ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Efficacy of midostaurin in systemic mastocytosis: a case report

Eficácia da midostaurina na mastocitose sistêmica – um relato de caso

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ABSTRACT

A 63-year-old female presented with an approximately 20-year history of systemic mastocytosis, which had become aggressive over the past 10 years. She experienced almost daily episodes of gastrointestinal and vasomotor manifestations. After multiple treatment attempts, she was started on midostaurin, a multikinase inhibitor. At 6 months of therapy, satisfactory control of symptoms was achieved, with a nearly 50% reduction in serum tryptase and complete resolution of cutaneous lesions.

Keywords: Systemic mastocytosis, tryptases, anaphylaxis, osteolytic lesions, malabsorption syndromes, multikinase inhibitor, midostaurin.

RESUMO

Paciente do sexo feminino, com 63 anos de idade, portadora de mastocitose sistêmica há cerca de 20 anos, sendo agressiva há 10 anos. Crises quase diárias com manifestações do trato gastrointestinal e vasomotoras. Após diversas tentativas de tratamento, iniciou uso de midostaurina, um inibidor multiquinase. Depois de 6 meses de uso, observou-se bom controle dos sintomas, diminuição em quase 50% da triptase sérica e desaparecimento completo das lesões cutâneas.

Descritores: Mastocitose sistêmica agressiva, triptase, anafilaxia, lesão osteolítica, síndrome de má absorção, inibidor multiquinase, midostaurina.

Introduction

Mastocytosis encompasses a group of disorders characterized by an abnormal proliferation and accumulation of clonal, neoplastic mast cells in several organs. Among these, systemic mastocytosis is the most severe form. It primarily affects adults, presenting with extracutaneous involvement and sometimes leading to dysfunction of one or more organs.[1-2] The estimated incidence of this condition is 4-5 cases per 1 million people annually.[3] Clinical manifestations are triggered by the release of vasoactive mediators and the damage caused to organs due to the infiltration of neoplastic mast cells.[4]

Most cases of systemic mastocytosis are associated with somatic gain-of-function mutations in the *KIT* gene, predominantly the D816V mutation. CD117 is a type III receptor tyrosine kinase that plays a crucial role in the normal development of mast cells. The interaction between *KIT* and its ligand (the stem cell factor) is fundamental in regulating mast cell proliferation, maturation, adhesion, chemotaxis, and survival.[4]

The aggressive form of systemic mastocytosis can manifest with a range of symptoms, including malabsorption syndrome with weight loss, hepatomegaly and/or splenomegaly with dysfunction of these organs, severe cytopenias, and osteolytic lesions, typically accompanied by significantly elevated serum tryptase levels. This condition is associated with

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a poor prognosis, with a median overall survival of only 3.5 years.[5]

The therapeutic approach for systemic mastocytosis should be individualized. Symptomatic treatment involves the use of H1 and H2 histamine receptor antagonists, leukotriene receptor antagonists, and mast cell stabilizers and aims to control symptoms and prevent recurrence of crises. Topical corticosteroids and calcineurin inhibitors can minimize skin lesions.[4]

Midostaurin is an oral multikinase inhibitor that inhibits D816V-mutated *KIT* and has proven efficacy in controlling systemic mastocytosis.[6] Additionally, this medication also inhibits IgE-dependent histamine release by acting on protein kinase C.[7] Serum tryptase levels and bone marrow involvement are used to monitor the effect of therapy.[8] The most common side effects of this medication are nausea, vomiting, diarrhea, and fatigue, with myelosuppression being the most limiting. Studies show that medication doses are often reduced due to adverse effects.[1]

Imatinib, a competitive inhibitor of a few tyrosine kinases (including *KIT*), does not perform as well as midostaurin, as it inhibits the growth of *KIT* V560G but does not act on cells carrying the *KIT* D816V mutation. Interferon-α (IFN-α), although associated with many side effects and poorly tolerated by many patients, shows only partial control of the disease in the majority of cases.[4]

Case report

A 63-year-old female domestic worker from the city of Osasco, state of São Paulo, Brazil, presented at 39 years of age with a diffuse hyperchromic maculopapular rash, predominantly on the back, which became erythematous with skin friction, heat, and stress, and sometimes was accompanied by pruritus. At age 50, she developed weekly episodes of gastrointestinal symptoms characterized by diarrhea and vomiting, associated with vasomotor symptoms such as flushing and hypotension. The condition worsened with the use of opioids and nonsteroidal anti-inflammatory drugs (NSAIDs), leading to multiple visits to the emergency room. At 56, she was hospitalized for anaphylaxis without a defined trigger, requiring orotracheal intubation. She denied being stung by an insect of the *Hymenoptera* order.

After being hospitalized at 58, a hypothesis of systemic mastocytosis was raised. A skin biopsy of the back was performed, and immunohistochemistry revealed regions in the dermis with dense infiltration of cells suggestive of mast cells, which were positive for CD117 (c-kit) and negative for CD2. To complete the diagnosis, a bone marrow biopsy was performed on the same occasion, which revealed hypercellular marrow (90%) with peritrabecular spindle cell infiltrate (40%) suggestive of mastocytosis, which was positive for CD117 (c-kit) and negative for CD2.

Three months later, the patient was admitted to a tertiary hospital under the care of the Clinical Immunology and Allergy team for further diagnostic workup. A positron emission tomography-computed tomography scan (Figure 1) for staging revealed glucose hypermetabolism in the axial and appendicular skeleton, with altered bone texture and both lytic and blastic lesions (SUVmax: 3.1 in the left proximal tibia). Abdominal ultrasound with Doppler showed parenchymal liver disease with signs of portal hypertension and portosystemic collateral pathways, as well as homogeneous splenomegaly. Liver biopsy revealed septal and perisinusoidal fibrosis with increased mast cells, which were positive for CD20, CD3, CD30, and CD117. Upper endoscopy and colonoscopy were normal. Finally, bone myelogram revealed an infiltrate of mast cells positive for CD117, CD25, and CD2 on immunohistochemistry.

The diagnosis of aggressive systemic mastocytosis was confirmed, involving the liver, bone marrow, skin, and bones. Treatment was proposed to control symptoms with loratadine 10 mg every 12 hours and ranitidine 150 mg every 12 hours. The patient was also advised to avoid medications such as opioids and NSAIDs and given an anaphylaxis action plan. However, the patient continued to experience daily episodes of diarrhea, vomiting, flushing, and hypotension, along with severe bone pain, and frequently used celecoxib.

At follow-up, the patient had developed a challenging cutaneous condition,[8] characterized by an erythematous papular rash with pruritus on the upper and lower limbs and the areolar, cervical, and abdominal regions, which also affected her husband. Skin scrapings confirmed the presence of *Sarcoptes scabiei* in both of them. Treatment with two doses of ivermectin 6 mg given 14 days apart and topical permethrin lotion 50 mg/mL led to complete resolution of scabies (Figure 2).

For the aggressive systemic mastocytosis, the Hematology team first attempted treatment with the tyrosine kinase inhibitor imatinib 400 mg/day

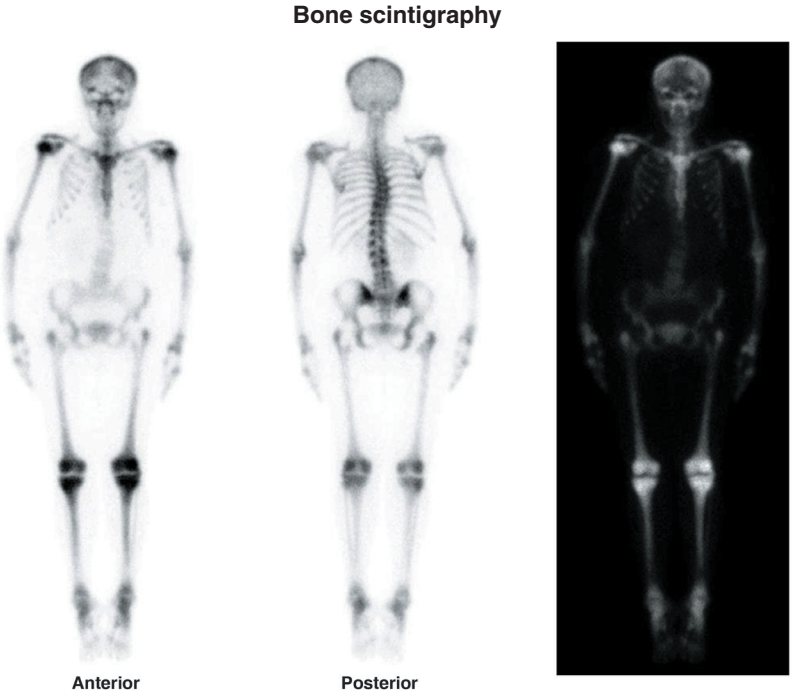

Figure 1
Anterior and posterior whole-body scan images with 99mTc-MDP revealing, in addition to hypointense areas in the proximal thirds of the femurs compatible with metal prostheses, diffuse hyperconcentration of the radiotracer in the axial and appendicular skeleton, suggestive of infiltration lesions

orally, which was discontinued after 4 months due to worsening gastrointestinal symptoms, anemia, asthenia, and lack of appetite. Subsequently, treatment with 3 million units of interferon-α 2b administered subcutaneously twice a week was started but stopped after 1 year and 7 months due to unavailability of the medication. The patient underwent a course of oral prednisone 60 mg/day but continued to have daily symptoms of flushing, hypotension, holocranial headache, and pruritus, along with weekly episodes of abdominal pain. The level of serum tryptase during this period was 200 µg/L.

In October 2022, at age 61, the oral multikinase inhibitor midostaurin (25 mg every 12 hours) was introduced. Three months later, the patient showed significant improvement, with milder and less frequent symptoms and a reduction in skin lesions. Attempts to increase the dose to 200 mg/day, as suggested for the treatment of advanced mastocytosis, were met with gastrointestinal intolerance characterized by severe nausea. A dose of 150 mg/day, taken twice daily, was tolerated by the patient.

After 6 months of continuous medication use, serum tryptase levels decreased to 118 µg/L. The patient experienced complete remission of skin lesions (Figure 3) and significant clinical improvement, with episodes characterized by mild symptoms of nausea, abdominal pain, flushing, and holocranial headache occurring every 10-15 days without the need for emergency care (Table 1).

Discussion

Midostaurin was shown to be effective in the treatment of patients with aggressive systemic mastocytosis due to its action as a multikinase inhibitor, including mutated KIT receptor and protein kinase C. Our patient had significant symptom improvement, a nearly 50% reduction in tryptase levels, and complete remission of skin lesions after

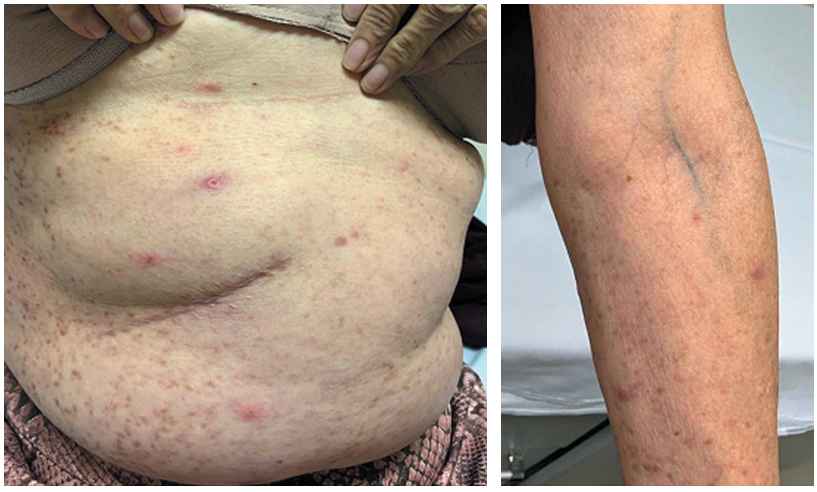

Figure 2
Erythematous papules with microvesicles in the abdominal region and left upper limbs (scabies) and brownish erythematous maculopapular rash (mastocytosis)

6 months of medication use, with management of side effects by dose reduction. The case described in this report illustrates the short-term efficacy and safety of midostaurin in treating aggressive systemic mastocytosis.

Although there are no direct treatment comparisons, a review of scientific evidence suggests the superiority of midostaurin in the survival of patients with advanced systemic mastocytosis compared with other traditionally used cytoreductive agents.[9] A real-world study from France reported a 1-year overall survival rate of 83%.[10] Additionally, studies have demonstrated the capacity of midostaurin to reverse organ damage, reduce splenomegaly and bone marrow mast cell burden, and provide benefits regarding patient-reported symptoms and quality of life.[11] Nausea, vomiting, and diarrhea are the most commonly encountered adverse effects of this medication, usually managed with symptomatic treatment and administration of midostaurin with meals.[11]

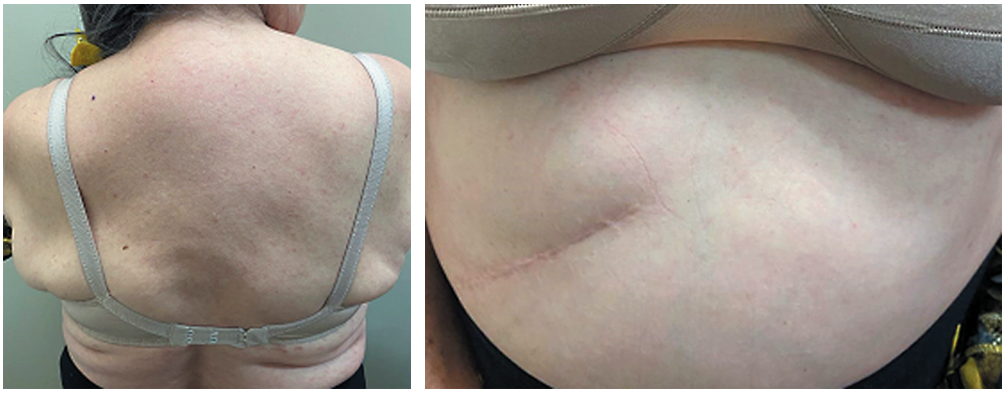

Figure 3
Skin of the back and abdomen showing remission of mastocytosis lesions after treatment with midostaurin

Table 1
Clinical and laboratory characterization before the use of midostaurin and after 6 months of using the medication

Parameter	Pre-medication	6 months after midostaurin use
Skin examination	Disseminated brownish erythematous maculopapular lesions	Absence of skin lesions
Symptoms	Daily gastrointestinal tract symptoms and vasomotor symptoms	Mild gastrointestinal symptoms that improved with symptomatic treatment
Tryptase (µg/L)	200	118

References

1. Pardanani A. Systemic mastocytosis in adults: 2021 Update on diagnosis, risk stratification and management. Am J Hematol. 2021;96(4):508-25.
2. Burgard C, Rosar F, Khreish F, Ezziddin S. Systemic Mastocytosis Treatment with Midostaurin: [18F]FDG PET/CT as a Potential Monitoring Tool for Therapy Outcome. Diagnostics (Basel). 2022;12(3):680.
3. Miettinen M, Lasota J. KIT (CD117): a review on expression in normal and neoplastic tissues, and mutations and their clinicopathologic correlation. Appl Immunohistochem Mol Morphol. 2005;13(3):205-20.
4. Velloso EDRP, Padulla GA, de Cerqueira AMM, de Sousa AM, Sandes AF, Traina F, et al. Diagnosis and treatment of systemic mastocytosis in Brazil: Recommendations of a multidisciplinary expert panel. Hematol Transfus Cell Ther. 2022;44(4):582-94.
5. Lim KH, Tefferi A, Lasho TL, Finke C, Patnaik M, Butterfield JH, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood. 2009;113(23):5727-36.
6. Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, et al. Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis. N Engl J Med. 2016;374(26):2530-41.
7. Krauth MT, Mirkina I, Herrmann H, Baumgartner C, Kneidinger M, Valent P. Midostaurin (PKC412) inhibits immunoglobulin E-dependent activation and mediator release in human blood basophils and mast cells. Clin Exp Allergy. 2009;39(11):1711-20.
8. Perez IL, Giavina-Bianchi M, Mamede LQ, Antila HG, Pereira GF, Kalil J, et al. Escabiose mascarada por mastocitose sistêmica. Arq Asma Alerg Imunol. 2020;4(1):141-4.
9. Chandesris MO, Damaj G, Canioni D, Brouzes C, Lhermitte L, Hanssens K, et al.; CEREMAST Study Group. Midostaurin in Advanced Systemic Mastocytosis. N Engl J Med. 2016;374(26):2605-7.
10. Rossignol J, Nizard S, Blanc AS, Filipovics A, Lortet-Tieulent J, Bouktit H, et al. Therapeutic management and outcome of patients with advanced systemic mastocytosis treated with midostaurin: A comprehensive real-life study in the French national healthcare database. Hematol Oncol. 2022;40(5):1030-40.
11. Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, et al. Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis. N Engl J Med. 2016;374(26):2530-41.

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