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CLINICAL CASE
КЛИНИЧЕСКИЙ СЛУЧАЙ

Monomorphic type clinical features of maculo-papular cutaneous mastocytosis

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Abstract. *Relevance.* A monomorphic type of maculo-papular cutaneous mastocytosis was allocated relatively recently. In children and adolescents with a monomorphic type of MPCM (adult type pattern), clinical manifestations persist into adulthood and can transform into a systemic process, which determines the need for regular monitoring of this category of patients. *The aim* was to analyse the results of clinical, laboratory and instrumental examinations of an adolescent with a monomorphic type of MPCM. *Materials and Methods*. The study of an adolescent patient included data of laboratory examination, pathomorphological examination, ultrasound examination of the abdominal organs and cKIT gene of an adolescent with a monomorphic type of MPCM, observed at "Moscow Scientific and Practical Center of Dermatovenerology and Cosmetology". *Results and Discussion.* The process was represented by multiple rashes on the skin of the trunk and limbs. Darier's sign is positive. The patient's serum tryptase level exceeded the age norm. The late onset (at the age of 12) of the disease, elevated tryptase levels, neurological symptoms, and the risk of anaphylaxis caused alertness regarding the development of the systemic form, therefore an ultrasound examination of the abdominal organs was performed and the presence of a mutation in the cKIT gene in peripheral blood was determined. *Conclusion.* Clinical report of an adolescent patient in Moscow Scientific and Practical Center of Dermatovenerology and Cosmetology was presented. Thus, the combination of clinical and laboratory data allows minimizing the number of invasive procedures in children with CM. Assessment of the tryptase level, mutation detection in the cKIT gene and ultrasound examination of abdominal organs can be useful for timely diagnosis of systemic mastocytosis, which allows to carry out the necessary correction of the disease status and drug therapy.

Keywords: maculo-papular cutaneous mastocytosis, monomorphic type, children, adolescents, diagnostics

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Conflicts of interest statement. Authors declare no conflict of interest.

Ethics approval. The study was approved by the bioethics commission of Moscow Scientific and Practical Center of Dermatovenerology and Cosmetology (Protocol № 28, 21.03.2022).

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Consent for publication. Informed consent form clearly explaining the study procedures, risks, and code of conduct in cases of any emergencies, was given to participant. The information consent was signed by the patient's mother. Personal information of participant was kept confidential and was only fairly used in the study.
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Introduction

Mastocytosis is a heterogeneous group of diseases characterized by the accumulation of neoplastic mast cells (MC) in one or more organs. Mostly, mastocytosis develops due to an acquired activating mutation in the KIT protein, which leads to an increased proliferation and survival of MC in tissues [1]. In children, the disease is usually limited to the skin, but sluggish systemic mastocytosis may develop. The most common form of cutaneous mastocytosis (CM) is maculo-papular cutaneous mastocytosis (MPCM) [2, 3]. The World Health Organization (WHO) identifies two main forms of maculo-papular cutaneous mastocytosis (MPCM): monomorphic and polymorphic. The monomorphic type, which is more common in adults, but can also be observed in children, is manifested by small, round, mostly flat, brown or red spotted (maculo-papular) rashes, which usually have a central symmetrical distribution over the body and are classically absent on the skin of the central part of the face, palms and soles [4, 5].

Variants of the course of MPCM have a predictive value. In patients with polymorphic type of MPCM, rashes tend to have regular spontaneous regression during puberty. In children and adolescents with a monomorphic type of MPCM (adult type pattern), clinical manifestations continue to persist into adulthood [5, 6]. Patients with a monomorphic type of skin lesions have been identified as a risk group for developing systemic mastocytosis since 2016 [7]. Several studies demonstrated that mastocytosis, with a debut in early childhood and large maculopapular skin rashes (polymorphic type of MPCM), is associated with lower serum tryptase levels, favourable outcome and relatively more frequent spontaneous remission [6-8]. Dynamic observation of children with mastocytosis in studies of the last decade has shown that systemic mastocytosis (SM) is diagnosed in children more often than at the beginning of the XXI century [3, 7, 9–10]. This is due to the progress made over the past few years in diagnostic studies, particularly, in the identification and quantitative evaluation of the KIT D816V mutation [11].

When diagnosing CM, data from the results of pathomorphological and immunohistochemical studies are taken into account [12]. In patients with CM, the average amount of MC in the affected dermis is about 3–8 times more than in the dermis of healthy people (about 40 MC/mm2), and about 2–3 times more than in those suffering from inflammatory skin diseases [2]. Recently, the use of sensitive, allele-specific quantitative polymerase chain analysis (ASq-PCR) KIT D816V for the study of mutations in blood serum

has become a standard screening examination in adults with manifestations of CM and persons with suspected mastocytosis without skin signs and symptoms [13, 14]. Carter et al. (2018) showed that the detection of KIT D816V in peripheral blood in combination with organomegaly, allows to identify a risk group of children with a high probability of developing a systematic process [7]. Thus, a comprehensive examination of patients with mastocytosis is necessary to determine the tactics of management and further prognosis of the course of the disease.

In available domestic literature, we have not found publications devoted to the description of clinical cases with the analysis of clinical, laboratory and instrumental studies in monomorphic type of maculo-papular cutaneous mastocytosis in children and adolescents.

Clinical report

Patient A., born in 2005 was under our supervision in Moscow scientific and practical Center of Dermatovenereology and Cosmetology. A mother with her 17 years old son addressed the clinic with their complaints of multiple rashes on the skin of the trunk and limbs in April 2023 for the first time. The rashes became brighter during temperature changes, and during physical and emotional stress. Occasionally, the teenager was disturbed by moderate itching of the skin. He also noted the feeling of rapid fatigue with physical and mental workload, in addition to frequent headaches.

The patient indicated that the onset of the disease occurred at the age of 12, when rashes appeared on the skin of the back. Gradually, the number of rashes on the skin of the trunk increased. Also, from the age of 12, the patient is worried about recurrent stomatitis, headaches with nausea but without vomiting, abdominal pain, and diarrhoea. At school, there were episodes of fainting during exams period. 5 years prior to the referral to Moscow Scientific and Practical Center of Dermatovenereology and Cosmetology, the diagnosis of mastocytosis was not established. The pigmented form of lichen planus, teardrop-shaped and lichenoid chronic pityriasis were assumed to be the possible diagnoses. No treatment was carried out.

The following is known from the anamnesis of life. Neuropsychiatric development is age-appropriate. Vaccination according to the National Calendar of Preventive Vaccinations. Past illnesses: acute respiratory viral infections, chickenpox. In 2022 — concussion of the brain. There were no operations. Taking ibuprofen induces hyperaemia of the skin and redness of rashes. He denies allergic reactions to food. Heredity for skin diseases is not burdened. His father has bronchial asthma.

Local status: the pathological skin process is represented by multiple small non-inflammatory spots of light and dark brown colour. All rashes have the same diameter — 0.4–0.5 cm. The rashes are localized symmetrically on the skin in the shoulders, trunk, hips and shins area, with a greater density in the back area (Fig. 1, 2). The spots aren't elevated above the skin surface.

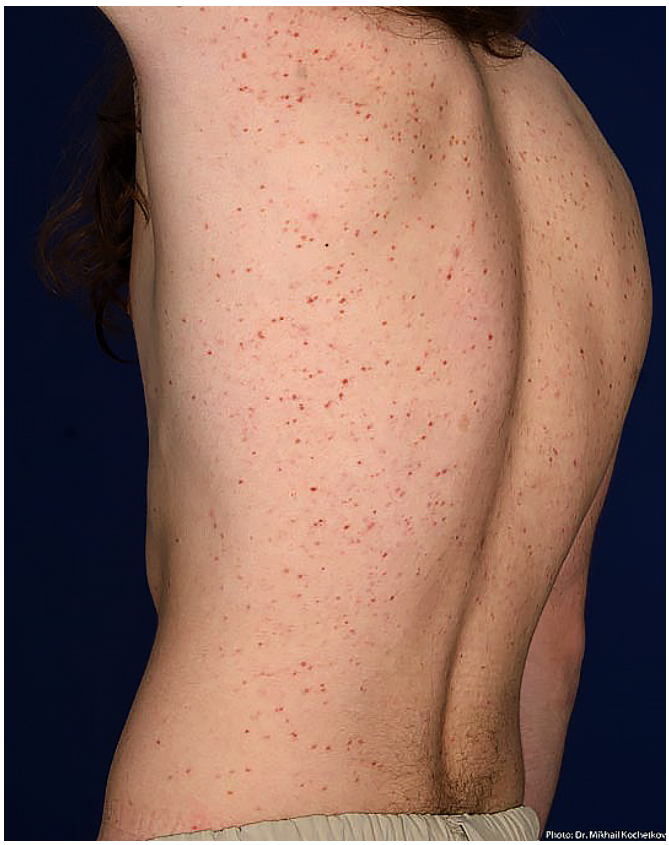

Fig. 1. Monomorphic type of MPCM. Rashes in the back area

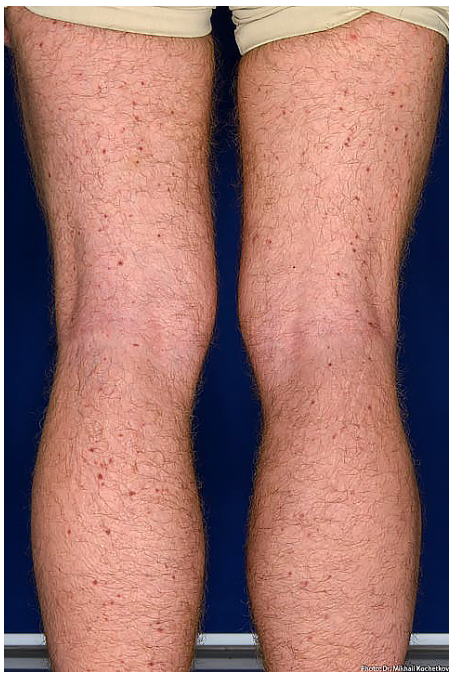

Fig. 2. Monomorphic type of MPCM. Rashes on the skin of the lower extremities

Darier's sign is positive with the formation of persistent hyperaemia and a blister. Visible mucous membranes, hair, nail plates on the hands and feet are not affected. Peripheral lymph nodes are not enlarged. Persistently red and urticarial dermographism.

Dermatoscopic examination of monomorphic rashes in spotted elements shows an increase in yellow-brown colour, maintenence of skin appendages, unchanged vellus hair shafts, pseudo-pigmentary network, a weakly pronounced vascular pattern of an asymmetric nature, moderate erythema in surrounding areas (Fig. 3).

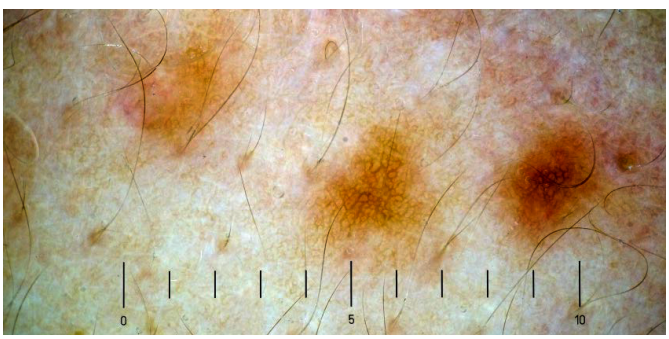

Fig. 3. Dermatoscopic picture of rashes of monomorphic type MPCM

The SCORMA index was 36 points. When assessing the skin process on a paediatric scale, the 2nd degree of severity was determined (moderate symptoms controlled by antimediator drugs). Systemic risk assessment on the scale of REMA SCORE = 4 (SCORE≥2 — high risk of clonal mastocytosis).

Laboratory and instrumental studies

Clinical blood test dated 04.27.23: erythrocytes — 5.6×1012 g/l (norm 4–5,3×1012 g/l), haematocrit — 47.8 % (norm 35–47 %), haemoglobin — 163 g/l (norm 130–160 g/l). The remaining indicators are within the age norm.

Biochemical blood test dated 04.26.23: glucose — 5.94 mmol/l (norm 3.5–6.1 mmol/L), ALAT — 11.9 U/l (norm 0–41 units/l), ACT — 18.3 U/l (norm 0–40 units/l), alkaline phosphatase — 68 U/l (norm 40–130 U/l), total bilirubin — 11.4 mmol/l (norm 3.4–18.8 mmol/l). All indicators are within the age norm.

Tryptase (ImmunoCAP) dated 06.27.2023: 12.7 mcg/l (norm < 11.0).

cKIT gene mutation detection in blood serum dated 06.27.23: mutation was not detected.

Ultrasound examination of abdominal organs dated 06.21.2013: echographic signs of dyscholia, gallbladder deformity, hepatomegaly due to the left lobe.

Histological examination

Histological examination of skin biopsy material dated 01.06.23 (Fig. 4): a fragment of skin without subcutaneous fat. The epidermis is slightly thickened, its layers are differentiated, pigmentation of keratinocytes of the basal layer of the epidermis shows no signs of pigment loss. There is moderate lymphomonocytic infiltration around the vessels of the superficial plexus, in which, with additional coloration with toluidine blue, a significant admixture of tissue mast cells is determined (Fig. 5). Collagen fibers without signs of structural changes. In the reticular layer of the dermis there are fragments of adnexal structures of the usual histological structure.

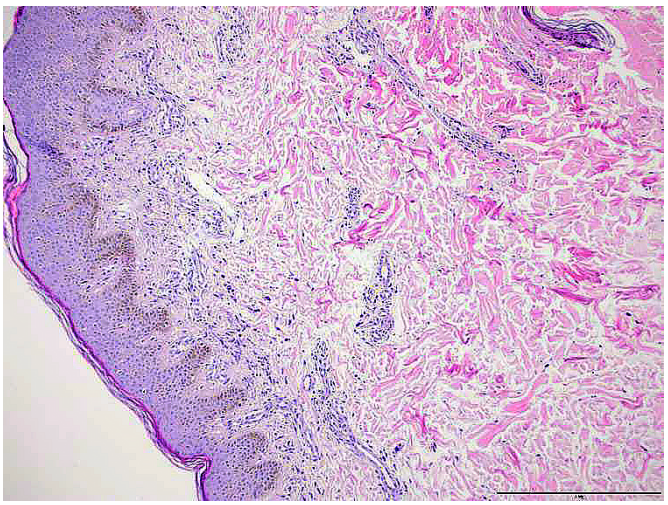

Fig. 4. A fragment of skin without subcutaneous fat. Hematoxylin-eosin staining, magnification × 200

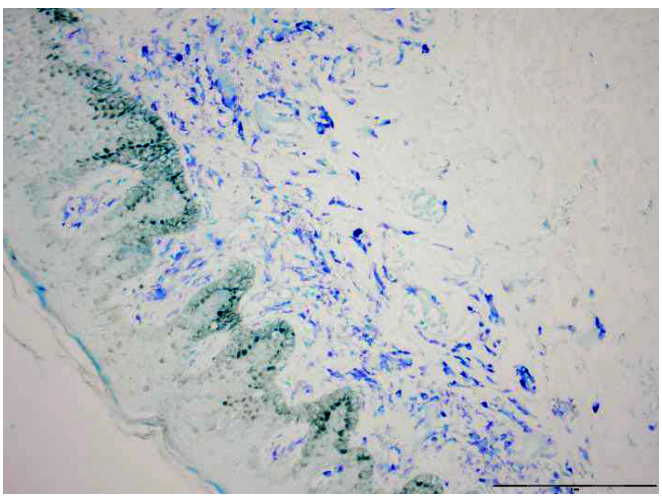

Fig. 5. A fragment of skin without subcutaneous fat. Toluidine blue staining, magnification x 200

Conclusion: within the biopsy, pathological changes correspond to mastocytosis.

Consultation of a neurologist dated 04.07.23: vegetative vascular dystonia according to vagotonic type. Multiple syncopation. Sleep disturbance. Anxiety.

Discussion

Managing children with cutaneous mastocytosis is a difficult task for a doctor. The variability of the clinical picture often leads to an erroneous interpretation of rashes with mastocytosis or ignoring these elements, especially considering the rarity of the pathology. There is evidence that the average time between the onset of the disease and the final diagnosis with subsequent initiation of treatment is 7 years [15]. In the clinical case presented by us, the diagnosis of mastocytosis was made 5 years after the appearance of the first rashes.

The presence of concomitant extracutaneous manifestations such as loss of consciousness and hypotension, headache accompanied by nausea, abdominal pain, diarrhoea attacks, rapid fatigue with physical and mental exertion became an obstacle for the prescription of the necessary antimediatory therapy. Analysis of anamnestic data, interpretation of primary morphological elements with the Darier-Unna phenomenon, dermatoscopic and pathomorphological examination allowed us to form a correct clinical diagnosis.

There is a well-established opinion that in children, the manifestations of CM disappear before or during puberty. In the last twenty years, this theory has been refuted by clinical studies. It has been shown that if the disease persists after adolescence, then in about 10 % of cases there is a transformation into a systemic process [16, 17].

In the patient we observed, a late debut (at 12 years old), the presence of extra-cutaneous symptoms of the disease, episodes of anaphylaxis, an elevated level of tryptase caused alertness regarding the development of a systemic form, thus, ultrasound examination of the abdominal organs was performed and the presence of a mutation in the cKIT gene in peripheral blood was determined.

Despite the absence of mutations in the cKIT gene, further dynamic monitoring of the patient should be continued. Prescription of antimediator therapy is mandatory for elevated levels of tryptase and the presence of itching.

Thus, the combination of clinical and laboratory data allows minimizing the number of invasive procedures in children with CM. Assessment of the tryptase level, determination of mutations in the cKIT gene and ultrasound examination of abdominal organs can be useful for timely diagnosis of systemic mastocytosis, which allows correction of the disease status and drug therapy.

Conclusion

Cutaneous and systemic forms of mastocytosis are a serious interdisciplinary problem. Numerous symptoms associated with degranulation of MC, such as flushing, anaphylaxis, abdominal cramps, diarrhoea, vomiting, runny nose, aggressive behaviour, anxiety, and others, in practice are extremely rarely associated by clinicians with mastocytosis. The situation is complicated by the lack of Russian clinical guidelines for the treatment and follow-up of patients. The lack of response of rashes to antimediator therapy significantly reduces the quality of life and socialization of children and adolescents suffering from mastocytosis. Therefore, a timely correct analysis of the anamnesis and clinical picture in combination with a dynamic assessment of laboratory and instrumental studies is important for the development of dynamic monitoring and treatment of patients with CM.

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Особенности клинического течения мономорфного типа пятнисто-папулезного кожного мастоцитоза

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Аннотация. *Актуальность.* Мономорфный вариант течения пятнисто-папулезного кожного мастоцитоза (ППКМ) был выделен относительно недавно. У детей и подростков с мономорфным типом ППКМ (паттерн взрослого типа) клинические проявления в дальнейшем сохраняются во взрослом возрасте и могут трансформироваться в системный процесс, что определяет необходимость регулярного наблюдения за данной категорией пациентов. *Цель.* Проанализировать данные результатов клинико-лабораторного и инструментального исследования у подростка с мономорфным типом ППКМ. *Материал и методы.* В статье представлены результаты наблюдения пациента-подростка в ГБУЗ «Московский центре дерматовенерологии и косметологии». При клинико-лабораторном обследовании и патоморфологическом исследовании был определен мономорфный тип ППКМ. Процесс был представлен множественными высыпаниями на коже туловища и конечностей. Феномен Дарье положительный. Уровень сывороточной триптазы у пациента превышал возрастную норму. Поздний дебют (в 12 лет) заболевания, повышенный уровень триптазы, неврологические симптомы, риск развития анафилаксии вызывали настороженность в отношении развития системной формы, в связи с чем были проведены ультразвуковое исследование органов брюшной полости и определение наличия мутации в гене KIT в периферической крови. *Заключение.* Сочетание клинических и лабораторных данных позволяет минимизировать количество инвазивных процедур у детей с КМ. Оценка динамики уровня триптазы, определение мутаций в гене KIT и УЗ-исследование органов брюшной полости могут быть полезны для своевременной диагностики системного мастоцитоза, что позволяет проводить коррекцию статуса заболевания и лекарственную терапию.

Ключевые слова: пятнисто-папулезный кожный мастоцитоз, мономорфный тип, дети, подростки, диагностика

Информация о финансировании. Авторы заявляют об отсутствии внешнего финансирования.

Вклад авторов: Е.И. Касихина, А.Я. Нада, О.В. Жукова — концепция, планирование исследования, сбор и систематизация данных, написание текста. М.А. Кочетков — фотодокументирование и дерматоскопия, описание результатов исследования. М.Н. Острецова, Р.А. Ханферьян — написание и редактирование текста. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Информация о конфликте интересов. Авторы заявляют об отсутствии конфликтов интересов.

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