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Transition from the smoldering systemic mastocytosis to chronic mast cell leukemia: a clinical case

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Summary

We describe a rare clinical case of smoldering systemic mastocytosis which progressed to mast cell leukemia. The malignant disorder was treated with targeted therapy resulting into clinical improvement after 3 months during therapy.

Keywords

Systemic mastocytosis, mast cells, allogeneic bone marrow transplantation.

Introduction

Systemic mastocytosis (SM) is a group of heterogeneous diseases associated with abnormal proliferation and infiltration of mast cells (MC) in extra-cutaneous organs. According to the WHO 2016 classification, it is a separate nosological category in the group of myeloproliferative neoplasias [1]. Systemic mastocytosis is sub-classified into five sub-categories as indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), systemic mastocytosis associated with hematologic neoplasm (SM-AHN) and mast cell leukemia (MCL). According to the results of event-free and total life expectancy, indolent and smoldering systemic mastocytoses are among the most favorable sub-categories in terms of life expectancy, statistically not significantly different than the control group [2]. In the present communication, we report a clinical case of smoldering systemic mastocytosis in young adult patient with later progression to mast cell leukemia, on targeted therapy with the partial response.

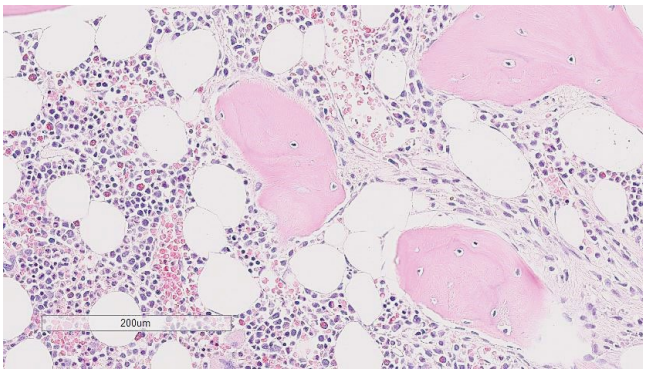
Case description

We describe a male patient, 1968 year of birth. The disease manifested at the age of 22 years with single monomorphic rash elements throughout the body, without involvement of the face, palmar and plantar parts of the arms and feet, respectively with Darier sign (skin becomes swollen, itchy and red after physical exposure at the point of contact), on symptomatic therapy with H1-histamine blockers (ketotifen and cetirizine) with partial response. Upon visit to RM Gorbacheva Research Institute of Pediatric Oncology, Hematology and Transplantology (July 2021), there were no deviations from the clinical blood test, with hepatomegaly shown at ultrasound examination (not palpable under the right costal arch), increased tryptase levels (>200 μg/mL Upon the bone marrow sample examination, high mast cell contents (10%), the features of dysgranulopoiesis and dyserythropoiesis, 46XY karyotype, KIT D816V mutation (allele burden,16.6%) were revealed. When examining bone marrow biopsy with immunohistochemistry (IHC), the following markers were found: >30% of the cells in the infiltrate were MS, CD117 +, MCTrypt +, CD25 +, CD2 +/- (Fig. 1 A, B). In view of all B-signs (high mast cell burden on BM biopsy: >30% infiltration by mast cells (focal, dense aggregates) and serum total tryptase level >200 ng/ml; signs of dysplasia or myeloproliferation, in non-mast cell lineage(s). There were, however, no sufficient criteria for definitive diagnosis of an associated hematological neoplasm (AHN), with

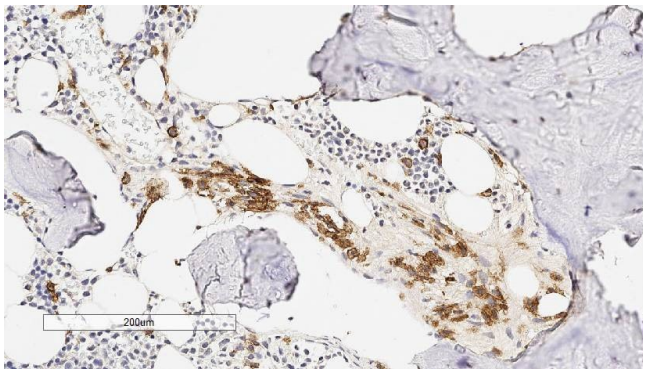
normal or only slightly abnormal blood counts. Moreover, hepatomegaly is not accompanied by altered liver function, palpable splenomegaly proceeds without hypersplenism, and/or lymphadenopathy upon palpation or visualization, however, in absence of C-signs (bone marrow dysfunction caused by neoplastic mast cell infiltration, manifesting by ≥1-lineage cytopenia(s); palpable hepatomegaly with impairment of liver function, ascites and/or portal hypertension; skeletal involvement with large osteolytic lesions with/without pathological fractures; palpable splenomegaly with hypersplenism; malabsorption with weight loss due to gastrointestinal mast cell infiltrates) [3]. On this basis, smoldering systemic mastocytosis was diagnosed, with KITD816V (+) mutation, 46XY karyotype, and typical skin damage registered from 07/2021. Continuous therapy with H1-histamine blockers was prescribed. 3 months later, an increased frequency of upper respiratory tract infections was noted. According to the results of repeated bone marrow puncture, 20% of mast cells were revealed in the bone marrow, which, in the absence of C-signs (without cytopenia, organ dysfunctions, malabsorption, skeletal involvement), and absence of mast cells in leukocyte formula fits the criteria of chronic mast cell leukemia (CMCL). This disorder is a rare form of SM that requires immediate targeted therapy and making a decision on allogeneic hematopoietic stem cell transplantation (HSCT) [4]. Due to lack of compatible donors, the feasibility of haploidentical HSCT still remains in question. Nonhematological toxicity (diarrhea) of 3rd degree, which is controlled by loperamide, was observed upon initiating therapy with midostaurin (200 mg/day). By the 3rd month of therapy, a clinical improvement was seen, in presenting as reduced bone marrow infiltration with MS from 20% to 5.8%, the KITD816V allelic mutation load decreased from 12.46 to 5.2% in BM, like as blood reduced serum tryptase (from 186 to 50 μg/mL) accompanied by partial resolution of skin lesions (Fig. 2B).

Discussion

Like as any other chronic myeloproliferative disease, SM may undergo progression to more unfavorable forms, e.g., ASM and MCL [5, 6] thus requiring immediate treatment

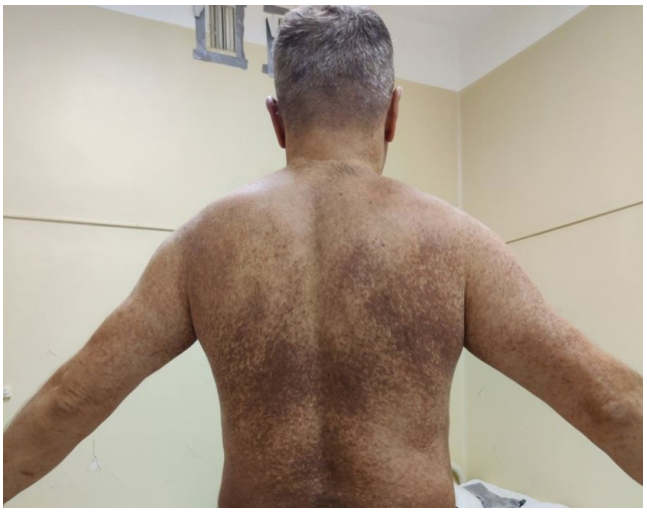


A

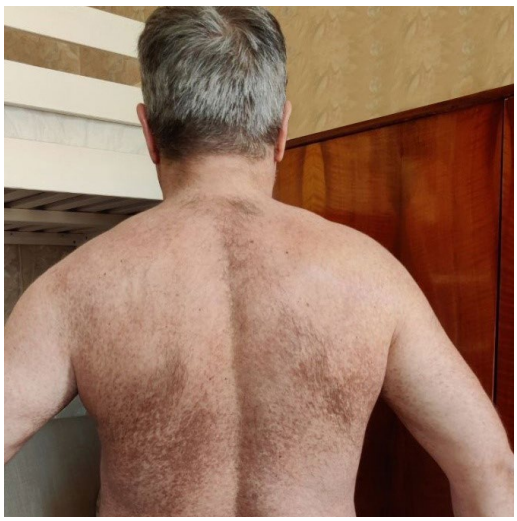


B

Figure 1. The bone marrow (BM) biopsy (H&E staining) (A); IHC staining CD117 in mast cells in BM (B). The microphotographs are presented by Prof. V. Baikov



A



B

Figure 2. Patient with the skin lesion before target therapy (A). B, Same case, after 3 months of treatment

(chemotherapy, therapy with inhibitors of FLT3- tyrosine kinases, HSCT). Currently, patients with smoldering systemic mastocytosis do not receive specific anti-tumor treatment in absence of symptoms/tumor proliferation syndromes. Potential treatment options in these cases include therapy with tyrosine kinase inhibitors imatinib, dasatinib [7], interferon alpha [8], hydroxycarbamide [7], which, however, show limited efficacy, and cannot affect the risk of potential transformation to ASM and MCL. Therapy with midostaurin FLT3-inhibitor is indicated in aggressive forms of SM and mast cell leukemia. Midostaurin is a small molecule affecting the KIT-kinase signaling activity. It inhibits aberrant signal transmission by KIT kinase, thus causing decreased cell proliferation and histamine release, as well as induction of mast cell apoptosis [9]. It should be noted that the drug is effective both in presence of a KITD816V mutation as well as without this mutation. In addition, midostaurin inhibits IgE-mediated release of histamine from basophils and mast cells, thus potentially reducing the severity of symptoms mediated by mast cell mediators and alleviating organ damage [10]. Thus, midostaurin is currently the first targeted drug that has shown efficacy in the treatment of systemic mastocytosis. For comparison, therapy with other drugs, such as cladribine and interferon alpha, imatinib was accompanied by lower frequency and duration of clinical response [11]. Prognosis in the case of mast cell leukemia in historical group was poor with median survival of only 2 months [7]. The result of study D2201 showed that the overall response rate in advanced systemic mastocytosis was 60% (95% confidence interval [CI], 49 to 70) with 45% of the patients showing a major response. Among 16 patients with mast-cell leukemia, the median overall survival was 9.4 months (95% CI, 7.5 to non-estimated) [12]. The overall response rate in the study A2213 was 69% (major/partial response: 50/19%), with clinical benefit in all advanced SM variants. Median overall survival was 18.5 months for MCL patients [13]. Therefore, the use of midostaurin as a monotherapy of mastocytic neoplasias is of great clinical interest.

Conclusion

Systemic mastocytosis is a heterogeneous and rare disease among other hematological neoplasms, with a complex polymorphic clinical picture that makes it difficult to diagnose and start therapy. There is a risk of ISM and SSM progression to advanced step (ASM, MCL and SM-AHN) requiring immediate therapy, thus and which determining the need for lifelong monitoring and invasive studies (BM puncture, trepanobiopsy). A dynamic follow-up of the patient is planned, followed by a decision on allogeneic bone marrow transplantation.

Conflict of interest

None declared.

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Прогрессия «тлеющего» системного мастоцитоза в хронический тучноклеточный лейкоз (клинический случай)

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Резюме

Нами приводится описание редкого случая прогрессии «тлеющего» системного мастоцитоза в тучноклеточный лейкоз. Проведено лечение злокачественного заболевания с применением таргетной терапии и достижением клинического ответа в течение 3 месяцев лечения.

Ключевые слова

Системный мастоцитоз, тучные клетки, аллогенная трансплантация костного мозга.