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Cephalalgia against the background of systemic mastocytosis: a clinical case

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ABSTRACT

The article presents a clinical case of comorbid pathology – development of migraine against the background of systemic mastocytosis. The classification and clinical manifestations of systemic mastocytosis, a rare blood disease, are given.

This clinical case illustrates an example of excessive mast cell degranulation (with the release of proinflammatory and vasodilating agents as a result of mast cell pathology). In this regard, in addition to the pathogen-specific therapy for systemic mastocytosis (including prevention of mast cell degranulation), it seems important to describe the effectiveness and the possibility of prescribing preventive and emergency therapy for migraine against the background of the underlying hematological disease – systemic mastocytosis.

Treatment of cephalalgia in patients with mastocytosis is a complex clinical task, in the solution of which it is necessary to take into account serious limitations in prescription of acetylsalicylic acid and other non-steroidal anti-inflammatory drugs.

Key words: cephalalgia, migraine, aura, mast cells, systemic mastocytosis.

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Цефалгический синдром на фоне системного мастоцитоза. Клинический случай

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РЕЗЮМЕ

Приведен клинический случай коморбидной патологии – развития мигрени на фоне системного мастоцитоза. Приводятся классификация, клинические проявления системного мастоцитоза – редкого клонального заболевания крови.

Данный клинический случай иллюстрирует пример избыточной дегрануляции тучных клеток (с выделением провоспалительных и вазодилатирующих агентов в результате патологии мастоцитов). В связи с этим, помимо патогенетической терапии системного мастоцитоза (включающей профилактику дегрануляции тучных клеток), нам представляется также важным отразить эффективность и возможность назначения профилактической и экстренной терапии мигрени на фоне основного гематологического заболевания – системного мастоцитоза.

Терапия головной боли у пациентов с мастоцитозом представляет собой сложную клиническую задачу, в решении которой необходимо учитывать серьезные ограничения в назначении ацетилсалициловой кислоты и других нестероидных противовоспалительных препаратов.

Ключевые слова: цефалгический синдром, мигрень, аура, тучные клетки, системный мастоцитоз.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Для публикации данного клинического случая было получено письменное согласие пациента. Исследование одобрено локальным этическим комитетом (протокол № 11-3/19 от 20.11.2019).

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INTRODUCTION

Cephalgic syndrome often accompanies the course of various pathological processes. The algorithm for examining a patient with headache (according to regional and international clinical guidelines) consists of anamnesis, clinical presentation, instrumental examination, and exclusion of secondary causes of headache. It is especially important to exclude these causes when alarming signs appear – markers indicating the need for additional examination. Such alarming signs include the first onset of headache after 50 years and thunder-like headache, progressively worsening and atypical for the patient, if accompanied by neurological symptoms and signs of intracranial hypertension [1–3].

Cephalalgia is often associated with giant cell arteritis, transient ischemic attacks, stroke, brain tumors, venous sinus thrombosis, subarachnoid hemorrhage, epilepsy, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cervical artery dissection, cervicalgia, and other diseases [2].

This article presents our own experience in treating cephalalgia in a patient with a verified diagnosis of mastocytosis. Mastocytosis is a rare blood disease that involves proliferation of mast cells (MCs) [4]. MCs were first described in 1863 by Frederick Recklinghausen (1833–1910) [5]; they play an important role not only in allergic reactions, but also in the immune response. The prerequisite for mastocytosis development is appearance of clonal MCs with a D816V mutation in the *c-KIT* gene. The product of this gene is transmembrane tyrosine kinase receptor CD117 for mast cell growth factor, and disturbances of the receptor apparatus lead to tumor transformation and inhibition of apoptosis.

The disease occurs among adults and children and is characterized by growth, activation, and accumulation of MCs in various organs and tissues of the body. With excessive accumulation of MCs in the skin (the so-called cutaneous mastocytosis), patients can be diagnosed with atopic dermatitis for many years under the supervision of dermatologists and allergists [6]. Another variant of the course is accumulation of MCs in other areas (skeletal system, gastrointestinal tract, liver, spleen, central nervous system), which is typical of systemic mastocytosis. According to the 2016 World Health Organization (WHO) criteria, mastocytosis can be divided into several subtypes: cutaneous mastocytosis, indolent (sluggish) systemic mastocytosis, smoldering systemic mastocytosis, systemic mastocytosis with associated hematological non-mast cell disease, aggressive systemic mastocytosis, mast cell leukemia, and mast cell sarcoma.

The cutaneous form of mastocytosis in children in 80% of cases independently regresses after puberty without any specific treatment. The aim of this article was not to discuss in detail the criteria for establishing the diagnosis of systemic mastocytosis. We only note that there are major criteria (multifocal dense infiltrates consisting of MCs (≥ 15 in the aggregate) and determined in a biopsy sample of the bone marrow and (or) other organs) and minor criteria (in biopsies of the bone marrow or other organs, > 25% of MCs located in the infiltrate are spindle-shaped or have atypical morphology, or > 25% of all MCs obtained from bone marrow aspirate smears are immature or atypical; D816V mutation of the *c-KIT* gene, mast cells in the bone marrow or organs express CD2 and / or CD25, serum tryptase levels are higher than 20 μg / l). The diagnosis is valid in the presence of one major and one minor or three minor criteria [7].

Typical symptoms of mastocytosis include urticaria, pruritus, rhinorrhea, nausea, dyspepsia, and nonspecific manifestations in the pulmonary system (wheezing, shortness of breath). In the nervous system, the most frequent manifestation of systemic mastocytosis is headache [8, 9]. Highly variable clinical presentation is due to paroxysmal degranulation of MCs in the tissue or in the systemic circulation, resulting in rhinorrhea, itching, syncope, diarrhea, and cephalalgia.

There is a sufficient number of studies describing the relationship between development of migraine in patients and pathology of MCs; hence, correction of cephalalgia remains the most important aspect in the treatment of patients with mastocytosis [10].

The role of MCs in the pathophysiology of migraine is widely discussed [11]. Peptides, such as calcitonin gene-related peptide, chemokine A, neurotensin, pituitary adenylate cyclase-activating peptide, and substance P, activate MCs, releasing vasoactive and proinflammatory mediators, which ultimately lead to the development of cephalalgia. In response to the effect of corticotropin-releasing hormone, MCs secrete proinflammatory and vasodilator molecules (interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), nitric oxide (NO), histamine). Such a pathological chain develops as a result of stress factors, playing an important role in the development of migraine attacks. It is known that vasodilation of extracerebral vessels and cortical spreading depression are also involved in the pathogenesis of migraine, which explains some of the aura symptoms [12].

The Mayo Clinic conducted a retrospective study on the association between headache and MC activity. It included 64 patients with an established diagnosis of systemic mastocytosis (7), of which cephalalgia was observed in 36 patients (56.2%). Of these, 21 patients were carriers of the D816V mutation in the *c-KIT* gene (28 people were examined), headache was determined according to the International Headache Criteria [13]. In patients suffering from migraine and other types of headache in the clinical presentation, the following symptoms were noted (during the attack): redness, local fever, heaviness in the chest, abdominal pain. This symptom complex allowed the authors of the study to suggest an association between activation of mast cells and development of cephalalgia. In this work, the authors also noted a five-fold increase in the prevalence of aura symptoms in comparison with the general population [14].

Treatment of patients with mastocytosis presents certain difficulties, since a sufficiently large number of drugs can be triggers of mast cell activation (including development of anaphylactic shock); therefore, their use is limited in this cohort of patients. These drugs include (among others) non-steroidal anti-inflammatory drugs, antibiotics (vancomycin, polymyxin), and vitamin B1 (thiamine).

CLINICAL CASE

Patient R., 45 years old, had an appointment with a neurologist at the Research Center of Neurology with complaints of headache attacks, mainly in the right side of the head, lasting from several hours to 2–3 days. Before the attack, the patient noted (not always) zigzagging lines, sometimes bright flashes before the eyes. Headache attacks were often triggered by drinking wine. The frequency of attacks varied from 1–2 times a month to 2–3 times a week, depending on the season (more often, in winter). To relieve these symptoms, the patient took metamizole sodium and triptans (no effect). Upon additional questioning, it turned out that triptans were taken during a full-blown painful attack (which may explain their ineffectiveness).

From the anamnesis, it is known that since 1998, the patient has been observed by dermatologists for cutaneous mastocytosis. In 2013, she went to the Research Center of Hematology, where an examination was carried out. A skin biopsy was performed. In the skin biopsy, the morphological pattern and immunophenotype (in the upper layers of the dermis, elongated cells expressed CD117, CD25, and Tryptase) corresponded to the diagnosis of mastocytosis.

A molecular genetic study of peripheral blood revealed a D816V mutation in the *c-KIT* gene. Serum tryptase level was 16.9 μg / ml (reference value is less than 11 μg / l). During the histological examination of the trepanobioptate, no data for the damage to the bone marrow were obtained. According to the ultrasound data, the sizes of the liver, spleen, and lymph nodes were within normal values. Complete blood test parameters were within normal values (hemoglobin – 141 g / l; erythrocytes – 4.63 10^{12} / l; platelets – 235 × 10^9 / l; leukocytes – 8.63 × 10^9 / l). Coagulogram revealed normal coagulation (activated partial thromboplastin time (APTT) – 25.3 sec; prothrombin index according to Quick – 92%; fibrinogen – 3.3 g / l); platelet aggregation with adenosine diphosphate (ADP) – 73%; with ristomycin – 86%; with collagen – 84%. The patient received symptomatic therapy: sodium cromoglycate, ketotifen – in case of itching. During the observation period, the patient noted the appearance of new maculopapular rash of red and brown color on the skin of the thighs, legs, hands, and neck. Darier's sign was positive. Headache was the predominant symptom in the clinical presentation.

Due to the appearance of complaints of headaches and the predominance of cephalalgia in the clinical presentation, it was recommended to contact the Research Center of Neurology. The general somatic status included a reduced body mass index (17 kg / m^2), a tendency to arterial hypotension (BP of 100 / 60 mm Hg), and heart rate of 59 beats per minute).

In the neurological status: conscious, correctly oriented in place, time and self. Emotional background: somewhat emotionally labile. There were no meningeal symptoms. Cranial nerves were intact. No paresis was detected, tendon and periosteal reflexes were lively and symmetric. There were no clear sensitivity disorders. There were no pathological pyramidal signs. The finger-nose test was performed with discoordination on both sides. Slight staggering during the Romberg test was observed. Subjective headache assessment on the Visual Analogue Scale (VAS) – 7 points.

Findings of instrumental and laboratory research methods. Magnetic resonance imaging (MRI) of the brain: a single focal lesion of vascular origin in the right frontal region was determined (migraine focus?); the rest of the departments were without pathology. Electroencephalography (EEG) revealed nonspecific signs of dysfunction of the brain bioelectrical activity and dysfunction of diencephalon structures. Duplex ultrasound of the main arteries of the head revealed no pathology.

Complete blood count and biochemistry within normal limits; the coagulogram showed normal coagulation. According to the data of platelet aggregation, an increase in their aggregation properties was noted: with ADP – 50 (37–43)%; with adrenaline – 48 (40–46)%.

Taking into account the clinical manifestations and the data of instrumental research methods, the diagnosis of migraine with aura was established. It was decided to prescribe tricyclic antidepressants in therapeutic doses (amitriptyline, 50 mg / day). As the background therapy, we did not prescribe calcium and beta-blockers (taking into account the tendency to hypotension and bradycardia), so we selected a caffeine-containing combination drug which also has antiplatelet properties.

Prescription of acetylsalicylic acid for mastocytosis is unacceptable due high risk of anaphylaxis. In addition, we recommended to take triptans to stop seizures (with a need to take it in the first minutes of

an attack or during aura symptoms). After 3 weeks, a positive trend was noted in the form of a decrease in the frequency and intensity of attacks. During the follow-up, a single attack was noted. A repeated blood test (after 3 weeks) of platelet aggregation with adrenaline and ADP showed a significant decrease in the aggregation properties of the latter (34 and 38%, respectively), which indicates an important contribution of antiplatelet therapy to prevention of cephalalgia.

CONCLUSION

An important aspect of neurological practice is management of comorbid patients with cephalalgia. One of the main aspects in treatment of headaches (as well as the underlying disease) against the background of mastocytosis is preventing activation of mast cells (degranulation of cytoplasmic compartments with release of histamine, prostaglandins, interleukins, etc.), which lead to variable clinical presentation, including the development of a migraine attack. Patients should avoid overheating (baths, saunas) and sun exposure and follow a strict diet that excludes seafood (especially shrimps, lobsters, crabs, caviar), alcohol, chocolate, tyramine-containing foods (cheeses, nuts, cereals, legumes), and canned food. Such restrictions are also effective in preventing the frequency of migraine attacks [15].

REFERENCES

1. Steiner T.J., Paemeleire K., Jensen R., Valade D., Savi L., Lainez M., Diener G., Martelletti P. European principles of management of common headache disorders in primary care. *J. Headache Pain*. 2007; 8 (1): S3–47. DOI: 10.1007/s10194-007-0366-y.
2. Osipova V.V., Filatova E.G., Artemenko A.R.,. Lebedeva E.R., Azimova Yu.E., Latysheva N.V., Sergeev A.V., Amelin A.V., Koreshkina M.I., Skorobogatykh K.V., Ekusheva E.V., Naprienko M.A. V., Isagulyan E.D., Rachin A.P., Danilov Al.B., Kurushina O.V., Parfenov V.A., Tabeeva G.R., Gekht A.B., Yakhno N.N. Diagnostics and treatment of migraine: recommendations of Russian experts. *Journal of Neurology and Psychiatry named after S.S. Korsakov*. 2017; 117 (1): 28–42 (in Russ.). DOI: 10.17116/jnevro20171171228-42.
3. Osipova V.V., Azimova Yu.E., Tabeeva G.R., Tarasova S.A., Amelin A.V., Kutsemelov I.V., Moldovanu I.V., Odobescu S.S., Naumova G.I. Diagnostics of headaches in Russia and the countries of the post-Soviet space: the state of the problem and ways to solve it. *Annals of Clinical and Experimental Neurology*. 2012; 6 (2): 16–21 (in Russ.).
4. Akin C., Metcalfe D.D. Systemic mastocytosis. *Annu. Rev. Med*. 2004; 55 (1): 419–432. DOI: 10.1146/annurev.med.55.091902.103822.
5. Recklinghausen F von. Über Eiter und Bindegewebskörperchen. Virchows *Arch. Pathol. Anat. Physiol. Klin. Med*. 1863; (28): 157–197.
6. Castells M., Austen K.F. Mastocytosis: mediator-related signs and symptoms. *Int. Arch. Allergy Immunol*. 2002; 127 (2): 147–152. DOI: 10.1159/000048188.
7. Valent P., Akin C., Metcalfe D.D. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood.* 2017; 129 (11): 1420–7. DOI: 10.1182/blood-2016-09-731893.
8. Scully R.E., Mark E.J., McNeely W.F., Ebeling S.H., Phillips L.D. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 20-1997. A 74-year-old man with progressive cough, dyspnea, and pleural thickening. *N. Engl. J. Med*. 1997; 336 (26): 1895–1903. DOI: 10.1056/NEJM199706263362608.
9. Georgin-Lavialle S., Gaillard R., Moura D., Hermine O. Mastocytosis in adulthood and neuropsychiatric disorders. *Transl. Res*. 2016; 174: 77–85.e1. DOI: 10.1016/j.trsl.2016.03.013.
10. Hermine O., Lortholary O., Leventhal P.S., Catteau A., Soppelsa F., Baude C., Lortholary O., Leventhal P.S., Catteau A., Soppelsa F., Cohen-Akenine A., Palmérini F., Hanssens K., Yang Y., Sobol H., Fraytag S., Ghez D. et al. Case-control cohort study of patients' perceptions of disability in mastocytosis. *PLoS One*. 2008; 3 (5): e2266. DOI: 10.1371/journal.pone.0002266.
11. Theoharides T.C., Donelan J., Kandere-Grzybowska K., Konstantinidou A. The role of mast cells in migraine pathophysiology. *Brain Res. Rev*. 2005; 49 (1): 65–76. DOI: 10.1016/j.brainresrev.2004.11.006.
12. Spierings E.L.H. Pathogenesis of the migraine attack. *Clin. J. Pain*. 2003; 19 (4): 255–262. DOI: 10.1097/00002508-200307000-00009.
13. The International classification of headache disorders; 2nd ed. *Cephalalgia.* 2004; 24 (1): 9–160. DOI: 10.1111/j.1468-2982.2003.00824.x.
14. Smith J.H., Butterfield J.H., Cutrer F.M. Primary headache syndromes in systemic mastocytosis. *Cephalalgia*. 2011; 31 (15): 1522–1531. DOI: 10.1177/0333102411421683.
15. Melikian A.L., Subortseva I.N., Goriacheva S.R., Kolosheinova T.I., Vakhrusheva M.V., Kovrigina A.M. et al. Mastocytosis. Review of the literature and description of clinical cases. *Ter. Arkh.* 2014; 86 (12): 127–134. DOI: 10.17116/terarkh20148612127-134.

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