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SYSTEMIC MASTOCYTOSIS IN CHILDREN – THERAPEUTIC PROBLEMS

UKŁADOWA MASTOCYTOZA U DZIECI – PROBLEMY TERAPEUTYCZNE

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Abstract

Systemic mastocytosis is a myeloproliferative disorder characterized by growth and accumulation of abnormal mast cells in one or more organs. The symptoms of the disease are due both to the mast cells infiltrating the organs and to the action of its degranulation products. Over 85% of adult patients exhibit point mutations of KIT at position 816 (D816V). Systemic mastocytosis is rare in both adults and children, so treatment is highly individualized; therapy and further treatment is adjusted to each patient's needs. The aim of this study was to present the case of a 14-year old female with systemic mastocytosis and the problems with her treatment. Multidisciplinary management is recommended in systemic mastocytosis.

Key words: systemic mastocytosis, KIT, pathogenesis, treatment, children

Streszczenie

Mastocytoza systemowa jest chorobą mieloproliferacyjną charakteryzującą się wzrostem i akumulacją nieprawidłowych komórek tucznych w jednym lub kilku narządach. Objawy tej choroby wynikają z naciekania narządów przez komórki tuczne oraz z działania ogólnoustrojowego wywieranego przez produkty ich degranulacji. U ponad 85% dorosłych pacjentów stwierdza się występującą mutację punktową D816V genu KIT. Układowa mastocytoza występuje rzadko zarówno u dorosłych, jak i u dzieci, dlatego też terapia jest indywidualizowana; leczenie i dalsze postępowanie jest dostosowane do potrzeb pacjenta. Celem pracy było przedstawienie 14-letniej chorej z układową mastocytozą i związane z nią trudności terapeutyczne. W tej chorobie jest rekomendowane postępowanie wielodyscyplinarne.

Słowa kluczowe: mastocytoza układowa, KIT, patogeneza, leczenie, dzieci

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INTRODUCTION

Systemic mastocytosis is a myeloproliferative disorder characterized by growth and accumulation of abnormal mast cells (MCs) in one or more organs, primarily skin, bone marrow, liver, spleen, and lymph nodes. The classification of mastocytoses adopted by the World Health Organization is shown in table I (1). Two main categories of this disease have been described: cutaneous mastocytosis (CM) with its several different forms, in which MCs infiltrate one or more lesions on the skin, and systemic mastocytosis (SM), in which infiltration occurs in at least one extracutaneous organ. The term "mastocytosis in the skin" was proposed to differentiate CM from SM (2). Mastocytosis is rare in both adults and children and occurs in less than 0.01% of the general population (3). In approximately 15% of patients the disease is congenital, and in approximately

Table I. WHO classification of mastocytosis (1).

Tabela I. Klasyfikacja mastocytozy wg WHO (1).

1. Cutaneus mastocytosis *Mastocytoza skóry*
2. Indolent systemic mastocytosis *Układowa mastocytoza o powolnym przebiegu*
3. Systemic mastocytosis with associated clonal haematological non – mast cell lineage disease *Mastocytoza układowa z klonalnym rozrostem linii komórkowych niemastocytarnych*
4. Agressive systemic mastocytosis *Agresywna układowa mastocytoza*
5. Mast cell leukemia *Białaczka mastocytarna*
6. Mast cell sarcoma *Mięsak mastocytarny*
7. Extracutaneous mastocytoma *Mastocytoma w narządach poza skórą*

50% the first symptoms develop before 2 years of age (4, 5). Genetic analysis shows various pathogenetic patterns of mastocytosis. Over 85% of adult patients exhibit activating mutations of the stem cell factor (SCF) receptor KIT in exon 17, which results in substitution of valine for aspartic acid at position 816 (D816V); mutations in other regions of the gene are less frequent (6, 7). The proto-oncogene *KIT* encodes the KIT receptor tyrosine kinase, which plays a major role in regulation of MC growth and differentiation (7). The D816V mutation in the activation loop of KIT causes relative resistance to the kinase inhibitor– imatinib. However, in some patients no mutations are present; so, in these cases, another mechanism is responsible for mastocytosis. MC proliferation is regulated by both SCF and KIT, as well as some cytokines, including interleukins 4, 6, 10 and 13 (8). In mastocytosis, eosinophilia is associated with poor prognosis (9). MCs are derived from CD34+ multipotent hematopoietic progenitor cells. Recently, CD30 (Ki-1) antigen has been considered a possible immunohistochemical marker to distinguish between advanced and indolent forms of mastocytosis (10). The treatment of SM is highly individualized. Despite progress in understanding the pathogenesis, and in the diagnosis and treatment of mastocytosis, the disease remains a challenge for dermatologists and hematologists. Here, we report a 14-year old female with diagnosed SM and treated in the Department of Oncology and Hematology.

CASE REPORT

The medical history of this patient began in early childhood. The light brown skin changes, distinct, concerning mainly the skin of scalp and trunk were correctly diagnosed as *urticaria pigmentosa,* later confirmed by skin biopsy CD117+. At the age of 8 years she experienced a sudden loss of consciousness three times, headaches, and weight loss. A bone marrow biopsy was performed and showed to contain more than 50% of MCs. Systemic mastocytosis was diagnosed. Even though many diagnostic methods were used, among them full gene sequencing, no *KIT* mutation (D816V substitution) was found in bone marrow. Serum tryptase was greater than 100 ng/ml (reference range, <11.4 ng/ml). On physical examination, hepatomegaly and splenomegaly were confirmed, without impaired organ function. Significant abnormalities in blood counts revealed eosinophilia. Flow cytometric analysis of bone marrow MCs did not detect CD2 and CD25 antigens. The patient's general condition was poor and included fatigue, weight loss, sweating, and skin symptoms with a positive Darier sign. Her main complaint were frequent, even several times a day, flushing resulting in lowering of blood pressure and continuous resorption of bones due to the activity of MC degranulation products. The patient was treated with corticosteroids for 2 years; she received two 6-week courses of full – dose prednisone with maintaining dose later-on. All the time she received H1 and H2-blockers and vitamin D_3 supplementation. We observed a decrease in tryptase level (60 ng/ml) and quite good control of flushing. However, the patient complained of pain in the vertebral column and limbs. Radiography revealed a L1 compression fracture. Dual-energy Xray absorptiometry scan resulted in a T-score of 0.436-0.534 g/cm in the lumbar vertebrae (56-64% of normal values). Because bone mineral density was low, laboratory tests of calcium, phosphorus, and 25-hydroxyvitamin D levels were performed, but no abnormalities were present. Bisphosphonate therapy was initiated. We observed an increase in serum tryptase (360 ng/ml) and the decision to administer 500 mg of hydroxyurea daily was made. However, the disease progressed and the level of tryptase exceeded 900 ng/ml. She received imatinib mesylate, but did not respond positively. We combined hydroxyurea with the imatinib, and serum tryptase dropped to 306 ng/ml. Interferon-α was recommended and administered to the patient as cytoreductive therapy. The patient's parents went abroad, so the patient was not treated in our department any longer.

DISCUSSION

Activated MCs degranulate and produce multiple mediators, including histamine, leucotrienes, proteases (tryptase, chymase, and carboxypeptidase), and proteoglycans (heparin and chondroitin sulphate E) (11). Depending on the type and course of mastocytosis, mediators released upon non-specific or allergen-induced degranulation may cause severe and recurrent symptoms, such as syncope, hypotensive shock, diarrhoea, bone pain, headache, and flushing, despite the use of antihistamine drugs (12). Typical changes in the skin, such as disseminated light brown plaques with Darier's sign, pruritus and urticaria, may be diagnostic; however, the diagnosis must be confirmed by biopsy. In our patient, the first diagnosis was urticaria pigmentosa – the most frequent form of mastocytosis of the skin. She received antihistamine treatment, but after some time her general condition deteriorated. She experienced syncope, flushing, and hypotensive shock periodically. Hannaford et al. described 173 pediatric cases of mastocytosis, only two of which were systemic disease

Table II. Criteria for the diagnosis of systemic mastocytosis according to WHO recommendations (1).
Tabela II. Kryteria diagnostyczne mastocytozy układowej wg WHO (1).

Major criteria *Kryterium większe*	1. Multifocal, dense infiltrates of mast cells (>15MCs in aggregates) detected in the bone marrow or other extracutaneous organs. *Wieloogniskowe, spoiste nacieki komórek mastocytarnych (>15 komórek w agregacie) wykrytych w szpiku kostnym lub w innych narządach poza skórą.*
Minor criteria *Kryteria mniejsze*	1. In the bone marrow or other extracutaneous organs, > 25% of mast cells in the infiltrate are spindle shaped or have atypical morphology, or in bone marrow smears >25% of MCs are immature or atypical. *W szpiku kostnym lub innych narządach poza skórą, >25% komórek mastocytarnych ma kształt wrzecionowaty lub atypową morfologię, lub w szpiku kostnym>25% komórek mastocytarnych jest niedojrzałych lub atypowych.* 2. Activating point mutation of KIT in codon 816 is present in bone marrow, blood, or other extracutaneous organ. *Punktowa mutacja w kodonie 816 genu KIT w komórkach szpiku kostnego, krwi lub innych narządach poza skórą.* 3. MCs in BM, blood, or other extracutaneous organs (CD117) express CD2 and/or CD25 in flow cytometry. *Komórki mastocytarne w szpiku kostnym, krwi lub innych narządach poza skórą wykazują ekspresję CD2 i/lub CD25 w cytometrii przepływowej.* 4. Serum tryptase persistently exceeds 20 ng/ml (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid). *Poziom tryptazy stale przekraczający 20 ng/ml (nie dotyczy przypadków, gdy mastocytoza skóry współistnieje z chorobami mielodysplastycznymi).*

Legend: BM – bone marrow, MCs – mast cells
Legenda: BM – szpik kostny, MCs – komórki mastocytarne, tuczne

(13). Because SM is extremely rare, the diagnosis is usually established late and with difficulty. Molecular criteria are crucial for establishing the diagnosis of SM (6, 14). SM is defined by one major and one minor criterion or at least three minor criteria (tab. II) (1). In the case of our patient typical B symptoms were noted. She had a high level of serum tryptase, so bone marrow examination was indicated, regardless of age (15). MCs express the tyrosine kinase receptor c-KIT, the extracellular domain of which binds SCF, on the plasma membrane (16). SCF is the principal MC growth factor and regulates MC differentiation and maturation, induces MCs chemotaxis, and stimulates MC degranulation and the release of mediators. Many tyrosine kinase inhibitors have been found to inhibit c-KIT activity. The most important is imatinib, which blocks c-KIT-mediated MC degranulation and inhibits SCF-dependent MC adhesion. Similar pharmacological activity has been reported for nilotinib, which inhibits MC-mediated immediate-type allergic reactions (17, 18). Dasatinib and midostaurin exhibit *in vitro* activity against KIT mutants, including D816V point mutation (19). In our patient, we did not observe a positive response to imatinib. Potential therapeutic effects of other c-KIT inhibitors, such as sunitinib or sorafenib, on MCs warrant investigation (20).

At present, imatinib is the only therapeutic drug approved for treatment of SM, specifically in adult patients with aggressive disease and without the D816V mutation or with unknown KIT mutation status (21, 22). However, no standard treatment exists for mastocytosis. Our patient did not respond to imatinib despite lack of any KIT mutations. The basis of the therapy are antagonists of histamine receptor. In patients with gastrointestinal symptoms, histamine receptor antagonists, proton pump inhibitors, and oral cromolyn sodium are recommended (23). Interferon-α is considered the first-line cytoreductive treatment. Its beneficial effects include improvement of bone density, as well as skin, gastrointestinal, and systemic symptoms associated with MC degranulation. It is interesting that the response to treatment is delayed by up to 1 year or longer (24). Serum tryptase level closely correlates with the course of mastocytosis and is used for the diagnosis and follow-up of the disease (25). This patient represented a SM diagnostic and treatment dilemma. She required sequential changes in therapy because her tryptase level was high, her general condition and quality of life was poor. She experienced multiple anaphylactic shocks and received adrenaline.

In conclusion, SM in children is extremely rare. Despite great progress in diagnosis and treatment of this disease, multidisciplinary management is recommended. Further studies of pediatric SM should be conducted to investigate new therapeutic approaches.

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