CASE REPORT

A case of aggressive systemic mastocytosis with bulky lymphadenopathy showing response to midostaurin

Mariarita Sciumè[1] (iD) | Fabio Serpenti[2] | Simona Muratori[3] | Valerio Pravettoni[4] |
Fabio Massimo Ulivieri[5] | Giorgio Alberto Croci[6] | Anna Chiara Migliorini[7] |
Andrea Esposito[8] | Maria Cecilia Goldaniga[1] | Giorgia Natascia Saporiti[1] |
Giulia Galassi[1] | Luca Baldini[1,2] | Francesco Onida[1,2] | Federica Irene Grifoni[1]

[1]Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[2]Università degli Studi di Milano, Milan, Italy

[3]Dermatology Unit, Department of Physiopathology and Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[4]U.O.C. General Medicine-Immunology and Allergology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[5]Nuclear Medicine, Bone Metabolic Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[6]Division of Pathology, Department of Pathophysiology and Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[7]Laboratorio di Ematologia, Servizio di immunoematologia e trasfusionale, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[8]Division of Radiology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Correspondence
Mariarita Sciumè, Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
Email: mariarita.sciume@policlinico.mi.it

Abstract

Management of systemic mastocytosis is an emerging challenge which requires a multidisciplinary diagnostic approach and personalized treatment strategy. Midostaurin can rapidly reduce the disease burden, also in cladribine refractory cases.

KEYWORDS

bulky lymphadenopathy, midostaurin, purine analogue, systemic mastocytosis

1 | INTRODUCTION

Systemic mastocytosis (SM) can be extremely heterogeneous and its treatment should be highly individualized. We reported a description of clinical management of an aggressive SM characterized at diagnosis by multiple organ involvement. The patient underwent to different lines of treatment, from standard chemotherapy to the novel tyrosine kinase inhibitor midostaurin.

Systemic mastocytosis (SM) results from a clonal proliferation of abnormal mast cells (MCs) in extracutaneous organs. It could be divided into indolent SM (ISM), smoldering SM (SSM), SM with an associated hematologic (non-MC lineage) neoplasm (SM—AHN), aggressive SM (ASM), and mast cell leukemia (MCL).[1-3]

Clinical features of SM could be related to MC mediator release or to uncontrolled growth and infiltration of clonal MCs in different organs.[2-5] The latter clinical features are divided into B findings (>30% MC infiltration on bone marrow biopsy and serum total tryptase level > 200 ng/mL, hepatomegaly with normal liver function, palpable splenomegaly without hypersplenism, and/or lymphadenopathy, signs of dysplasia or myeloproliferation in non-MC lineage, but not diagnostic of an associated hematological neoplasm) or C findings (cytopenias such as absolute neutrophil count <1x10^9/L, hemoglobin < 10 g/dl, or platelets < 100x10^9/L, hepatomegaly on palpation with impairment of liver function, ascites, and/or portal hypertension, palpable splenomegaly with hypersplenism, malabsorption within weight loss from gastrointestinal tract MC infiltrates). [2-4] Diagnosis of ISM is established with < 2 B findings and no C findings; when ≥ 2 B findings but no C findings are present, the diagnosis is SSM, and when one or more C findings are detected ASM can be diagnosed. [2-4].

The treatment of adult SM should be highly individualized; while the backbone of therapy in ISM and SSM is symptom management, for aggressive and leukemic forms cytoreductive treatment is indicated. [3,4] Historically, cytoreductive agents include interferon-α and cladribine. [3,4,6,7] Allogeneic stem cell transplant could be considered in SM—AHN when the associated hematologic neoplasm has an indication to transplantation and in ASM patients with relapsed/refractory disease or in those with acute MCL. [8]

With the advent of the tyrosine kinase inhibitors (TKIs) era, many efforts have been made to find proper inhibitor of SM KIT–driver mutation. Midostaurin has been shown to induce major clinical responses with improvement or disappearance of one or more C-findings, a decrease in the MC burden, organomegaly, and mediator-related symptoms. [9]

Hereby, we report an extended description of a real-life management of an ASM patient conditioning bulky lymphadenopathy who has undergone to multiple lines of treatment.

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013.

2 | CASE REPORT

In 2009, a 30-year-old Caucasian man was referred to our Center for a ten-year history of maculopapular rash, intractable itching, flushing, and a six-month history of diarrhea (3-4 bowel movements per day with loose stools associated to a < 10% weight loss). The medical history was otherwise unremarkable, except for a non-steroidal anti-inflammatory drug-induced anaphylaxis.

Complete blood count, common coagulation, liver, and renal function tests were in a normal range. A computed tomography (CT) scan showed diffuse lymphadenopathy (up to 4 cm) and mild hepatosplenomegaly. The screening serum tryptase level was 209 ng/ml (normal level < 5 ng/ml). Gastric, duodenal, distal ileal, and colonic biopsies revealed a diffuse mucosal mast cell infiltration, with abnormal expression of CD2 and CD25, compatible with SM diagnosis. An abdominal lymph node biopsy also confirmed the SM diagnosis and excluded a lymphoproliferative disease. At bone marrow biopsy, multifocal clusters of spindling mast cells CD25 + were equal to 70% of total cellularity. Aspirate smears showed < 5% of mast cells and a direct sequencing of the KIT gene was positive for the D816V mutation. A total skeleton X-ray was negative for a bone lytic or sclerotic involvement, while osteoporosis was diagnosed on the basis of reduced bone mineral density at dual-energy X-ray absorptiometry scan for which calcium/vitamin D supplements were started. Since the patient presented only B-findings, diagnosis of SSM was made and he was not considered a candidate for a cytoreductive treatment. The patient was instructed to avoid triggers of MC degranulation and therapy with H1-H2 histamine receptor blockers; sodium cromolyn was started with a symptomatic purpose for itching and diarrhea obtaining a good control.

During the follow-up, patient's general conditions slowly worsened with the appearance of a pathological weight loss (>10%), a more severe diarrhea and a progressive enlargement of abdominal lymph nodes, liver, and spleen. In April 2017 confluent abdominal lymphadenopathy had a maximum diameter of 6 cm, conditioning appearance of ileal displacement and ascites due to SM liver involvement (histologically confirmed). Liver and spleen had a diameter of 24 and 17 cm, while bone marrow involvement remained unchanged as for biopsy and morphology. Blood count was normal and serum tryptase level raised to 332 ng/ml. We concluded for aggressive evolution of SM. First line cytoreductive therapy was started in April 2017 with subcutaneous cladribine 0.14 mg/Kg per day for 5 days per cycle. A total of 5 cycles every 6 weeks were administered. Therapy was overall well tolerated and no grade 3/4 hematologic toxicities were observed.

By the end of the fifth cycle the disease had not yet reached a response with persistence of symptoms, 60% of MC involvement at bone marrow biopsy, and stable lymphadenopathy and hepatosplenomegaly. Serum tryptase level was 173 ng/ml.

From December 2017 midostaurin was obtained through an expanded access use and started at a dosage of 25 mg twice daily, gradually increased to 100 mg every 12 hours daily.

Rapidly after starting midostaurin, the patient experienced a considerable improvement of general condition, clinical symptoms, and body weight. After 3 months of midostaurin therapy, a bone marrow biopsy highlighted the reduction of MC infiltration to 30%-40%, lymphadenopathy decreased to a diameter of 27 mm, hepatic and splenic diameter were 22

and 13 cm. Serum tryptase was 26 ng/ml. Unfortunately, the CT scan allowed to incidentally diagnose a subclinical pulmonary embolism of a segmental artery in the superior left lobe. Pulmonary embolism is reported among adverse events during midostaurin treatment; therefore, we stopped the TKI treatment and start anticoagulant therapy. Midostaurin was safely resumed one month later; evaluation at 6 months showed only 10% of MC in the bone marrow biopsy and further reduction of lymphadenopathy to a maximum diameter of 22 mm. Figures 1 and 2 respectively show the reduction of bone marrow MCs infiltrate and organomegaly over time.

Today the patient is still on midostaurin 100 mg bid, completely asymptomatic and with good tolerance to the therapy.
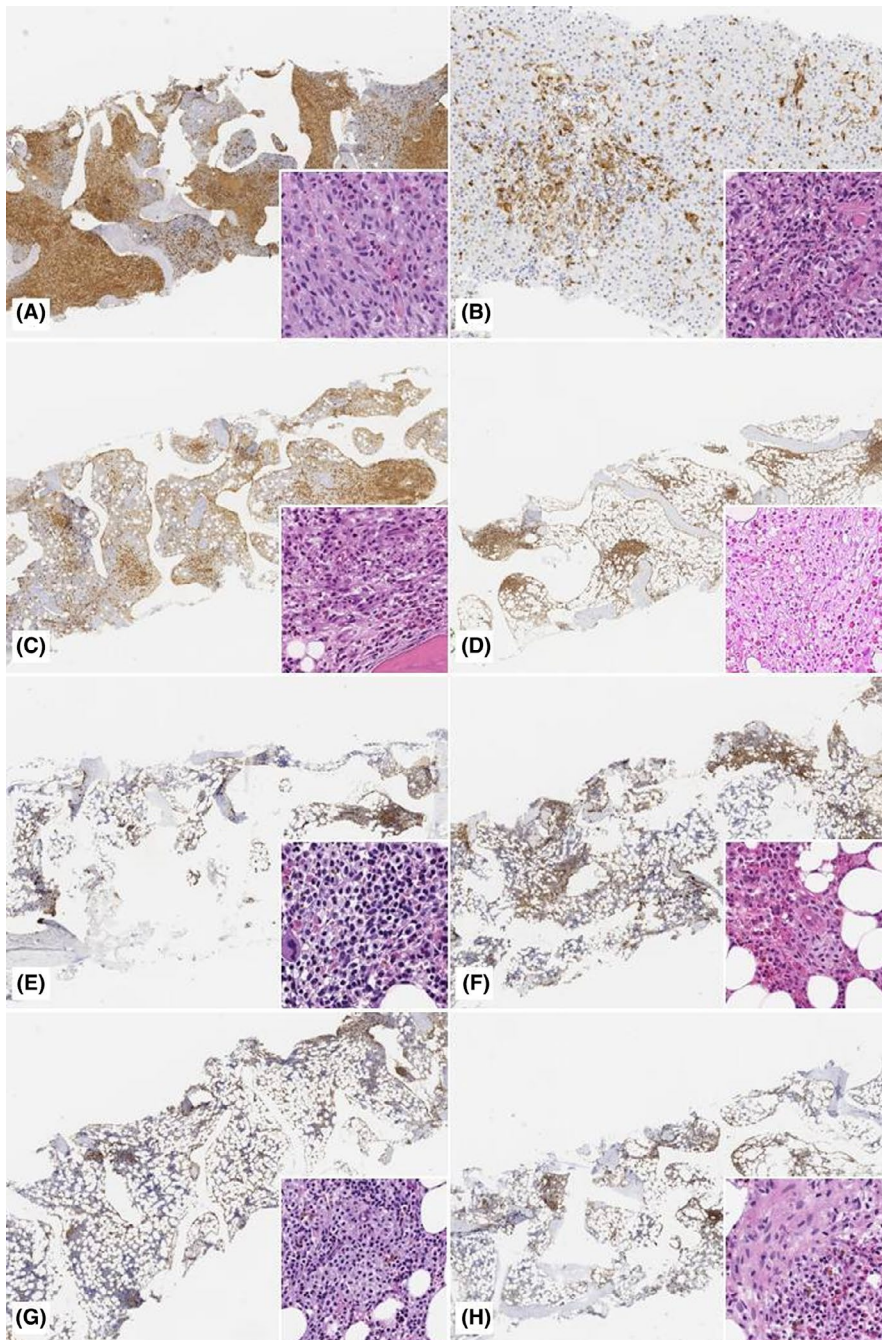

FIGURE 1 A, Bone marrow biopsy (tryptase, 4×) at diagnosis showing hypercellularity due to extensive infiltration by a tryptase positive mast cell proliferation, featuring spindle to ovoidal morphology (inset; Hematoxylin-Eosin, 20×); B, concurrent hepatic biopsy (tryptase, 10×) showing a tryptase-positive cellular infiltrate in the portal spaces and within the sinusoids, composed of spindle to ovoidal mast cells admixed with eosinophils (inset);sequential biopsies (tryptase, 4×; inset, Hematoxylin-Eosin, 20×) show progressive reduction of the tryptase-positive mast cell burden, corresponding to C, December 2017, D, March 2018, E, July 2018, F, January 2019, G, June 2019, and H, January 2020
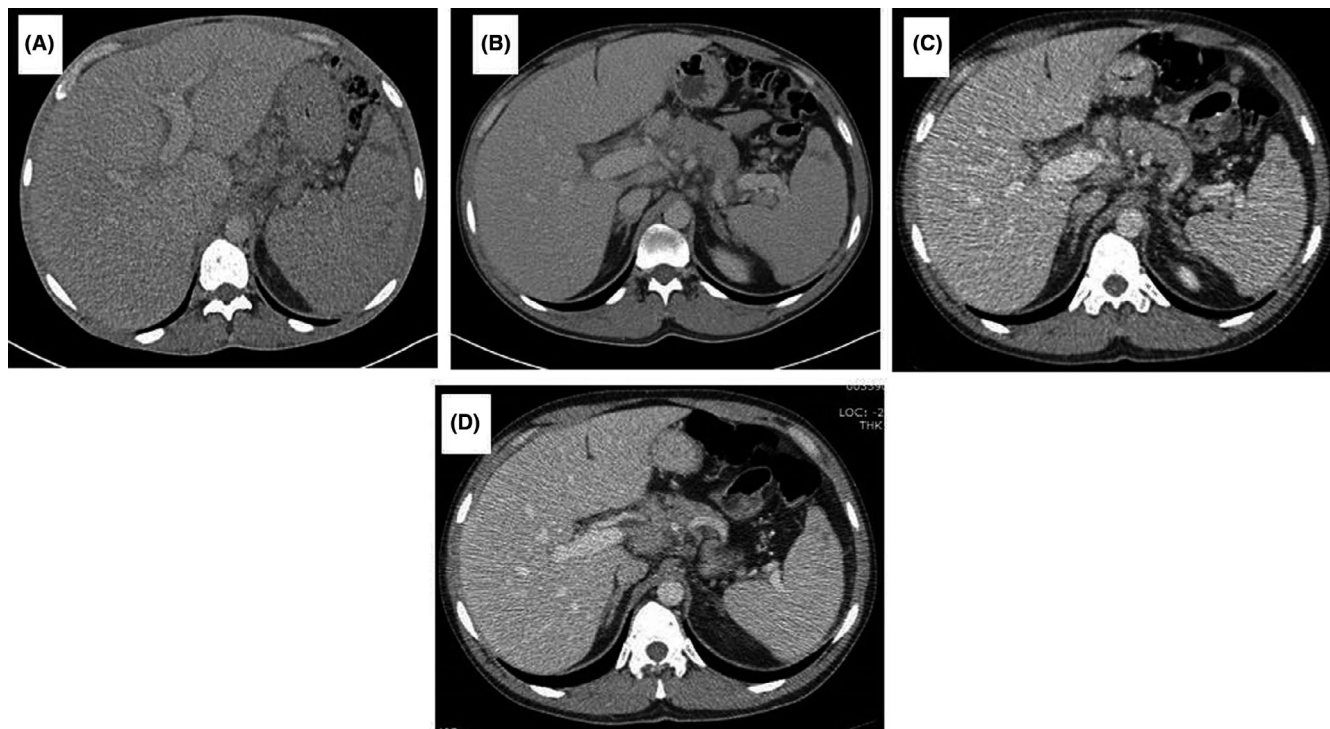
FIGURE 2 Computed Tomographic Scan shows hepatosplenomegaly and abdominal lymphadenopathy A, at cladribine start, B, after 3 mo from midostaurin start, C, after 12 mo from midostaurin start, D, after 24 mo from midostaurin start

A human leukocyte antigen typing was performed, but allogeneic stem cell transplant isn't currently taken into consideration. At the last assessment (February 2020) maximum diameter of abdominal lymphadenopathy and spleen were 1.5 and 13 cm, serum tryptase level was 27 ng/ml, and bone marrow MCs have stabilized on 10% of the global cellularity. The response was classified as partial according to Gotlib et al [10]

For the clinical management of a SM patient the most relevant questions are whether the patient has or develops advanced SM and what treatment can be applied. Although the risk is relatively low, patients with ISM may progress to ASM, SM-AHN, or MCL. [1-5].

Here, we report the gradual evolution of an SSM case in ASM, characterized by hepatomegaly with impairment of liver function and ascites, splenomegaly, and abdominal lymphadenopathy with ileal displacement.

According to the current guidelines, ISM therapy is generally focused on symptom relief. [3,4] All patients should be advised to avoid any potential triggers (food, drinks, drugs) that may provoke MCs activation. High risk patients are advised to carry epinephrine self-injector-pens. Treatment options include histamine H1/H2-blockers, sodium cromolyn, leukotriene inhibitors, topical agents, aspirin, ketotifen, omalizumab, corticosteroids, and MC cytoreductive therapy only in severe/refractory cases. [3,4] In our case, during the smoldering phase, the patient received H1-H2 histamine receptor blockers and sodium cromolyn for itching and diarrhea obtaining a good control.

When an aggressive phase was diagnosed, considering the burden of the disease and the absence of comorbidities, we decided to offer a cytoreductive treatment with cladribine. MC reducing therapy is indicated in advanced SM to prevent further organ damage, extend survival, often at the expense of significant side effects. [6,7] Cladribine was one of the first agent used for symptom relief and rapid MC debulking, with a demonstrated therapeutic activity in all SM subtypes and an overall response rate (ORR) of 50-60%. [6,7] Myelosuppression and lymphopenia are the most frequent adverse events. [6,7] In our case, cladribine was well-tolerated without grade 3/4 toxicities. With the advent of KIT-targeted TKIs, the use of cytoreductive therapy has declined. [3,4] The multikinase inhibitor midostaurin is currently approved for patients with advanced SM. In this population it demonstrated a 60% ORR and a good tolerability with few reported adverse events apart from hematological toxicity, nausea, vomit, and diarrhea. [8]

Our patient received midostaurin after failure of first-line therapy with cladribine. Midostaurin lead to a significant improvement of organomegaly, liver function and body weight; moreover, a substantial reduction in MC burden and mediator-related symptoms were observed, translating into a significant improvement of patient's life quality. This treatment is still ongoing, with almost 2 years of therapy, allowing to obtain and keep a partial response.

In conclusion, mastocytosis is a rare disease with a complex biology and an unpredictable clinical course. The diagnosis and management of MC neoplasms is an emerging

challenge and requires vast knowledge, a multidisciplinary diagnostic approach and personalized treatment strategy.

CONFLICT OF INTEREST

FIG received compensation by Novartis as expert testimony and as a member of advisory board. The remaining authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

MS, FS, MCG, GNS, GG, LB, FO, and FIG provided the patient data regarding the hematological disease; MS, FS, and FIG wrote the manuscript; SM, VP, and FMU provided patient data for what concerns dermatological, allergological, and rheumatological aspects; GAC performed the histological examinations of bone marrow, provided iconographic materials, interpreted these data, and integrated them in the manuscript; ACM revised patient peripheral blood smears; AE provided radiological iconographic material. All authors critically read and approved the final manuscript.

ETHICS STATEMENT

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. Informed written consent for publication was obtained from the patient.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Mariarita Sciumè [ID] https://orcid.org/0000-0001-7958-4966

REFERENCES

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.
2. Horny HP, Metcalfe DD, Akin C, et al., et al. Mastocytosis. In: Swerdlow SH, ed. *WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues*. International Agency for Research and Cancer (IARC): Lyon, France; 2017:62-69.
3. Pardanani A. Systemic mastocytosis in adults: 2019 update on diagnosis, risk stratification and management. *Am J Hematol*. 2019;94(3):363-377.
4. Scherber RM, Borate U. How we diagnose and treat systemic mastocytosis in adults. *Br J Haematol*. 2018;180(1):11-23.
5. Lim KH, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood*. 2009;113:5727-5736.
6. Lim KH, Pardanani A, Butterfield JH, Li CY, Tefferi A. Cytoreductive therapy in 108 adults with systemic mastocytosis: outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorode-oxyadenosine. *Am J Hematol*. 2009;84:790-794.
7. Barete S, Lortholary O, Damaj G, et al. Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. *Blood*. 2015;126:1009-1016.
8. Ustun C, Gotlib J, Popat U, et al. Consensus opinion on allogeneic hematopoietic cell transplantation in advanced systemic mastocytosis. *Biol Blood Marrow Transplant*. 2016;22:1348-1356.
9. Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. *N Engl J Med*. 2016;374(26):2530-2541.
10. Gotlib J, Pardanani A, Akin C, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. *Blood*. 2013;121(13):2393-2401.