

Systemic Mastocytosis Causing Refractory Pruritus in a Liver Disease Patient

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ABSTRACT

Systemic mastocytosis (SM) results from clonal, neoplastic proliferation of abnormal mast cells. Patients become susceptible to itching, urticaria, and anaphylactic shock, which occurs due to histamine release from mast cells. SM may coexist alongside other systemic diseases, thus confounding the overall clinical presentation. We discuss a 23-year-old woman with refractory pruritus, which was initially attributed to primary sclerosing cholangitis but had a nonresponse to antihistaminics, ursodiol, and cholestyramine. Concurrent evaluation for polyarthritides revealed increased uptake in the proximal femur on a bone scan, and subsequent bone marrow biopsy revealed indolent SM, and this was understood to be the cause of her intractable pruritus.

INTRODUCTION

Systemic mastocytosis (SM) is a rare disorder resulting from clonal neoplastic proliferation of abnormal mast cells in 1 or more organs. Mast cells are derived from pluripotent CD34⁺ stem cells in spleen and bone marrow, which then migrate to connective tissues of various organs, where they are terminally differentiated.^{1,2} They are located in most tissues but are denser at interfaces between the internal and external environment, where they act as defense cells against pathogens and foreign antigens in the mucous linings of the respiratory tract, gastrointestinal (GI) tract, urogenital system, and dermis of skin.¹ These cells have dense cytoplasmic granules mainly composed of histamine and heparin, the release of which is responsible for the systemic manifestations seen in SM. These granules may be released in response to antigen-immunoglobulin E (AG-IgE)-mediated binding to membrane bound receptors or in response to many physical stimuli like cold or hot temperatures, exercise, alcohol, friction, or various exogenous substances.¹ The symptoms associated with SM are either from release of these mediators or from infiltration of organs with mast cells. Systemic mastocytosis should be suspected in any patient with unexplained flushing or anaphylaxis, unexplained GI abnormalities including peptic ulcer disease, malabsorption, diarrhea, peripheral blood abnormalities, unexplained hepatosplenomegaly, lymphadenopathy, unexplained bone fractures, and radiologic abnormalities including osteopenia, osteoporosis, and osteosclerosis. The manifestations of SM may coexist with other systemic diseases, thus confounding the overall clinical presentation and posing management dilemmas.

CASE REPORT

A 27-year-old white woman with history of Crohn's disease after ileocelectomy and primary sclerosing cholangitis (PSC) resulting in well-compensated cirrhosis presented with refractory pruritus of 8 years of duration. She first developed intense pruritus in 2005, followed by a diffuse erythematous macular rash, and was evaluated by dermatology. Multiple skin biopsies failed to provide any clear etiology. Concurrently, abnormally elevated liver enzymes (especially alkaline phosphatase) were noted and further workup with magnetic resonance cholangio-

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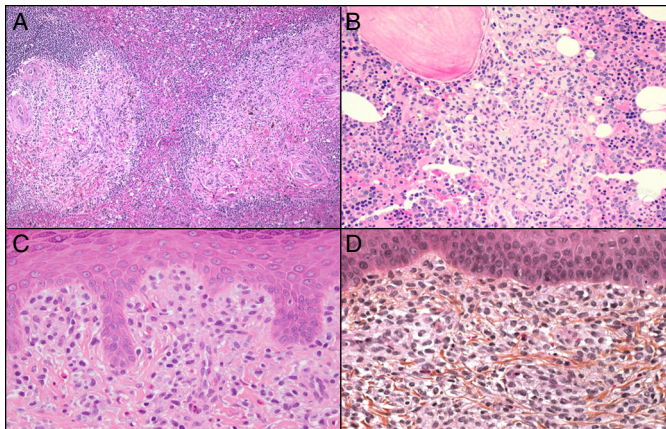


Figure 1. Histopathology of bone biopsy showing multifocal aggregates of (A) CD117+ cells, (B) tryptase positive cells, (C) mast cells with >25% showing abnormal morphology, and (D) mast cells with coexpression of CD25+.

pancreatography and liver biopsy at outside hospital led to the diagnosis of PSC. Her pruritus, which at this point was attributed to PSC, was managed with several agents, including ursodiol, antihistamines, cholestyramine, rifampin, and sertraline, but rather ineffectively. Patient was then referred to our institution for consideration for a liver transplant, in view of her refractory pruritis.

During our exam, she endorsed multiple joint pains in both shoulders, elbows, and knees, with occasional swelling. X-ray of her joints showed no pathology. Rheumatologic evaluation was negative for any obvious autoimmune disorder. Magnetic resonance imaging of her knees revealed abnormal marrow signal intensity, worrisome for a marrow replacing process. Subsequently, bone scan revealed increased uptake around bilateral knees and elbows. A bone biopsy of right distal femur showed multifocal aggregates of CD117+/tryptase+ mast cells with >25% showing abnormal morphology and coexpression of CD25 (Figure 1). Pathology findings were suggestive of indolent SM. Bone marrow biopsy showed involvement of marrow. Along with multiple biopsies of ileum, duodenum, and stomach, she also underwent a repeat liver biopsy 1 year later, although immunohistochemistry did not reveal increased mast cells. Cladribine chemotherapy and adjuvant antihistaminic agent alleviated the pruritus. Although mast cell cholangiopathy was not actively looked for with endoscopic retrograde cholangiopancreatography brushings, an established diagnosis of inflammatory bowel disease-associated PSC and absence of mast cell infiltration on liver biopsy would make mast cell cholangiopathy less likely, albeit a reasonable differential.

DISCUSSION

Cutaneous mastocytosis (CM), more common in children, can be classified as diffuse, urticarial pigmentosa, or

mastocytoma of skin. On the contrary, SM is more common in adults and is classified as indolent SM, SM with associated hematologic clonal, non-mast cell lineage disease, aggressive SM, or mast cell leukemia.³⁻⁵ The underlying etiology of the clonal proliferation of mast cells is poorly understood. Although most reported cases are sporadic, genetic mutations in KIT receptors on surface of mast cells have also been implicated.⁶⁻⁸ These KIT receptors are transmembrane tyrosine kinase receptors that interact with stem cell factor, released by fibroblasts and endothelial cells in surrounding tissues, resulting in growth and differentiation of mast cells in the peripheral tissues. These proliferated mast cells infiltrate various tissues like skin, bone marrow, GI tract, liver, and spleen, causing diverse clinical symptoms. Although major mediator is histamine, other proteins present in the granules, such as heparin, tryptase, prostaglandins, leukotrienes, growth factors like interleukin (IL)-3, IL-5, IL-6, and tumor necrosis factor- α , also play a role.³

Common SM symptoms include intense pruritus, itching, hypotension, vasodilation, flushing, anaphylaxis, and urticaria. Gastrointestinal symptoms of SM, including diarrhea, abdominal pain, bloating, and nausea, are attributable to histamine-mediated effects on smooth muscle contraction via H₁-H₄ receptors. Histamine also increases gastric acid, with higher incidence of peptic ulcer disease,⁷ and contributes to a mild degree of malabsorption and high levels of vasoactive intestinal peptide and gastrin. Although degree of clinical manifestations of SM does not correlate well with the histologic features,⁹ involvement of liver, spleen, and lymph nodes is usually seen with aggressive disease. Musculoskeletal involvement is common, and patients may have bone pain or pathological fractures, with imaging suggesting osteolysis and sclerosis, easily confused with osteoporosis. Bone marrow involvement presents with mono-, bi-, or pancytopenia resulting in bleeding complications and susceptibility to infections. Less commonly, patients may have intense pruritus resistant to treatment or an anaphylaxis to blood transfusions.¹⁰

Systemic mastocytosis is diagnosed by presence of 1 major plus 1 minor criterion, or 3 minor criteria.³ The major criterion is multifocal clusters of mast cells (>15) in the bone marrow. Minor criteria include elevated serum tryptase level, presence of KIT D816V, and mast cell expression of CD25 and/or CD2. A biopsy with histological confirmation is a must to identify patients with SM. Unlike children who have predominantly skin involvement in SM, almost all adult SM patients have involvement of bone marrow and hence should undergo bone marrow biopsy. Once the diagnosis of SM is confirmed, the category is identified by associated "B" and "C" findings. "B" findings denote organ involvement without dysfunction that occurs due to infiltration of cells, while "C" findings denote organ dysfunction due to excessive infiltration and indicate aggressive disease with poor prognosis.

Management of SM is mostly palliative. Patients are educated to identify potential triggers of histamine release to exercise suitable caution. H₁ and H₂ antihistaminic agents are used for symptomatic treatment of itching, flushing, abdominal pain, heartburn, cramping, and diarrhea. Osteoporosis monitoring is essential, and patients with bone involvement must be supplemented with vitamin D and calcium. Antileukotriene agents and corticosteroids are used for H₁ and H₂ unresponsive patients or for severe symptoms. Aggressive disease with severe hematologic and bone involvement could be treated with interferon- α 2b, 2-CdA, and cladribine.¹¹⁻¹³ Imatinib has a therapeutic role in the presence of KIT mutation or in KIT D816-unmutated patients.¹⁴ Patients with KIT D816 mutation may respond to newer investigational drug PKC412.^{6,15-17} Role of stem transplantation is yet unclear.

DISCLOSURES

Author contributions: NS Addepally and JS Klair searched literature and wrote the manuscript. M. Girotra, J. Jones, and F. Aduli supervised the manuscript preparation and approved the final version. F. Aduli is the article guarantor.

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