Aggressive systemic mastocytosis with diffuse skin erythema showing response to midostaurin

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INTRODUCTION

Advanced systemic mastocytosis (advSM) is characterized by presence of the *KIT* D816V mutation and pathologic accumulation of neoplastic mast cells (MCs) in various tissues, leading to severe symptoms and organ damage (eg, cytopenias, liver dysfunction, portal hypertension, malabsorption, and weight loss). Treatment with midostaurin, an orally active multikinase/KIT inhibitor now approved for advSM, resulted in a high rate of response accompanied by reduced MC infiltration of the bone marrow and lowered serum tryptase level[1]. Patients with SM often have cutaneous involvement, which is characterized by erythaematous-brown fixed maculopapular lesions. Adults with ISM usually manifest monoporphic maculopapular lesions, whereas children with CM develop polymorphic maculopapular lesions. Maculopapular skin lesions observed in patients with ISM and those with CM also occur in patients with advanced SM. It is estimated that approximately 80% of patients with ISM exhibit skin lesions compared with only approximately 50% of patients with advanced SM[2]. We report a case of patient with aggressive systemic mastocytosis and significant cutaneous involvement that showed symptoms control and lightening of the lesions with midostaurin treatment.

CASE REPORT

A 45-year-old male from the countryside of Sao Paulo - Brazil, who was diagnosed with Systemic Mastocytosis several years ago, presents with an episode of anaphylaxis. Follow-up began in 2007, with tryptase elevation and immunohistochemical bone marrow biopsy showing several anomalous mast cells associated with positive CD2 and histological findings compatible with Systemic Mastocytosis. The patient had progressive clinical worsening, in addition to PET/CT on 02/21/2020 showing involvement of multiple abdominal and cervical lymph nodes, and involvement of the bone marrow of the axial and appendicular skeleton. We have used positron emission tomography (PET-CT) in patients with advanced systemic mastocytosis to assess the degree of involvement of various organs infiltrated by mast cells. The patient also had significant vomiting and diffuse abdominal pain. Upper digestive endoscopy of 09/14/2020 showed erosive esophagitis, hypertrophy of gastric folds, enanthematous pangastritis, and area of irregularity of the duodenal bulb mucosa. Interferon alfa was administered for 6 months, but an important and limiting adverse reaction of syncope required modification of therapy. Interferon alfa was replaced by imatinib 400 mg/day and high dose antihistamines, with partial response at the beginning of treatment. We could not perform the genetic study of our patient.

Then there was disease progression, with increase in symptoms, serum tryptase of 223, worsening of the diffuse skin erythema. Imatinib was suspended due to therapeutic failure.

Midostaurin 100 mg twice daily was started. The patient had nausea and it was necessary to ad ondansetron to the therapy. The patient has been using the medication for 10 months, with control of systemic symptoms and improvement of skin lesions.

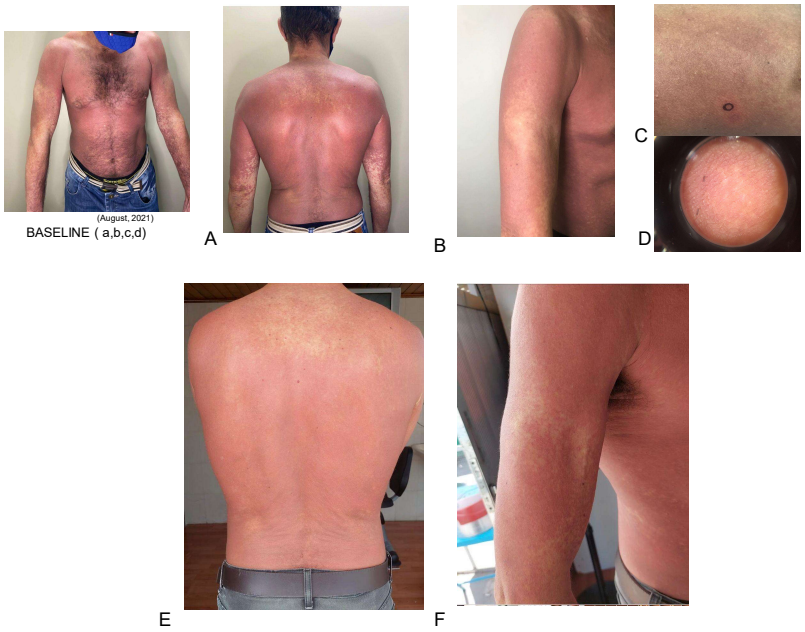

***Figure 1**. Phototype III (Fitzpatrick,1988) (**a**) and (**b**) **Baseline** - diffuse brownish erythematous rash on trunk, upper limbs; (**c**) Darier's sign before skin biopsy (**d**) Dermoscopy : homogeneous erythematous pattern (**e**) And (**f**) **10 months later** -* clearing of diffuse erythema of the skin with midostaurin treatment, 100 mg twice daily.

DISCUSSION

Clinical efficacy and safety of oral midostaurin at a dose of 100 mg twice daily was demonstrated in a clinical trial with 116 patients. 89 were included in the primary efficay population for having organ damage as a result of mast cell infiltration. Among these, 16 had aggressive systemic mastocytosis, 57 had systemic mastocytosis with associates hematologic malignancy, and 16 had mast cell leukemia. The overall response rate was 60% (95% CI, 49 to 79); 45% of the patients had a very relevant response, which was defined as complete resolution of at least one type of mastocytosis-related organic lesion. The median percentage of reduction in bone marrow mast cell load and serum tryptase level were - 59% and - 58%, respectively.[3] Patients had improved quality of life and symptoms associated with mast cell mediators. [1,2,3,4]

Midostaurin constitutes a therapeutic advance for patients with systemic advanced mastocytosis, allowing disease control, decreasing symptoms, and improving quality of life in a relevant proportion of patients. The presente case illustrates midostaurin efficacy and safety.

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