Mastocytosis as an Unusual Cause of Hip Fracture in an Elderly Woman

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ABSTRACT

Mastocytosis is a type of myeloproliferative neoplasm characterized by accumulation and proliferation of morphologically and immunophenotypically abnormal mast cells in 1 or more organ systems. Clinical manifestations vary depending upon the organ involved and chemical mediators released by mast cells along with constitutional symptoms and musculoskeletal complaints. We report a case of isolated bone marrow mastocytosis in an 87-year-old woman who presented with a fall resulting in proximal femur fracture. Bone marrow biopsy revealed mastocytosis, and no evidence of systemic involvement or peripheral mastocytosis was found. Physicians should be aware of this entity, especially in patients with osteoporosis.

CASE PRESENTATION

An 87-year-old woman with significant medical history for osteopenia presented with a mechanical fall. She had been diagnosed with osteopenia 1 year previously and was treated with alendronate. Upon presentation, her physical examination was remarkable for limited painful motion in her left hip with superficial bruising. The initial workup was remarkable for anemia hemoglobin (Hgb 9.5 ng/dL). An x-ray of the left hip showed osteoporosis and a femur neck fracture with suspicion of a pathologic fracture. The patient underwent open reduction and internal fixation where a bone marrow biopsy was taken for pathologic fracture workup that showed hypercellular marrow (40%) with sheets of mast cells (Figure 1A). Granulocyte, erythroid, and megakaryocyte precursors were normal with normal maturation. An increase in mononuclear cells with round nuclei and numerous distinct metachromatic granules were noted. These cells had cytological and cytochemical features of mast cells. The Giemsa stain showed aggregates and diffuse infiltration of these mast cells. Immunohistochemical analysis was positive for leukocyte common antigen and CD15 and negative for pancytokeratin and S–100 stains. These cells also were positive for CD117 (Figure 1B), CD2 and CD25 expressions, tryptase, and aberrant mast cell phenotype by flow cytometry. The patient did not follow up after discharge, but presented to the emergency department a month later after another fall, where she was found to have right intertrochanteric and left tibial fractures. The patient was lost to follow-up after consultation with oncology (outpatient setting) when she opted for comfort care. Upon our review, we found that she later died.

DISCUSSION

Systemic mastocytosis (SM) is classified as a myeloproliferative neoplasm according to revised World Health Organization (WHO) classification 2008 for myeloid neoplasms.[1] SM is characterized by mast cell infiltration of extracutaneous organs like bone marrow, the gastrointestinal tract, liver, and spleen.[1,2] Cutaneous mastocytosis (CM) frequently presents in children under 2 years and regresses spontaneously in most of the cases.[3] Incidence of SM is about 5 to 10 per million,[4] and it typically manifests in the 5th to 8th decades of life.[5] Indolent systemic mastocytosis (ISM)—the most common form of SM—is slowly progressive, whereas aggressive systemic mastocytosis (ASM) is rare and typically presents with constitutional symptoms, organ dysfunction such as hepatic fibrosis and portal hypertension, malabsorption, cytopenias, or pathological fractures.[6] Smoldering systemic mastocytosis (SSM) is a type of ISM, characterized by high mast cell burden (> 30% of the bone marrow), high tryptase levels (> 200 ng/mL), liver or spleen enlargement without signs of hypersplenism or functional liver impairment, and subtle signs of myelodysplasia or myeloproliferation. Isolated bone marrow

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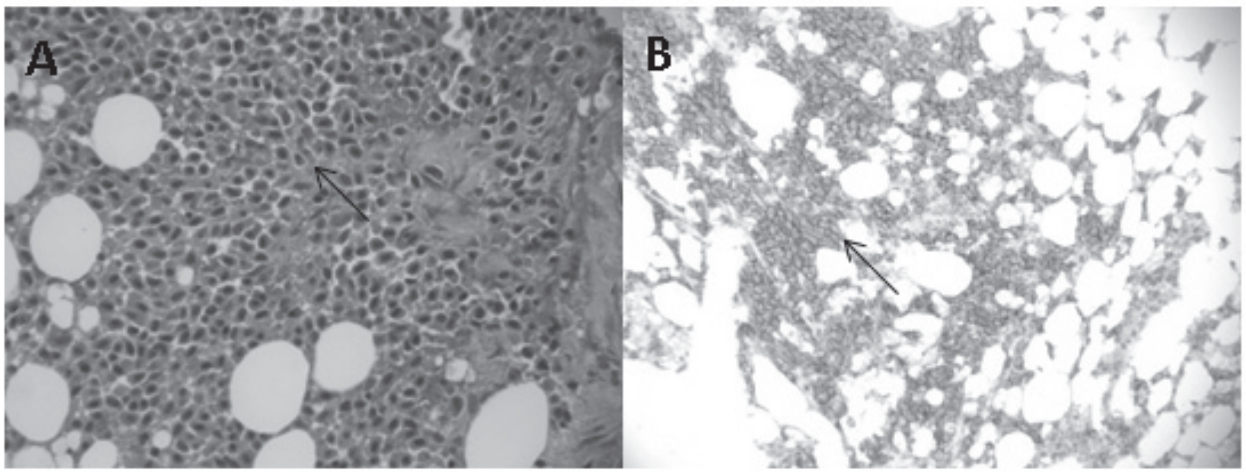
Figure 1. Hematoxylin and Eosin Stain of Bone Marrow Biopsy



mastocytosis (BMM) is also a type of ISM that involves the bone marrow without skin involvement and serum tryptase level is usually less than 30 ng/mL. Patients with BMM appear to be at increased risk of osteopenia and osteoporosis regardless of the age group.[7] The long bones and vertebrae are commonly affected in patients with SM, causing back pain, diffuse musculoskeletal pain, or a pain syndrome resembling fibromyalgia. Osteoporosis is thought to be due to effects of mast cell mediators such as histamine, heparin, and cytokines on bone.[8] Presentation of SM can be confused with metastatic lesions and require a bone marrow biopsy for diagnosis.

The diagnosis of SM is made by either presence of the major criterion and 1 minor criterion; or 3 minor criteria. The major criterion is detection of multifocal, dense infiltrates of mast cells (≥ 15 mast cells in aggregates) in sections of bone marrow and/or other extracutaneous organs. Minor criteria are more than 25% morphologically immature or atypical mast cells in the bone marrow, presence of KIT codon 816 mutation, expression of CD2 and/or CD25 by mast cells in addition to normal mast cell markers, and serum total tryptase more than 20 ng/mL.[7]

A bone densitometry is recommended for evaluation of osteoporosis, whereas skeletal scintigraphy is used to characterize the extent of disease.[9,10] Advanced imaging like multidetector computed tomography and magnetic resonance can be helpful when bone scintigraphy and densitometry are inconclusive.[5]

Prognosis and survival for SM are variable and depend upon the subtypes. ISM has better survival than other types, whereas ASM carries poor prognosis with 41 months median survival and 5% leukemic transformation.[2,7] Other poor prognostic factors include old age at onset, weight loss, high lactate dehydrogenase, high alkaline phosphatase, low hemoglobin levels, low albumin, low platelet count, hepatosplenomegaly, and ascites.[5,7]

Patients with ISM and stable SSM are treated with symptomatic management including histamine receptor blockers, glucocorticoids, epinephrine or immunotherapy, and bisphosphonates.[11] Cytoreductive therapy is used to inhibit mast cell proliferation in high grade SM variants,[6] whereas interferon α-2b plus prednisone is used as first-line therapy for ASM. Cardiotoxicity, thrombocytopenia, and depression are known adverse effects of interferon α-2b.[12] Cladribine, a purine analog chemotherapeutic agent has transient response and hence is used as a second-line treatment.[13] Tyrosine kinase inhibitors like imatinib, dasatinib, nilotinib, and midostaurin are used in patients with C findings where there is organ dysfunction; however, currently imatinib is the only Food and Drug Administration approved treatment specifically for ASM without KIT mutation. Other tyrosine kinase inhibitors currently are under investigation and their use is not recommended outside the clinical trials.[14] In young patients with suitable donor, hematopoietic stem cell transplantation (SCT) induces remission in advanced SM but has not been shown to improve survival.[15] Hydroxyurea is used for cytoreduction in resistant cases although data on efficacy of hydroxyurea in SM is limited.[16]

Our case of isolated bone marrow involvement was unusual due to old age at presentation, however, the case met major criterion (multifocal mast cells) and 2 minor criteria (positive for surface markers CD2, CD25 and greater than 25% of the tissue cells) confirming the diagnosis of systemic mastocytosis.

CONCLUSION

In summary, BBM represents a clinical challenge due to co-existence of osteoporosis and absence of cutaneous manifestations, especially in an elderly patient. SM should be considered in the

differential diagnosis of fracture of unknown origin in elderly patients with a high index of suspicion. Physicians should keep in mind mastocytosis as a plausible, but very rare cause of a long bone fracture, especially in patients with osteoporosis.

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