



CLINICAL PROBLEM SOLVING

A physician or group of physicians considers presentation and evolution of a real clinical case, reacting to clinical information and data (boldface type). This is followed by a discussion/commentary

Diagnostic and therapeutic challenges in mast cell sarcoma

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1 | CASE PRESENTATION

A 45-year-old woman was diagnosed with “mastocytosis in the skin” in 2010. Her previous medical history was unremarkable. Due to the lack of clinical symptoms and low tryptase level (8.0 µg/L), she did not initially undergo bone marrow biopsy until February 2014 when, after the onset of epigastralgia, a grade 1 esophagitis was documented by endoscopy. A complete diagnostic workout concluded for systemic mastocytosis with *KIT* D816V mutation, indolent variant according to WHO.¹ No osteoporosis was highlighted by DEXA scan. Anti-mediator therapy was started with stability of symptoms at periodical follow-up.

Systemic mastocytosis (SM) encompasses a heterogeneous group of disorders that displays wide variability of clinical manifestations and disease course. The general indication for indolent variant envisions a conservative approach, thus not including cytoreductive treatment, as life expectancy is not impaired significantly.^{2,3} The use of anti-mediators is generally recommended for mildly symptomatic patients. The risk of evolution into an advanced variant does not exceed 5% overall,³ but a watchful wait approach must be adopted to avoid overlooking disease-related complications that might deserve a timely therapeutic intervention. Although a careful monitoring of

C-findings is crucial, it may fail at catching some subtle clinical manifestations resulting from rare modalities of disease evolution.

From 2019, she started complaining of pain at right inferior limb, which was suggestive of lumbar discopathy at L4-L5. In June 2019, she underwent surgery (discectomy L5-S1) with intra-table incidental finding of neoplastic tissue, which was partially excised. A subsequent CT scan revealed a mass (36 × 44 mm), which incorporated the right transverse process of L5 and extended to the conjugation foramina L4-L5 and L5-S1. There was density alteration of L5 and S1 soma from neoplastic infiltration without signs of vertebral collapse. At PET scan, an abnormal accumulation of ¹⁸F¹⁸FDG was revealed in the right paravertebral area at L5 without further pathological accumulation. The histological analysis of the mass documented high-grade malignant neoplasia, with cells of blastic appearance and medium to large size (Figure 1 – Panel A). The cells presented diffuse positivity for CD117 (Figure 1 – Panel B) and CD4, proliferation index (MIB1) about 70–80%, positivity for MYC (45–50%); rare neoplastic cells displayed positivity for tryptase (Figure 1 – Panel C). The histological picture was consistent with a diagnosis of mast cell sarcoma (MCS). The analysis by RT-PCR on DNA extracted from the mass biopsy confirmed *KIT* D816V positivity; on the same sample, no mutations in *SRSF2*, *ASXL1*, and *RUNX1* were detected by NGS.

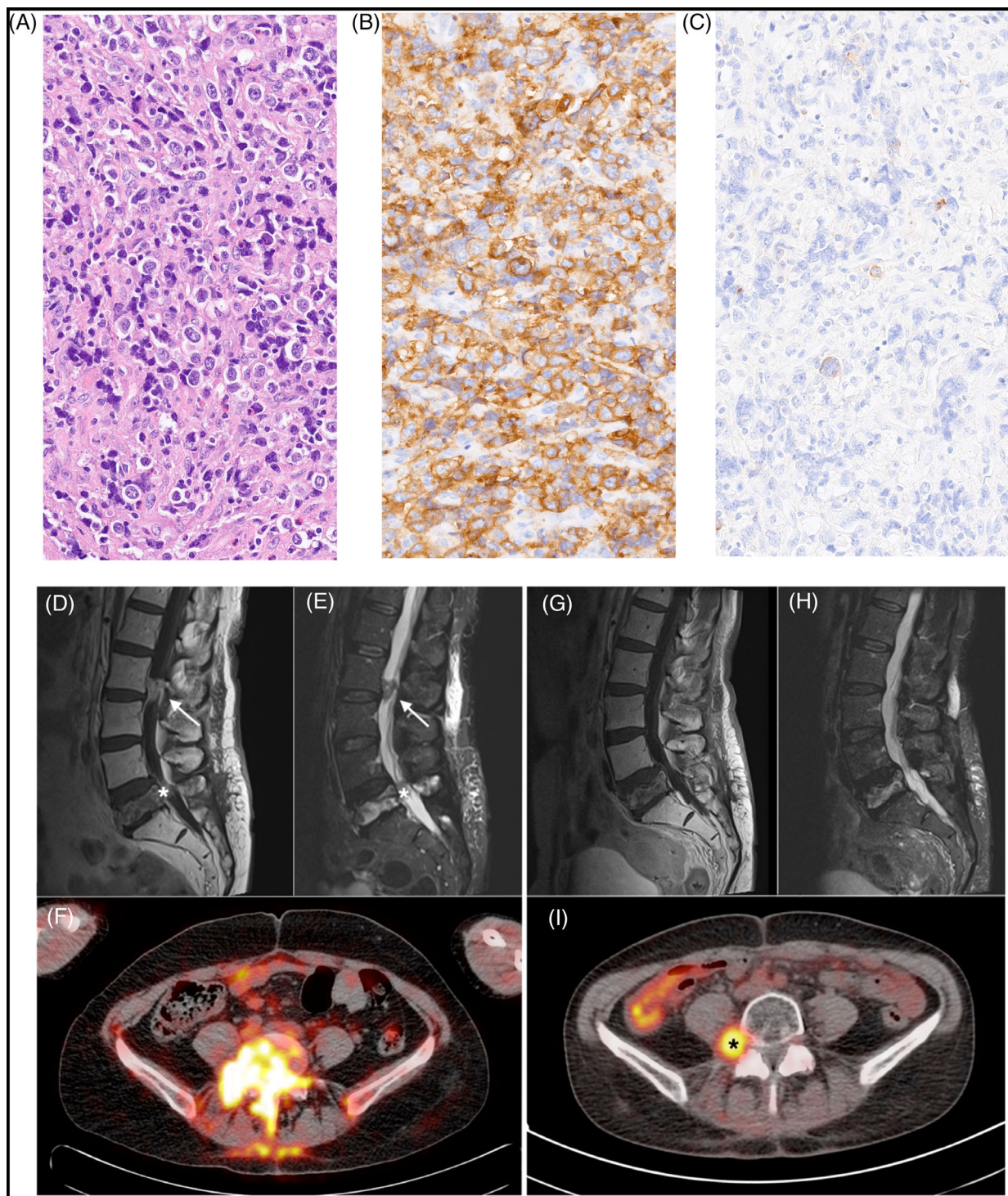


FIGURE 1 Histopathology of the mast cell sarcoma (upper panels) and results from pre and post treatment imaging (lower panels). The histological analysis of the mass documented high-grade malignancy neoplasia, with blastic appearance, extremely heterogeneous cell dimensions (from medium to large) (A). The cells presented diffuse positivity for CD117 (B) and CD4, proliferation index (MIB1) about 70–80%, positivity for MYC (45–50%); rare neoplastic cells displayed positivity for tryptase (C). MRI and ^{18}F FDG-PET imaging obtained before (panels D–F) and 8 months (panels G–I) after the beginning of the therapy with Avapritinib. Sagittal MR contrast-enhanced T1w and STIR images (Panels A–B and G–H) show the complete disappearance of neoplastic tissue in the vertebral canal at the L2–L3 level (white arrow) and a marked decrease of the L5 lesion (white asterisk). ^{18}F FDG-PET imaging (panels F–I) confirmed the partial response of the L5 lesion, with regression of the vertebral involvement and residual hypermetabolic tumor focus (black asterisk) located at the L4–L5 right foramina [Color figure can be viewed at wileyonlinelibrary.com]

On July 2019, a hematologic reassessment was consistent with the persistence of an indolent variant in BM with a mast cell infiltrate consisting of dispersed elements with spindle-shaped morphology. Tryptase level was 7.1 µg/L.

Mast cell sarcoma (MCS) is an exceptionally rare variant of mastocytosis featured by the extra-hematological growth of malignant mast cells, with solid tumor-like tissue infiltration and metastatic capability.^{4,5} The highly atypical morphological appearance of neoplastic cells often presents a risk of misdiagnosis, due to the similarity with carcinoma metastases, anaplastic lymphomas, or histiocytic neoplasms.⁵ The sparse literature shows a dramatic prognosis, also due to the rapid evolution to mast cell leukemia (MCL).^{6,7}

In addition to the classical MCS variant, MCS-like progression of SM can be observed, with persistence of the mutant *KIT* as the driver of the disease (more rarely observed in de novo MCS) and molecular mechanisms of evolution yet to be elucidated.⁸

Due to severe pain, the patient received radiotherapy (DTF 44/44 Gy, fractioning 2 Gy/d for 5 days per week), experiencing transient amelioration of symptoms. A systemic treatment with midostaurin (at 100 mg bid) was initiated in September 2019. After 7 days from starting, a dosage reduction to 50 mg bid was needed due to sinus tachycardia with QT elongation (471 msec), with prompt resolution of cardiac abnormalities. After 3 months of treatment, the MRI demonstrated progressive disease, with neoplastic tissue extending to the vertebral specum, to D12, involving conjugation foramina at L2-L3. Of note, skin involvement significantly improved at clinical examination, with marked lesion darkening and reduction in number.

Due to disease progression, the patient was switched to salvage treatment with 2-CdA 0.13 mg/kg days 1–5 intravenously for two 28-day cycles. An MRI after second cycle showed dimensional increase of previously described neoplastic paravertebral lesions with complete obliteration of conjugation foramina L2-L3 and L4-L5, compression of cauda equina toward L4-L5 laminae, and infiltration of right psoas.

As per clinical picture, the patient had ECOG PS 1, no constitutional symptoms, full hematological recovery from treatment with 2-CdA, but complained of severe pain especially extending from right hip to ipsilateral lower limb, and requiring opioid therapy.

Current therapeutic options are largely inadequate. Localized treatments (surgery and/or radiotherapy) are suitable for management of organ complications but are devoid of long-term disease control. Conventional chemotherapeutic agents established in non-MCS variants, such as cladribine (2-CdA), did not demonstrate appreciable results due to primary resistance.⁴ Polychemotherapy combinations adopting acute leukemia- or lymphoma-like modalities also yielded transitory responses.^{5,9,10} Tyrosine kinase inhibitors represent the emerging therapeutic approach in advanced systemic mastocytosis (SM), with relatively high rate of responses across different variants [either aggressive (ASM), MCL, or SM with associated hematological neoplasms (AHN)], also depending on *KIT* mutant type.^{11–13} However, since clinical trials generally exclude MCS, results cannot be generalized to this patient subset and the efficacy of *KIT* inhibition is generally modest, as far as it can be derived from scattered case reports.^{4,9}

On March 2020, a compassionate use program (CUP) for the *KIT* inhibitor avapritinib (BLU-285) was obtained and the drug was started at 200 mg QD orally. The drug had shown preliminary activity in an open-label, dose-escalation phase 1 trial (NCT02561988),¹⁴ and was being tested within a phase 2 trial in advanced SM (NCT03580655) at the time of CUP request, formulated because the patient did not meet the trial inclusion criteria.^{15,16} In 2020, FDA and EMA had approved the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (*PDGFRA*) exon 18 mutation, including *PDGFRA* D842V mutations, and as monotherapy for the treatment of adult patients with unresectable or metastatic GIST harboring the *PDGFRA* D842V mutation, respectively. Overall, the treatment was well-tolerated with mild leucopenia, not requiring medical intervention. Due to a potential pharmacokinetic interaction with fentanyl, the patient was shifted to oxycodone and tapentadol for pain control, that caused moderate side effects such as nausea and confusion. After the first 6–8 weeks of treatment, pain blockers were successfully tapered and withdrawn. In June 2020 (after 3 months from avapritinib start) an MRI of the spine showed significant reduction of neoplastic masses. In October 2020, after 8 months on avapritinib, a disease restaging was carried out. At BM assessment, no abnormal mast cells were highlighted either morphologically (core biopsy and BM smear) or by flow cytometry, whereas *KIT* mutation tested positive by RT-PCR. Imaging restaging of the disease was also performed by using MRI and ¹⁸F-FDG-PET scans (Figure 1 – Panels D-I). MRI demonstrated the complete disappearance of neoplastic tissue in the vertebral canal at the L2-L3 level and a marked decrease of intra- and extra-osseous components of the L5 lesion. ¹⁸F-FDG-PET imaging confirmed the partial response of the L5 lesion, with regression of the vertebral involvement and residual hypermetabolic tumor focus located at the L4-L5 right foramina. At this time-point, the patient obtained the best response without the achievement of complete remission.

The patient experienced disease progression in March 2021 (1 year after avapritinib start), with re-emergence of severe chronic pain involving right hip and ipsilateral lower limb. The clinical picture worsened despite dose increase up to 300 mg QD (from March 2021), and the drug was then withdrawn in October 2021. The patient died due to progressive disease in January 2022.

2 | DISCUSSION

The case we report is a rare, virtually always fatal, evolution of systemic mastocytosis. Coherently with most published experiences, MCS turned out to be resistant to the conventional available therapies. The response we observed with avapritinib indicates the drug as effective on tumor-like extra-hematological masses, an information not immediately obtainable from the results of the clinical trial that established the efficacy in advanced systemic mastocytosis.¹⁵ Furthermore, the agent proved to be able to overcome previous resistance to midostaurin, consistent with a published report.¹⁷

Although transient, the response after the failure of three preceding lines of treatment suggests that potent and selective inhibition of KIT could induce apoptosis of high-grade, de-differentiated mast cells potentially representing an effective therapeutic modality in this clinical setting and a potential bridge to allogeneic transplant in eligible patients.

AUTHOR CONTRIBUTIONS

Contribution: FM conceived and coordinated the research, managed the patient, and wrote the manuscript; FG, CM, and FV performed research and analyzed data; FM and VB analyzed imaging data; PG collected clinical data, and advised on revision of the manuscript; SL and RS analyzed pathological data; and AMV designed and coordinated research and advised on revision of the manuscript.

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CONFLICT OF INTEREST

FM, AMV: participation to advisory board for Blueprint and Novartis. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

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REFERENCES

- 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.
- Lim KH, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood*. 2009;113(23):5727-5736.
- Trizuljak J, Sperr WR, Nekvindová L, et al. Clinical features and survival of patients with indolent systemic mastocytosis defined by the updated WHO classification. *Allergy*. 2020;75(8):1923-1934.

- Monnier J, Georjgin-Lavialle S, Canioni D, et al. Mast cell sarcoma: new cases and literature review. *Oncotarget*. 2016;7(40):66299-66309.
- Ryan RJH, Akin C, Castells M, et al. Mast cell sarcoma: a rare and potentially under-recognized diagnostic entity with specific therapeutic implications. *Modern Pathol*. 2013;26(4):533-543.
- Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood*. 2016;129(11):1420-1427.
- Singh A, Alkhateeb H, Pardanani A, et al. Mast cell sarcoma: 2 Mayo Clinic cases. *Am J Hematol*. 2022;97(10):1381-1383.
- Valent P, Akin C, Hartmann K, et al. Updated diagnostic criteria and classification of mast cell disorders: a consensus proposal. *Hema*. 2021;5(11):e646.
- Georjgin-Lavialle S, Aguilar C, Guieze R, et al. Mast cell sarcoma: a rare and aggressive entity—report of two cases and review of the literature. *J Clin Oncol*. 2012;31(6):e90-e97.
- Krauth MT, Födinger M, Rebuzzi L, Greul R, Chott A, Valent P. Aggressive systemic mastocytosis with sarcoma-like growth in the skeleton, leukemic progression, and partial loss of mast cell differentiation antigens. *Haematologica*. 2007;92(12):e126-e129.
- Alvarez-Twose I, Matito A, Morgado JM, et al. Imatinib in systemic mastocytosis: a phase IV clinical trial in patients lacking exon 17 KIT mutations and review of the literature. *Oncotarget*. 2015;5:68950-68963.
- Gotlib J, Kluijn-Nelemans HC, George TI, et al. Efficacy and safety of Midostaurin in advanced systemic Mastocytosis. *N Engl J Med*. 2016;374(26):2530-2541.
- Singh A, Al-Kali A, Begna KH, et al. Midostaurin therapy for advanced systemic mastocytosis: Mayo Clinic experience in 33 consecutive cases. *Am J Hematol*. 2022;97(5):630-637.
- Drummond MW, DeAngelo DJ, Deininger MW, et al. Preliminary safety and clinical activity in a phase 1 study of Blu-285, a potent, highly-selective inhibitor of KIT D816V in advanced systemic Mastocytosis (SM). *Blood*. 2016;128(22):477.
- Gotlib J, Reiter A, Radia DH, et al. Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial. *Nat Med*. 2021;27:2192-2199.
- DeAngelo DJ, Radia DH, George TI, et al. Safety and efficacy of avapritinib in advanced systemic mastocytosis: the phase 1 EXPLORER trial. *Nat Med*. 2021;27(12):2183-2191.
- Lübke J, Naumann N, Kluger S, et al. Inhibitory effects of midostaurin and avapritinib on myeloid progenitors derived from patients with KIT D816V positive advanced systemic mastocytosis. *Leukemia*. 2019;33(5):1195-1205.

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