EJCRIM
European Journal
of Case Reports
in Internal Medicine

AGGRESSIVE SYSTEMIC MASTOCYTOSIS PRESENTING AS DIFFUSE OSTEOBLASTIC BONE DISEASE: A DIAGNOSTIC PITFALL MIMICKING METASTATIC CANCER

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Received: 04/01/2026
Accepted: 13/01/2026
Published: 16/02/2026

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Informed consent was obtained from the patient for the publication of this case report and any accompanying images.
Acknowledgements: The authors wish to acknowledge the contributions of the medical and nursing staff involved in patient care, as well as colleagues who provided technical and administrative support.
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How to cite this article: Melício A, Gonçalves HD, Dias M, Vasconcelos-Teixeira S, Madeira Lopes J. Aggressive systemic mastocytosis presenting as diffuse osteoblastic bone disease: a diagnostic pitfall mimicking metastatic cancer. *EJCRIM* 2026;**13**:doi:10.12890/2026_006143

ABSTRACT

Background: Systemic mastocytosis is a rare clonal disorder characterised by the proliferation and accumulation of mast cells in one or more extracutaneous organs. Its clinical presentation is highly heterogeneous and aggressive variants may mimic metastatic malignancy, leading to significant diagnostic delay.

Case description: We report the case of an 83-year-old woman presenting with fatigue, weight loss, low-grade evening fever and night sweats over two months. Laboratory evaluation showed pancytopenia, mild inflammatory response, and normal hepatic and renal function. Imaging studies revealed diffuse osteoblastic lesions throughout the axial skeleton, initially interpreted as bone metastases from an unknown primary tumour. Further imaging demonstrated hepatosplenomegaly and prominent periportal lymph nodes. Bone biopsy of an iliac lesion revealed replacement of marrow by sheets of epithelioid mast cells (CD117+, tryptase, CD68+). Serum tryptase was elevated (56.3 ng/ml), fulfilling World Health Organization (WHO) diagnostic criteria for systemic mastocytosis. The patient was diagnosed with aggressive systemic mastocytosis and started cladribine therapy with antimicrobial prophylaxis, with progressive improvement of constitutional symptoms and she remains under follow-up in the haematology department.

Discussion: Aggressive systemic mastocytosis presenting with diffuse osteoblastic bone lesions is extremely uncommon and may closely mimic metastatic carcinoma, particularly of breast or prostate origin. Diagnosis requires a high index of suspicion and confirmation through histopathology, immunophenotyping and serum tryptase measurement. KIT mutations, especially D816V, are frequent but were absent in this case.

Conclusion: This case highlights the importance of considering systemic mastocytosis in the differential diagnosis of osteoblastic bone disease, particularly in elderly patients with constitutional symptoms and unexplained cytopenias. Early recognition allows timely initiation of appropriate therapy and avoids unnecessary oncology investigations.

KEYWORDS

Systemic mastocytosis, aggressive systemic mastocytosis, osteoblastic metastasis, cladribine, diagnostic challenge

EFIM
European Federation of Internal Medicine

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LEARNING POINTS

- Aggressive mastocytosis can rarely present with diffuse osteoblastic bone lesions mimicking metastatic disease.
- Elevated serum tryptase and histopathological confirmation are essential for diagnosis, even when KIT mutations are absent.
- Early recognition prevents unnecessary oncologic investigations and allows timely initiation of cytoreductive therapy.

INTRODUCTION

Systemic mastocytosis (SM) is a heterogeneous group of clonal myeloid neoplasms characterised by abnormal proliferation and accumulation of mast cells in the bone marrow and other extracutaneous organs. Clinical manifestations vary widely, ranging from indolent forms to aggressive systemic mastocytosis (ASM) and mast cell leukaemia, reflecting differences in mast cell burden and organ involvement[1,2].

The diagnosis of SM is based on the World Health Organization criteria, which integrate histopathological, immunophenotypic, biochemical and molecular features. These include one major criterion – multifocal dense infiltrates of mast cells in bone marrow or other extracutaneous organs – and several minor criteria, such as atypical mast cell morphology, aberrant expression of CD25 and/or CD2, elevated serum tryptase levels (>20 ng/ml) and activating KIT mutations[3-5].

Aggressive forms of SM are characterised by organ damage related to mast cell infiltration, including cytopenias, hepatosplenomegaly, malabsorption and skeletal involvement. While osteolytic or mixed bone lesions are common, purely osteoblastic lesions are exceptionally rare and may be misinterpreted as metastatic disease, particularly in elderly patients[6,7].

CASE DESCRIPTION

An 83-year-old woman was admitted with a two-month history of progressive fatigue, unintentional weight loss, evening low-grade fever and night sweats. Her medical history was notable for degenerative osteoarticular disease with partial dependence in activities of daily living.

On admission, she was afebrile and haemodynamically stable. Physical examination revealed marked pallor and a distended but non-tender abdomen. No palpable lymphadenopathy or overt organomegaly was detected.

Laboratory evaluation demonstrated pancytopenia with haemoglobin 8.7 g/dl, leukocytes 2.8 $\times 10^6$/l and platelets 127 $\times 10^6$/l, with normocytic indices. Renal and hepatic function tests were within normal limits. Inflammatory markers were modestly elevated (C-reactive protein 3.9 mg/dl). Urinalysis suggested cystitis, and urine cultures grew extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*, which resolved with targeted antibiotic therapy.

Chest radiography showed minimal bilateral pleural blunting. Contrast-enhanced computed tomography of the abdomen and pelvis revealed hepatosplenomegaly and multiple diffuse sclerotic bone lesions involving the axial skeleton (*Fig. 1 and 2*), raising suspicion for metastatic bone disease of unknown primary origin.

Bone marrow aspiration was inconclusive due to inadequate sampling. However, an iliac bone biopsy demonstrated extensive replacement of marrow spaces by sheets of epithelioid mast cells with clear cytoplasm. Immunohistochemical staining was positive for CD117, tryptase and CD68 (*Fig. 3*). Serum tryptase level was markedly elevated at 56.3 ng/ml (reference <20 ng/ml). Molecular analysis for the KIT D816V mutation was negative.

Based on these findings, WHO diagnostic criteria were fulfilled (one major and one minor criteria), and a diagnosis

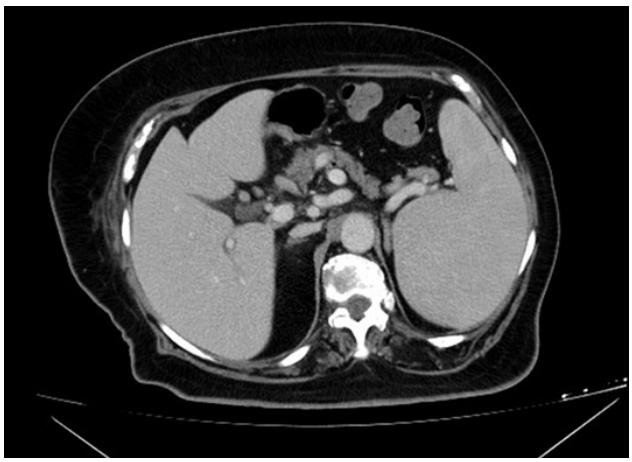


Figure 1. *Abdominal CT showing hepatosplenomegaly and periportal lymphadenopathy.*



Figure 2. *Axial CT view demonstrating diffuse osteoblastic lesions in the vertebral bodies.*

of ASM was established. The patient was started on cladribine (2-chlorodeoxyadenosine) with prophylactic acyclovir, fluconazole and trimethoprim-sulfamethoxazole. Clinical evolution was favourable, with improvement in constitutional symptoms and stabilisation of haematologic parameters.

DISCUSSION

SM is a clonal haematologic neoplasm characterised by abnormal proliferation and accumulation of mast cells in one or more extracutaneous organs, most commonly the bone marrow, liver, spleen, lymph nodes and gastrointestinal tract. In most cases, it is driven by somatic mutations in the KIT gene, particularly the D816V variant, which leads to constitutive activation of the KIT receptor and autonomous mast cell growth and survival[1,2,4].

Clinical manifestations result from both tissue infiltration by mast cells and the release of mast cell mediators. Symptoms may include flushing, pruritus, syncope, gastrointestinal complaints, hepatosplenomegaly, lymphadenopathy, cytopenias and skeletal involvement, such as osteolytic lesions or pathologic fractures. The spectrum of disease ranges from indolent SM, associated with near-normal life expectancy, to ASM, characterised by organ dysfunction and reduced survival[1,2,5,8].

Diagnosis relies on WHO criteria and the International Consensus Classification, requiring histopathologic evidence of multifocal dense mast cell clusters in bone marrow or other extracutaneous organs, aberrant mast cell immunophenotype, elevated serum tryptase levels and detection of KIT mutations[3-5,8]. The National Comprehensive Cancer Network (NCCN) recommends a multidisciplinary approach and referral to specialised centres for both diagnosis and management[3].

SM is classified into subtypes – indolent SM, smouldering SM, ASM, SM with associated haematologic neoplasm and mast cell leukaemia, with prognosis and management tailored according to subtype and risk stratification[3,5,8].

SM is driven by constitutive activation of KIT receptor tyrosine kinase signalling, most commonly due to the KIT D816V mutation, leading to autonomous mast cell proliferation and survival[1,2,4]. In ASM, high mast cell burden results in extensive tissue infiltration and organ dysfunction, manifesting as cytopenias, hepatosplenomegaly and skeletal disease[8].

Skeletal involvement is observed in up to 90% of patients with SM; however, most cases present with osteopenia, osteoporosis, osteolytic lesions or mixed patterns[6,7]. Purely osteoblastic or sclerotic lesions are exceedingly rare and represent a significant diagnostic challenge. Such radiological findings may closely resemble metastatic carcinoma, particularly from breast, prostate or neuroendocrine origin, often prompting extensive oncologic workup and delaying correct diagnosis[6].

In this case, the combination of constitutional B symptoms, pancytopenia, hepatosplenomegaly and diffuse sclerotic bone lesions strongly suggested disseminated malignancy. The absence of a detectable primary tumour and the inconclusive bone marrow aspirate further complicated the diagnostic process. A definitive diagnosis was achieved through bone biopsy, highlighting the critical role of histopathological evaluation in atypical presentations of SM.

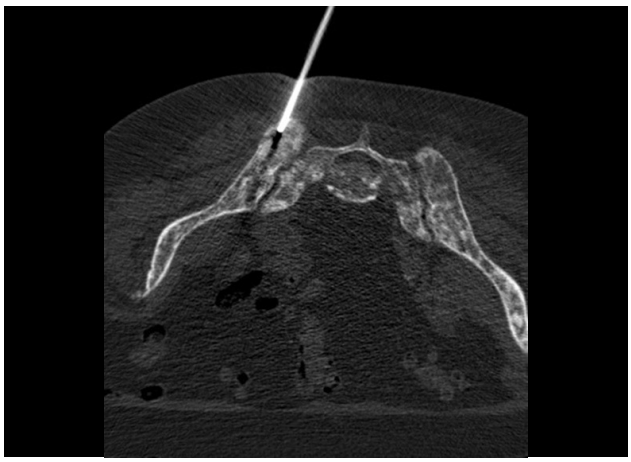


Figure 3. Axial CT image used as guidance for bone marrow biopsy.

Elevated serum tryptase is a valuable diagnostic biomarker and constitutes a minor WHO criterion for SM. Although KIT D816V mutations are detected in many cases, their absence does not exclude the diagnosis. Alternative KIT mutations, low allele burden or technical limitations may account for false-negative molecular results, particularly in elderly patients or when non-optimal tissue samples are analysed[4,8].

Therapeutic strategies for ASM focus on cytoreduction and symptom control. Current guidelines recommend cladribine or interferon-α as first-line cytoreductive therapies, while tyrosine kinase inhibitors such as midostaurin or avapritinib may be considered in selected patients, particularly those harbouring activating KIT mutations[3,8]. In frail or elderly patients, cladribine remains a well-established option, demonstrating efficacy in reducing mast cell burden and improving clinical outcomes.

This case underscores the importance of maintaining a broad differential diagnosis when evaluating diffuse osteoblastic bone disease. Recognition of SM as a potential mimic of metastatic cancer is essential to avoid unnecessary investigations and to ensure timely initiation of appropriate therapy.

CONCLUSION

ASM should be considered in the differential diagnosis of diffuse osteoblastic bone lesions, especially in patients presenting with constitutional symptoms and unexplained cytopenias in the absence of an identifiable primary malignancy. Histopathological examination and serum tryptase measurement remain central to diagnosis, even when KIT mutations are absent. Early recognition of this rare entity allows prompt initiation of targeted therapy and may significantly improve patient outcomes.

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