CASE REPORT

Symptomatic response to imatinib mesylate in cutaneous mastocytosis associated with chronic myelomonocytic leukemia

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ABSTRACT

Mastocytosis is an uncommon disorder defined by increased and abnormal mast cells in one or more tissues. Cutaneous mastocytosis (CM) is limited to the skin, with varying degrees of rash, pruritus, and disfigurement. Systemic mastocytosis (SM) typically involves the bone marrow, sometimes in association with other bone marrow disorders, including chronic myelomonocytic leukemia (CMML). Mastocytosis has been associated with somatic mutations in the gene encoding the tyrosine kinase Kit, leading to identification of Kit as a therapeutic target. The Kit inhibitor imatinib mesylate is approved for aggressive SM. We present an unusual patient with disabling pruritus from telangiectasia macularis eruptiva perstans, a subtype of CM, and CMML, but with no evidence of systemic mast cell disease. She was treated with imatinib and experienced marked improvement in her pruritus. Concomitant CM and CMML have not previously been reported, and the present report is the first of successful imatinib therapy in an adult patient with CM.

KEY WORDS

Mastocytosis, chronic myelomonocytic leukemia, imatinib, pruritus, cutaneous, tyrosine kinase inhibitor, TMEM

1. INTRODUCTION

Mastocytosis comprises disorders characterized by the presence of increased and abnormal mast cells in one or more tissues. Mastocytosis may present as systemic mastocytosis (SM) or cutaneous mastocytosis (CM). There are 6 subtypes of SM and 4 clinical variants of CM. Table 1 lists the characteristics of the two entities.

Cutaneous mastocytosis is diagnosed based on presence of abnoraml mast cell infiltration into the dermis; SM is diagnosed based on presence of either 1 major and 1 minor, or 3 minor World Health Organization diagnostic criteria, which are listed in Table 1. Although cutaneous and systemic involvement can occur together in adults, children rarely experience systemic manifestations and often have self-limiting disease. The treatment of SM in adults remains a challenge, in part because of its chronicity and heterogeneity.

2. CASE DESCRIPTION

A 67-year-old white woman presented with progressive and debilitating pruritus of 5 years’ duration. Her symptoms had begun with intermittent pruritus of her arms, which then progressed to involve unexposed areas. The condition was unresponsive to treatment with histamine antagonists and ultraviolet B phototherapy. Two years later, she was noted to have peripheral blood monocytosis. Bone marrow (BM) examination demonstrated hypercellularity, dysplastic erythroid precursors and megakaryocytes, and increased monocyte precursors (Figure 1), but no increase in blasts. Blood and marrow findings were diagnostic of chronic myelomonocytic leukemia (CMML). Mast cell numbers and morphology were normal.

When the patient presented to our tertiary care centre, her pruritus had become constant and involved her entire body. She was unable to sleep unless medicated with sedatives. She was struggling to work and was having suicidal thoughts. Hot showers exacerbated her pruritus, but symptoms persisted even with avoidance of triggers. She noted a chronic truncal rash and erythematous patches on her arms. She denied flushing, wheezing, and diarrhea. Her medical history was otherwise unremarkable.

Physical examination revealed a fine maculopapular rash with tan lesions over the patient’s anterior trunk, concentrated near the umbilicus and under the breasts, and erythematous plaques on the left arm. She did not have dermatographia.

White blood cell count was 6.8×10³/μL, with 19% monocytes and 1% eosinophils. Hemoglobin...
was 13.9 g/dL, and platelet count was 127×10^3/μL. Serum chemistries were normal. Serum tryptase was 7.41 μg/L (upper limit of normal: 11.5 μg/L), and 24-hour urine histamine level was 19 μg (upper limit of normal: 62 μg).

Biopsy of the macular lesions revealed a perivascular and focally interstitial mononuclear cell infiltrate around prominent dilated capillaries of the superficial venous plexus. Giemsa stain identified up to 20 mast cells per high-power field, with metachromatic cytoplasmic granules (Figure 2), consistent with telangiectasia macularis eruptiva perstans (TMEP), a subtype of CM. KIT mutation status was not ascertained at the time of biopsy.

The patient was treated with H1 and H2 antagonists and oral cromolyn sodium and gabapentin 3000 mg daily. Her symptoms did not resolve, and the sedating effects of the medications limited her ability to work.

After previous therapies had failed, the patient was initiated on imatinib mesylate 400 mg daily in an effort to treat her debilitating symptoms. She reported significant relief of pruritus within 2 weeks and an ongoing response at 23 months. When asked to quantify her relief after 2 months of therapy, she reported a 75% improvement from her previous level of debility. She was able to discontinue H2 blockers.

### TABLE I: Typical characteristics and subtypes of systemic mastocytosis and cutaneous mastocytosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Systemic</th>
<th>Mastocytosis type</th>
<th>Cutaneous</th>
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</thead>
<tbody>
<tr>
<td>Age group most commonly affected</td>
<td>Adults</td>
<td>Indolent</td>
<td>Children</td>
</tr>
<tr>
<td>Sex linkage</td>
<td>Slight female predominance</td>
<td>Aggressive</td>
<td>Slight male predominance</td>
</tr>
<tr>
<td>Organ or organs affected</td>
<td>Bone marrow, spleen, liver, lymph nodes, respiratory tract, with or without skin involvement</td>
<td>Systemic mastocytosis with associated clonal hematologic non-mast-cell lineage disease</td>
<td>Skin</td>
</tr>
<tr>
<td>Subtypes</td>
<td>1. Indolent</td>
<td>1. Urticaria pigmentosa</td>
<td></td>
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<tr>
<td></td>
<td>2. Aggressive</td>
<td>2. Isolated mastocytoma</td>
<td></td>
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<tr>
<td></td>
<td>3. Systemic mastocytosis</td>
<td>3. Diffuse (erythrodermic) mastocytosis</td>
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<td></td>
<td>with associated clonal hematologic non-mast-cell lineage disease</td>
<td>4. Telangiectasia macularis eruptiva perstans</td>
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<tr>
<td></td>
<td>4. Mast-cell leukemia</td>
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<tr>
<td></td>
<td>5. Mast cell sarcoma</td>
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<td></td>
<td>6. Extracutaneous mastocytoma</td>
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<td>Clinical course</td>
<td>Chronic, persistent</td>
<td>Acute, remitting^b^</td>
<td></td>
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<tr>
<td>Treatments</td>
<td>Imatinib mesylate,^c^ oral cromolyn, epinephrine, interferon alfa, cladribine</td>
<td>Antihistamines, topical cromolyn, leukotriene modulators, topical glucocorticoids, phototherapy</td>
<td></td>
</tr>
</tbody>
</table>

^a Almost always involved in systemic mastocytosis.

^b The disease is often limited and resolves spontaneously in children, but can have a prolonged course during childhood and is often chronic in adult patients.

^c Approved only for the aggressive subtype.

### TABLE II: Diagnosis of systemic mastocytosis based on World Health Organization criteria^a^

**Major criterion**

Multifocal, dense aggregates of at least 15 mast cells in the bone marrow or other extracutaneous organs.

**Minor criteria**

- More than 25% mast cells in the bone marrow or other extracutaneous organs, with an atypical or spindle-shaped morphology
- A codon 816 KIT mutation
- Aberrant CD25 or CD2 expression (or both) on mast cells
- Persistent elevation in serum tryptase (>20 ng/mL)

^a Requires the major and 1 minor criterion, or 3 minor criteria.
and cromolyn sodium, requiring only fexofenadine and gabapentin 1800 mg daily (40% dose reduction) in addition to imatinib.

The patient’s blood counts have remained stable. She has not developed any evidence of sm, and her serum tryptase level remains low at 4.71 μg/L. Repeat BM evaluation revealed cellularity of 70% with 17% monocyte precursors and 7% blasts, still consistent with CMML-1. Cytogenetic analysis showed a normal karyotype, and molecular studies showed absence of PDGFRA and PDGFRB rearrangement, BCR-ABL translocation, and JAK2 V617F mutation. Polymerase chain reaction–based DNA sequencing of exon 17 of the KIT gene (CD117, SCFR) revealed no mutation, and the D816V mutation was specifically not present. Staining of BM for Kit was positive in less than 1% of cells, and tryptase stain was negative. There were no clusters of spindle cells.

3. DISCUSSION

Our patient was diagnosed with CM. Her BM showed no indication of SM, but did reveal a hematologic stem-cell disorder consistent with CMML. A BM evaluation is recommended for cutaneous disease in adults (in contrast to most pediatric cases), because 10%–70% of adult patients will have evidence of systemic involvement6,7. As an additional consideration, aggressive forms of SM less often manifest with cutaneous lesions, suggesting that skin involvement may be a favourable prognostic factor in SM6,7.

A hematologic malignancy–associated CM is rare. Urticaria pigmentosa has previously been reported in association with lymphocytic lymphoma, acute myelomonocytic leukemia, “evolving” myelomonocytic leukemia, Hodgkin disease, and chronic lymphocytic leukemia8, and TEMP with essential thrombocythemia, multiple myeloma, and polycythemia vera9–11. The association of CM with CMML seen in our patient has not previously been reported.

A rare variant of CM, TEMP is more commonly seen in adults and is often persistent and refractory to treatment, as occurred in our patient. It typically presents as tan-brown macules, papules, or plaques with telangiectasias. Histologic features include an infiltrate of mast cells concentrated around venules and dilated capillaries of the superficial venous plexus of the upper dermis12. A recent study using dermoscopy in CM described four patterns: light brown blot, yellow-orange blot, pigment network, and reticular vascular. The reticular vascular pattern was seen in all patients with TEMP and was associated with a more frequent need for anti-mediator therapy13, also consistent with the severity of the symptoms seen in our patient.

Cutaneous and systemic mastocytosis have both been associated with somatic mutations in the gene encoding Kit, a type III receptor tyrosine kinase14–16. The D816V mutation, a gain-of-function point mutation resulting in substitution of valine for aspartic acid at codon 816 within exon 17, is present in more than 90% of adult patients with SM15. This mutation has been demonstrated in 38% and 100% of CM skin biopsy specimens by polymerase chain reaction testing and gene sequencing respectively17,18. KIT mutations cause constitutive activation of the receptor, leading to downstream signalling independent of stem-cell factor binding and, further, to dysregulated cell growth and potential neoplastic transformation15.

In a recent study of 48 patients with SM with associated clonal hematologic non-mast-cell lineage disease (SM-AHNMD), the D816V KIT mutation was demonstrated in mast cells in 45 patients (94%) and in cells involved in the AHNMD in 17 patients (35%), including 8 of 9 (89%) with SM-CMML, suggesting that the SM and CMML both derived from the same clone. Our patient did not fulfill the diagnostic criteria for SM-AHNMD, or specifically SM-CMML, because she did...
not have increased or abnormal mast cells or an 816 codon mutation in her BM. The nature of the relationship between CM and CMML in our patient is unclear.

Therapies for CM are aimed at symptom control. They include avoidance of triggers—such as alcohol, heat, and stress—that lead to mast cell release4,6. Patients with CM are prone to anaphylactic reactions, and it is recommended that they carry self-injectable epinephrine. Treatment strategies aimed at controlling itching, flushing, and rash include oral antihistamines and leukotriene modulators, topical cromolyn or glucocorticoids, and ultraviolet phototherapy5,6,12. Pediatric CM typically resolves spontaneously, eliminating the need for aggressive or sustained therapies.

There is no cure for SM, and earlier treatment strategies using interferon alfa and cladribine have not yielded durable responses3,14,16, prompting investigation of tyrosine kinase inhibitors targeting the Kit receptor. Imatinib mesylate has demonstrated in vitro inhibition of proliferation of mast cells with wild-type KIT15. When studied in 27 patients, imatinib 400 mg daily produced an overall response rate of 18% in SM (17% with the D816V mutation and 33% without) and 50% in aggressive SM16. Imatinib has not been systematically evaluated in CM, but its successful use has been reported in 3 pediatric patients at doses of 100 mg daily19,20. All 3 had complete resolution of pruritus and rash, and no recurrence of disease after discontinuation. All expressed an exon 8 KIT mutation, and one also had an exon 18 mutation (no exon 17 D816V mutations were found)19,20. Imatinib is approved by the U.S. Food and Drug Administration for treatment of aggressive SM without the D816V KIT mutation or with unknown mutation status. Treatment with this drug for other mast cell disorders is off-label.

Other tyrosine kinase inhibitors have been evaluated in SM, including dasatinib and nilotinib, with overall response rates of 33% and less than 20% respectively, in patients with the D816V mutation3,14,21. Midostaurin, a multi-kinase inhibitor, and masitinib mesilate, a new tyrosine kinase inhibitor, have recently shown benefit in both SM and CM3,14,22,23.

4. SUMMARY

We report an unusual case of CM, TMEM subtype, in a patient with CMML without SM. KIT mutation was not present. This patient was treated with imatinib 400 mg daily, achieving symptomatic improvement at 2 weeks and durable response at 23 months. To our knowledge, this report is the first of concomitant CM and CMML and the first of successful imatinib therapy in an adult patient with CM.

5. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to disclose.

6. REFERENCES


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