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Severe course of cutaneous mastocytosis in a child. Case report

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Summary

Mastocytosis is a disease of the blood system with the accumulation of clonal mast cells in one or more organs. In children, the skin is most often affected. In most cases, the disease regresses spontaneously, regardless of severe clinical manifestations.

Case description

The disease was diagnosed after birth. Mastocytosis manifested with severe typical urticular and vesicular rash, daily hot flashes and itching. Skin infiltration with mast cells was confirmed by immunohistological examination of the skin. Symptomatic treatment was carried out with antihistamine drugs and short courses of glucocorticosteroids. The disease started to resolve since 4 months of age, with reduction of: hot flashes, abdominal pain, rash, and itching, thus decreasing the needs for drug therapy. At the age of 2 years 9 months, the child underwent radical surgery for osteoblastoma. Currently, moderate skin itching persists, the child develops according to his age, takes antihistamines only occasionally. Hence, this clinical observation demonstrates benign course of mastocytosis, even in severe cases.

Keywords

Mastocytosis, case report, pigmented urticaria, tryptase, C-KIT, mast cells.

Introduction

Mastocytosis is a clonal disease of mast cells. The frequency reaches 1:10000 of the population [1]. In adults, mastocytosis most often proceeds for a long time and is benign, and in children, as a rule, it regresses within several years [1, 2].

Mast cells are normally resident in connective tissue and proliferate under the influence of stem cell growth factor. The activating signal is transmitted by the receptor tyrosine kinase KIT. Somatic mutation in the *C-KIT* proto-oncogene leads to hyperproduction of the activating KIT receptor molecule, which causes excessive proliferation of mast cells. Up to 86% of children with mastocytosis have a somatic mutation in the *C-KIT* gene [3]. In addition to mast cells, the proliferation of melanocytes also depends on the KIT pathway, thus most likely causing typical pigment rashes [4]. Despite proven clonal growth, the aggressive course of mastocytosis in children, unlike adults, is extremely rare [5].

In aggressive course of the disease, chemotherapeutic approaches are similar to the strategy in adults. The variant with *C-KIT* mutation is crucial: if the *C-KIT D816V* is not detected, imatinib is effective [6, 7]. When the *C-KIT D816V* is revealed, cladribine and interferon alpha are used as the main drugs showing similar efficacy reaching about 50% [8]. New tyrosine kinase inhibitors (avapritinib and midostaurin) are also effective [9, 10]. Currently, allogeneic hematopoietic stem cell transplantation (HSCT) is recognized as the only curative method of aggressive mastocytosis. Appropriate experience with children is limited, however, there are reports on curative effect of HSCT [11].

The most frequent symptoms of mastocytosis are caused by permanent or periodical degranulation, i.e., release of various cytokines and biologically active substances from cytoplasmic granules of the mastocytes. The intensity of degranulation determines the variety of complaints: from their absence to severe itching, bullous rash, anaphylactoid

reactions, abdominal pain requiring daily pharmacotherapy [12]. The release of cytokines is provoked by certain medications, bathing, mood swings and other factors [13]. The main therapeutic actions are aimed at avoidance of provoking factors, reducing the degranulation reaction and neutralizing the effect of histamine release. Due to the fact that the prognosis for non-aggressive forms of mastocytosis is generally favorable, and the disease regresses spontaneously in most patients, the main goal of attending physician is to improve the quality of life and ensure psychological welfare of the child and parents before the disease resolves. In this respect, we present a clinical case of skin mastocytosis with later developing osteoblastoma in an infant.

Case report

The boy was born full-term, weight 3190, body length 51 cm, head circumference 33 cm. At birth, there was a polymorphic rash on the baby's skin, including the formation of blisters (Fig. 1). Urticaria pigmentosa was clinically diagnosed.

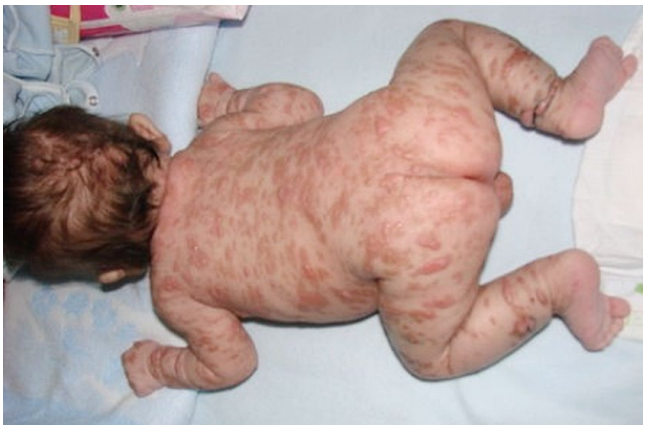

Figure 1. Newborn baby with severe course of urticaria pigmentosa, a clinical feature of skin mastocytosis

In addition to the typical skin changes, mastocytosis was manifested by constant severe itching with the need for daily intake of antihistamines. During the first two weeks after birth, histamine crises spontaneously occurred 1-2 times a day, which looked like sudden redness of the skin, short-term appearance of blisters, an increase in itching, screaming and extreme excitement, turning into a fainting state. The duration of the crisis varied from several minutes to an hour. With a strong attack, wheezing on inspiration was noted, once the attack was accompanied by a stop of breathing for 10-15 seconds.

Since early childhood, the child complained of episodic abdominal pain of a pulling-stabbing nature. The attack lasts 30-60 minutes, there is no convincing effects of drotaverine and nonsteroidal anti-inflammatory drug administration. There were unmotivated weekly episodes of vomiting, with no stool changes. Evident causes of pain and vomiting were not revealed, endoscopic studies were not performed.

At the age of three months, the child was re-examined. We present the results of the survey. Histological analysis of the skin revealed changes typical of mastocytosis. A widespread proliferate was found, consisting mainly of cells with partially elongated fragmented nuclei expressing tryptase and CD117. No expression of Langerin, CD1a and S100 was detected. A mutation of the *KIT D816V* gene was detected in DNA from skin biopsy using PCR technique. The concentration of tryptase in the blood was 17.3 (normally, 11.4) μg/l. The dermatological diagnosis of urticaria pigmentosa has been confirmed. Additional analyses were performed to determine the aggressiveness and the degree of organ involvement. The concentration of hemoglobin, reticulocytes, the number of platelets, leukocytes with a leukocyte formula, the rate of erythrocyte sedimentation within the age norm. The blood clotting INR, prothrombin and thromboplastin time, concentration of potassium, sodium, urea, creatinine, uric acid, bilirubin, C-reactive protein, albumin, β-2 microglobulin, immunoglobulin E, fibrinogen, activity of alanine and asparate aminotransferase, lactate dehydrogenase and antithrombin III were within normal ranges. Histological and cytological analysis of the bone marrow revealed normal pattern, with only reactive changes. Ultrasound examination showed normal condition of abdominal organs. There were no signs of aggressive mastocytosis such as cytopenia, liver and bone impairment.

From birth, the child received cetirizine in maximum doses. In severe crises, dimethinden, betamethasone were added, and prednisone was administered once.

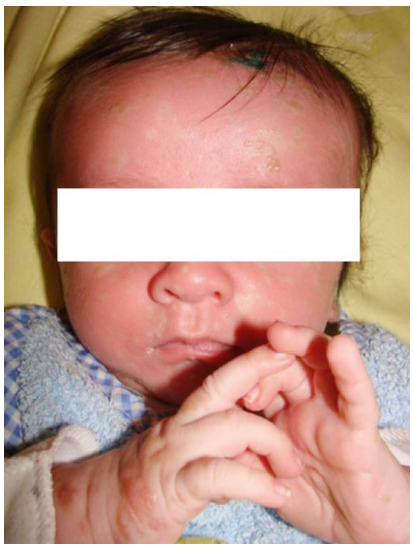

Figure 2. Histamine crisis in a child with skin mastosytosis. Redness of the skin, vesicular eruptions at the nasolabial triangle, at the tip and back of the nose, in the suborbital areas, on the back of the hand and wrist

The parents reported that the main provoking factors were temperature changes, hot water, emotions, eating hot food, rubbing clothes, as well as acute infectious diseases. From four months of life, the frequency and severity of the crises decreased, from 6 months the vesicular rash disappeared, and from 12 months these crises ceased. However, skin itching with a marked decrease in the quality of life and the need for daily intake of antihistamines, as well as occasional intake of betamethasone, persisted for several years. The itching decreased after sunlight exposure during the summer time. At the age of two, the concentration of blood tryptase returned to normal. Since the age of three, hypersensitivity to changing air and water temperature has decreased.

At 2 years and 8 months, pain and impaired movement evolved in the left shoulder joint. A neoplasm was detected in the left humerus. According to histological and immunohistochemical analysis, osteoblastoma was diagnosed. After the month radical excision of the tumor within healthy tissues was performed. The operation proceeded without complications.

During the following years, abdominal complaints persisted but the rash decreased, with residual moderate skin itching requiring occasional administration of antihistamines. Focal pale hyperpigmentation of the skin is noted (see Fig. 3). Currently, the boy attends primary school.

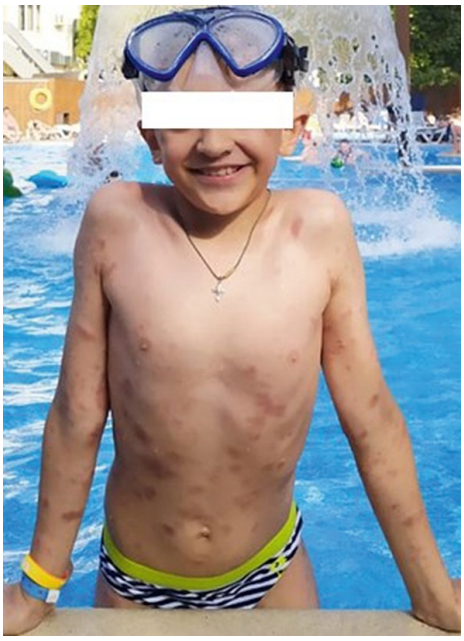

Figure. 3. The patient is 10 years old. Residual manifestations of mastocytosis on the skin

Discussion

Mastocytosis is a poorly understood clonal disorder with a generally favorable prognosis. As in the presented case, mastocytosis most often appears in the first two years of life. The results of the analysis of a large group of children showed that in 23% of cases, the disease manifests immediately after birth [14]. Recent studies show that the childhood and adult mastocytosis is a clonal neoplasm by its origin. The *C-KIT D816V* mutation detected in the presented child is one of the most frequent. In the study of Bodemer C. it was found in 42% of children with mastocytosis [3]. The detection of the mutation in the presented child confirmed the diagnosis, since there was no need for chemotherapy.

The vast majority of children, despite the mast cell clonality, develop a complete or partial regression of the symptoms within the first years of life [2, 14]. In our experience, upon observation of 163 children with mastocytosis, the median time of clinical resolution was 34 (2-226) months [5]. The probability of regression increases with the onset of the disease in early childhood and does not depend on the severity of mastocytosis manifestations [5, 14, 15].

Due to high probability of spontaneous regression, parents and the attending physician should provide symptomatic treatment so that the child could tolerate the disease until its resolution. According to various studies, 29.5-64% of children with mastocytosis require pharmacological treatment [2, 16-18]. Most often, long-term use of H1 and H2 histamine blockers, as well as cromoline sodium, a stabilizer of mast cell membranes, is recommended to relieve the symptoms. Treatment with short courses of glucocorticosteroids is acceptable when the effect is not complete, [13, 19]. The therapy has been satisfactorily tolerated for many years, being quite safe, as shown by the present case and other observations [20]. A follow-up of 111 children with mastocytosis showed that the number of patients with severe course is less than 5%, while, in most cases, the disease either does not require regular treatment or is easily controlled by antihistamines [16]. In our clinical case, the antihistamine therapy proved to be insufficient, thus requiring usage of glucocorticosteroids. However, this severe course seems to be uncommon in mastocytosis.

Despite the severity of the complaints, there were no signs of aggressive mastocytosis in the child. Signs of aggressiveness include pronounced organomegaly, anemia, osteolytic syndrome and intestinal damage with weight loss. There were no indications for bone marrow analysis, however, both puncture and trephine biopsy were made and did not reveal specific infiltration [13]. In everyday practice, the severity of symptoms encourages doctors to conduct an in-depth examination of the patient, sometimes being excessive [5].

Osteoblastoma refers to rare bone tumor diseases with a favorable prognosis. According to the analysis of 99 patients, approximately half of them have a lesion of the vertebrae or humerus. Surgical treatment leads to recovery [21]. Localization of osteoblastoma, course, therapy and stable response to treatment of the humerus in the presented child, corresponded to the published data. According to the SEER register analysis (Surveillance, Epidemiology and End Results), where the results of observation in 421 patients with mastocytosis, including children, were analyzed, there was no increase in the number of secondary malignant diseases compared to the average population [22].

Conclusion

The presented clinical observation again confirms that, even in severe skin form of mastocytosis, the prognosis is favorable. The main efforts of attending doctor should be focused on improving the quality of life and emotional comfort of the child and his parents.

Conflict of interest

None declared.

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Клиническое наблюдение ребенка с тяжелым течением кожного мастоцитоза

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Резюме

Мастоцитоз – заболевание системы крови с накоплением кланальных тучных клеток в одном или нескольких органах. У детей чаще всего поражается кожа. У большей части болезнь регрессирует самостоятельно, независимо от тяжести клинических проявлений.

Описание случая

Заболевание дебютировало сразу после рождения в виде тяжелой типичной уртикарной и везикулярной сыпи, ежедневных приливов и зуда. Проводилось симптоматическое лечение антигистаминными препаратами и короткими курсами глюкокортикостероидов. С 4 месяцев началась положительная динамика: разрешились приливы, прошли боли в животе, уменьшились сыпь, зуд, снизилась потребность в фармакотерапии. В 2 года и 9 месяцев ребенок был радикально прооперирован по поводу остеобластомы. В настоящее время сохраняется умеренный кожный зуд, ребенок растет и развивается по возрасту, антигистаминные препараты принимает лишь эпизодически.

Заключение

Клиническое наблюдение демонстрирует самостоятельный регресс заболевания даже при тяжелом течении.

Ключевые слова

Мастоцитоз, клиническое наблюдение, пигментная крапивница, триптаза, антигистаминные средства, C-KIT, тучные клетки.