenant compte de la capacité des médicaments à influencer à la fois le système hémostatique et la progression des hémangiomes.

Mots-clés: syndrome de Kasabach-Merritt, hémangiome, pneumonie extra-hospitalière, enfants, trouble du caillement sanguin.

Introduction

The vascular tumors are one of the most common neoplasms in children[1,2]. Despite the skin hemangiomas' multiplicity and size, their diagnosis does not cause significant difficulties, and the benign course leads to a favorable prognosis[1,3,4].

However, in 0.3-1% of hemangiomas cases, complicating disorders, such as the Kasabach–Merritt syndrome (KMS), occur[5-7]. This is a rare disease that infants may suffer at birth or in later life and is characterized by hemangioma's size increasing, coagulopathy, thrombocytopenia, hemolytic anemia, and severe bleeding complications[3,6-8]. Approx. 80% of Kasabach-Merritt syndrome cases are diagnosed in children during the 1st year of age, and the registered mortality range from 10% to 37%[5,6,9].

Considering the fact that the Kasabach–Merritt syndrome is a life-threatening illness, other diseases that may appear in patients with this syndrome have certain evolution and therapeutic particularities. On the one hand, the development of thrombocytopenia and hemolytic anemia complicates the course of many diseases, including pneumonia, on the other hand, acute inflammatory diseases and prescribed drugs can adversely impact on the course of the Kasabach–Merritt syndrome. Such a rare combination of community-acquired pneumonia and Kasabach–Merritt syndrome is a serious challenge for any pediatrician.

Case presentation

We report the case of a 4.5-month-old girl, who was admitted to Ternopil Regional Children's Hospital, Ukraine, complaining of wet cough, decreased appetite, body temperature up to 37.2° C. The history showed that the child had concretion and soft-tissue swelling in the area of the dextral lateral surface of the breast since birth. At the age of 2 months, in the center of the concretion, which was gradually increasing and reached 10x8 cm, the skin turned into blue-cherry color without sharp contours and 2 cm in diameter. After specialists' examination and follow-up examination, a capillary hemangioma of the dextral lateral surface of the breast was diagnosed. Three days after, an altered general condition was noted: subfebrility, restlessness, appetite loss and general weakness appeared, the hematoma covered most dextral half of the trunk and dextral lower limb. Kasabach–Merritt syndrome was diagnosed: cavernous hemangioma of the dextral chest wall; severe thrombocytopenia; moderate post-hemorrhagic anemia; hemorrhagic syndrome: hematoma of the dextral half of the trunk, subcutaneous hematoma of the extremities, dextral hemothorax (drainage of the dextral pleural cavity). The packed red cell transfusion, fresh frozen plasma transfusion and platelet transfusion, anticoagulation reversal, antimicrobial therapy, and glucocorticosteroids were prescribed. As a result of the treatment, the general status

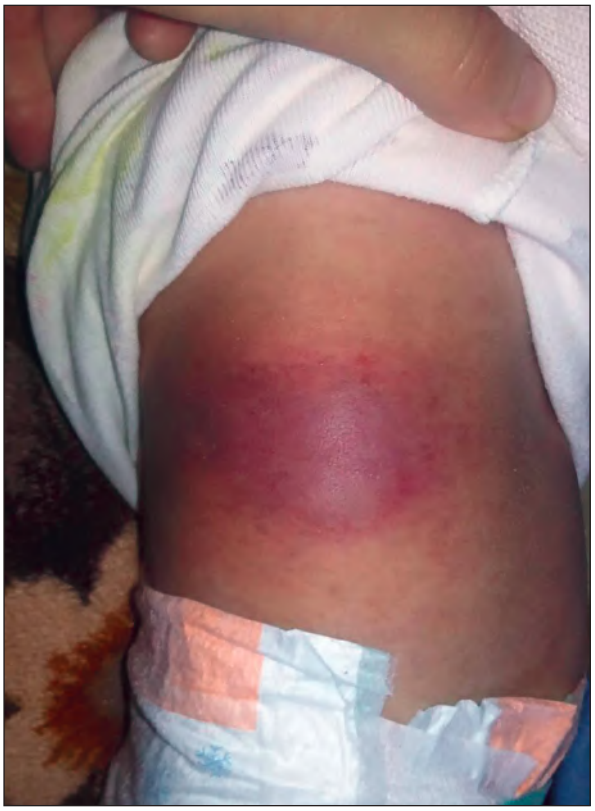

Figure 1. Cavernous hemangioma of the right half of the chest wall in a child

improvement was noticed and the child was referred to the Republican Center on Pediatric Hematology «Okhmatdyt», Ukraine. In the clinic, the diagnosis has been confirmed and it has been established that the surgical removal of the hemangioma is impossible, due to the large volume of neoplasm and germination in surrounding tissues. The conservative treatment with corticosteroids and propranolol was assigned. A post-discharge improvement in child's health was noticed, the tumor marginally decreased in size, the signs of hemorrhagic syndrome subsided.

Five days before the current admission to the hospital, the child's condition has deteriorated, and the above-mentioned complaints have appeared. On physical examination, the general child's condition was moderately severe. She had visible mucous membranes of pale pink color, infiltration of the skin with a red-blue color and poorly demarcated round shape, 7 cm in diameter, was noted in the area of the dextral surface of the chest (Fig. 1). There were petechiae hemorrhages and signs of intradermal hemorrhages around the navel extending over the entire surface of the dextral half of the trunk, with the transition to the back and the anterior abdominal wall. The tumor was elastic, akinetic, with no evidence of inflammation on palpation. The patient was eupneic, with nasal breathing, frequency of respiratory movements – 42 per minute, dullness on percussion over the lungs in the lower sections of the right and between the shoulder blade was concluded. By auscultation – crackles and crepitations were heard on the right hemithorax, in the lower sections. The cardiac sounds were rhythmic, with a heart rate of 132 beats per minute. No pathological findings were detected at the abdominal examination. Bowel and bladder habits were normal. At chest X-ray examination, a consolidation in the basal segments of the right lung was observed, with increased pulmonary vascularity. Blood tests revealed anemia (hemoglobin 9.0 g/dL), thrombocytopenia (118 x 10^9/dL), normal leukocytes and no increase in the number of immature forms of neutrophilic leukocytes. C-reactive protein – 6 mg/dL. The biochemical analysis of blood and urine were normal. The ultrasound examination revealed a small amount of fluid in the right pleural sinus. The child consulted a hematologist, a cardiologist, an oncologist, a thoracic surgeon, and other specialists. She was diagnosed with community-acquired right-focal pneumonia, and Kasabach–Merritt syndrome: cavernous hemangioma of the right chest wall, mild thrombocytopenia, moderate anemia.

Conservative treatment was initiated, including antimicrobial therapy (amoxicillin + clavulanic acid (daily dose – 40 mg/5 mg per kg) intravenously, expectorants (ambroxol, daily dose – 15 mg), oxygen therapy, vitamin E 0.5 ml of 10% solution per day, aminocaproic acid 5% – 2.5 ml, 4 times a day. During follow-up, the amelioration of clinical signs was noticed, but during the 4th day, the platelet level decreased to 98x10^9/dL. Glucocorticoids were added to treatment (prednisolone 2.5 mg per kg per day). The condition of the child improved, a positive change on the X-ray was established, and the level of platelets by the end of treatment was 209x10^9/dL. The duration of the antibiotic therapy was 10 days, the length of hospital stay – 12 days. The child was discharged in satisfactory condition.

Discussion

The Kasabach-Merritt syndrome was first described by Haig Haiguni Kasabach and Katharine Krom Merritt in 1940, when they observed infants with gigantic capillary hemangiomas and thrombocytopenic purpura. This is a rather rare pathology and the total number of described cases was toward 200. Every major hemangioma doesn't have to be accompanied by the development of KMS. The mortality rate is less than 10% in cases of skin lesions and reaches 60% in the presence of retroperitoneal tumors[8,10].

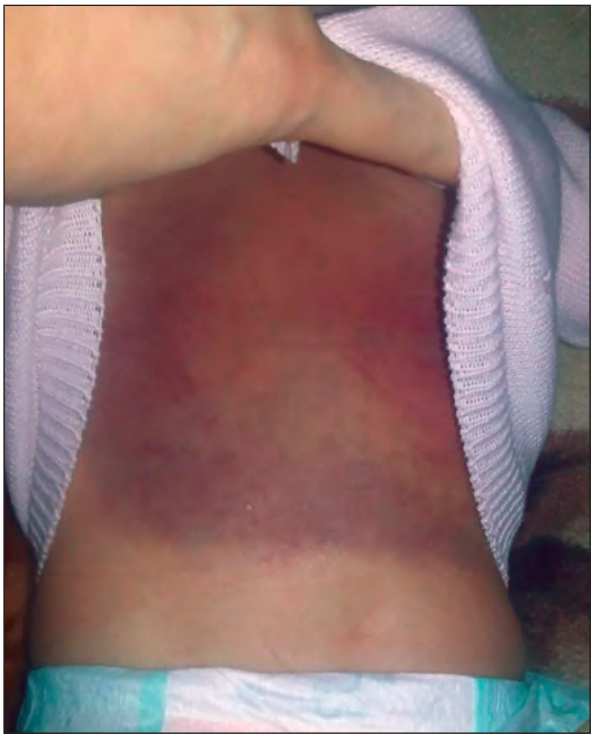

Figure 2. Petechiae and extensive intradermal hemorrhages in a child with Kasabach-Merritt syndrom

The exact etiology and pathogenesis of the disease are unknown, but in some cases, the hereditary pattern of this pathology has been discovered, autosomal dominant type[11], although some papers deny this[12].

By mechanism, the processes that occur in hemangioma are the chronic form of disseminated intravascular blood coagulation. Blood circulation slowing, with a large number of microtubes and increased use of platelets occurs in a giant hemangioma, which has a branched vascular network. The coagulopathy occurs preferentially due to the defects in the endothelium of the vessels inside hemangioma, which cause platelet activation[6]. In normal conditions, the vascular endothelium prevents thrombocytopenia in many ways[13,14]. The endothelium damage or its dysfunction is a key factor in platelet activation inside hemangioma in the Kasabach-Merritt syndrome. The blood flow abnormality inside hemangioma due to excessive blood transfusion contributes more to the platelets activation[15]. As a result, secondary (acquired, symptomatic) thrombocytopenia and coagulopathy develop, which are associated with an increase in blood loss in hemangiomas. Thrombocytopenia contributes to the reduction of thrombocyte production, as the functional depletion of reserves occurs, connected with the constant increased destruction of platelets in hemangioma[12,16].

Sometimes, the diagnosis of Kasabach-Merritt syndrome is not difficult, due to the tumor predominant localization on the skin surface, as in our case, and the presence of blood clotting disruption signs. The disorders which occur due to thrombocytopenia lead to spontaneous bleeding accompanied by ecchymoses, petechiae and hemangioma's rapid size increase[12,17]. In case of severe thrombocytopenia, the bleeding from the mucous membrane of the nasal cavity and the gastrointestinal tract, with subsequent development of severe anemia may occur[12,16].

In the context of the described clinical picture, there were also multiple signs of disruption of blood coagulation (petechiae and extensive intradermal hemorrhages) (Fig. 2). Therefore, in Kasabach-Merritt syndrome and another disease (in our case, community-acquired pneumonia), one should be prepared for the complications associated with the risk of hemorrhagic syndrome. In case of pneumonia, the development of a severe hemorrhagic process in lungs, intra-pulmonary haemorrhage, hemothorax and other organs hemorrhage (gastrointestinal tract, hematuria, etc.) may be encountered. Due to the absence of a severe clinical course of pneumonia, our patient did not have such complications.

Nevertheless, an important issue is the choice of the most appropriate treatment in the presence of such combination of pathological processes. The difficulties in choosing the right treatment are based on several important points:

1. Can the drugs used for the Kasabach-Merritt syndrome treatment (or gigantic capillary hemangiomas) increase the risk of pneumonia?

2. Can the drugs used for the Kasabach-Merritt syndrome treatment (or gigantic capillary hemangiomas) complicate the course of community-acquired pneumonia in children?

3. Can the drugs used for pneumonia treatment worsen the course of the Kasabach-Merritt syndrome?

Taking into consideration the fact that the various therapy methods of the Kasabach-Merritt syndrome have shown ambiguous results, there are still no optimal treatment modalities. The reason is the rarity of the syndrome and the low effectiveness of the suggested treatment modality, the percentage of positive results of their usage does not exceed 50%[3,6]. Involution of the tumor and correction of life-threatening coagulopathy are the main objectives of the treatment of Kasabach-Merritt syndrome[3]. Currently, different options of treatment are suggested, which include pharmacological therapy, vascular embolisation, radiation therapy and surgical removal of the tumor[3,6,7,12,18,19].

Despite the radicality of the previously described treatment modalities, the most commonly used are drugs which facilitate the hemangioma involution (Table 1)[20].

Table 1. The main drugs used for the treatment of Kasabach-Merritt syndrome.

Drugs	*Expected positive impact*	*Side effects*
Glucocorticoids	Mechanisms remain completely unclear, but apparently the effect is related to vasoconstriction, suppressing fibrinolysis (by suppressing the production of tissues of plasminogen activators and increasing in plasminogen activator inhibitors)[8], prolonging platelet counts and angiogenesis disorder[21]	Child's growth and developmental disorders, reversible osteoporosis, increased sensitivity to infection[21], edema, due to the sodium chloride and water delay in the body, increased blood pressure, petechia, ecchymosis, thrombosis, psychiatric disorders, Itsenko-Cushing's syndrome, etc. [22]
Interferon alfa-2b	Inhibition of angiogenesis and proliferation, inhibition of expression of the main factor of fibroblasts growth (bFGF) and angiogenic protein in hemangiomas[21].	Fever, weakness and fatigue, increased liver enzymes, nausea, renal failure, neutropenia and anemia, hypothyroidism, bone marrow depression, myalgia, ataxia, paresthesia, numbness, eye paralysis, retinopathy, spasmodic dislocation[21].
Vincristine	Increase in number of platelets and a significant reduction in size of the vascular tumor[6].	Reversible alopecia, nausea, vomiting, autonomic neuropathy, peripheral paresthesia, jaundice, ataxia and hyponatremia due to inappropriate hypersecretion of antidiuretic hormone syndrome[3], abdominal pain, irritability and temporary loss of deep tendon reflexes[6].
Beta-blockers (propranolol)	Stop in growth and boost in the involution of hemangioma by vasoconstriction, decrease in expression of vascular endothelial growth factor (VEGF) and genes, the main factor of fibroblasts growth (bFGF) and initiation of capillary endothelial cells apoptosis[3]	Hypotension, bradycardia, hypoglycemia and bronchospasm, heart failure, neurological disorders[3].

Hormonotherapy with corticosteroids for the Kasabach-Merritt syndrome in children should be considered as a primary treatment method, if the surgery cannot be performed[3,17,20,21,23]. However, these drugs effectiveness, as indicated by most researchers, is ambiguous[6,19]. Additionally, after dose interruption, a rapid tumor growth occurs, hence the need for repeated courses of treatment, with increased risk of side effects[6]. Corticosteroids accelerate the symptoms disappearance, reduce the incidence of relapse of the disease, can improve the parameters of alveolar-arterial oxygen transfer and reduce the need for artificial ventilation of lungs[24].

Interferon or propranolol can be used in case of hormonotherapy failure. Combined modality treatment using specified drug groups (steroids, IFNα, and propranolol) is the most commonly suggested[19]. Currently, propranolol is a first-line drug in the gigantic hemangiomas treatment without Kasabach-Merritt syndrome. In our case, before hospitalization, the child received combined therapy with corticosteroids and propranolol, and according to information provided by mother and medical records, a positive clinical effect was observed (hemangioma's size reduction and reduction of the hemorrhagic syndrome manifestations).

It should be noted that almost all drugs used for the Kasabach-Merritt syndrome treatment can increase the risk of pneumonia, by immune depression and opportunistic infection development. This particularly concerns the use of corticosteroids, vincristine, and interferon.

Impaired coagulation correction is also an important treatment for the Kasabach-Merritt syndrome. The lack of precise information on the etiology of coagulopathy has led to the application of both substitution therapy and drugs used for disseminated intravascular blood coagulation treatment (antiplatelet therapy, anticoagulants, fibrinolysis inhibitors, etc.)[14]. Heparin and antiplatelet therapy in the Kasabach-Merritt syndrome treatment have problematical success[6,14,21]. The best results have been observed with the usage of fibrinolysis inhibitors, such as tranexamic acid and ypsilon-aminocaproic acid[14,21]. In our case, γ-aminocaproic acid in particular was used for the treatment.

As many researchers consider, the transfusion of plasma and platelets is the basis of the Kasabach-Merritt syndrome treatment[25]. Blood transfusion should be retained if there is no evidence of bleeding, since cytokines from the transfusive blood can aggravate the angiogenic process and lead to increase in hemangioma's size[21].

Another important issue is the impact of medications used for the community-acquired pneumonia treatment on the KMS course. The antibacterial agents, anti-inflammatory therapy and expectorants form the basis of the community-acquired pneumonia treatment[26]. Antibiotics of different groups are one of the main medications that can actively influence

coagulation, and in particular platelet hemostasis[27]. Thus, antibiotics of the aminoglycoside structure increase the platelet adhesion[28].

The penicillin suppresses platelet aggregation and reaction of biologically active substances release, blocking the ability of platelets to convert the arachidonic acid into thromboxanes. Besides, it arrests α2 adrenoreceptors that causes the loss of affinity for thromboxane A2 and prostaglandin H2, and leads to an ionized calcium concentration decrease in platelets. These effects explain the irreversible inhibition of platelet functions in vitro and in vivo experiments[29]. The cephalosporins disrupt platelet functions, as they can affect the platelet aggregation, inhibiting the action of aggregation agonists (ADP, collagen)[30,31].

There are publications that report the lack of semi-synthetic β-lactam antibiotics effect on hemostasis[32,33]. Taking into consideration this fact, we chose the antibiotic amoxicillin in combination with clavulanic acid, as an agent with the least effect on coagulation, for the community-acquired pneumonia treatment in our patient.

Conclusions

The Kasabach-Merritt syndrome is a severe disease that can lead to severe complications and significant deterioration of the course of other diseases, such as community-acquired pneumonia in children. This occurs due to coagulation disorders that contribute to the development of severe hemorrhagic complications. Such combination of diseases should be treated considering the drugs effects on both hemostasis system and progression of hemangioma's growth.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study"

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