

Sustained improvement in urticaria pigmentosa and pruritus in a case of indolent systemic mastocytosis treated with cladribine

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Summary

Systemic mastocytosis (SM) is a myeloproliferative disorder, characterized by a clonal proliferation of abnormal mast cells accumulating in internal organs and sometimes in the skin, leading to cutaneous and systemic symptoms. Mutations within the gene *KIT*, which encodes the receptor tyrosine kinase (KIT) on mast cells, is found in most patients with SM. We report a case of a 62-year-old woman presenting with a pruritic rash on her limbs and trunk. Several years later she developed gastrointestinal symptoms, associated with raised serum tryptase. Skin and bone marrow biopsies confirmed a diagnosis of SM, initially presenting with urticaria pigmentosa. Responses to multiple therapies, including potent topical steroids, oral antihistamines, phototherapy and the tyrosine kinase inhibitor, nilotinib, were inadequate. Treatment with cladribine (2-chlorodeoxyadenosine) produced a marked and sustained reduction in her symptoms and serum tryptase level.

Mastocytosis results from a clonal proliferation of morphologically and immunophenotypically abnormal mast cells that accumulate in one or more organs. Presentation ranges from skin-limited disease (cutaneous mastocytosis; CM) to systemic mastocytosis (SM), in which mast cells infiltrate extracutaneous organs, with or without skin involvement, which may be associated with multiorgan dysfunction.¹ The World Health Organization classifies mastocytosis into CM (urticaria pigmentosa, diffuse cutaneous mastocytosis and mastocytoma of the skin) and SM, which is divided into four subcategories: (i) indolent SM (ISM), which shows little or no evidence of organ dysfunction; (ii) ISM with evidence of organ dysfunction [further subcategorized as smouldering SM (SSM)]; (iii) aggressive SM (ASM; evidence of end-organ failure), and (iv) SM associated with a clonal haematological non-mast cell lineage disease (SM-AHNMD) or mast

cell leukaemia (MCL).² The incidence of mastocytosis is unknown.

Mast cell development is dependent upon stem cell factor and its type 3 receptor tyrosine kinase, KIT. Somatic gain-of-function mutations within *KIT*, the gene encoding the KIT receptor protein, are strongly associated with both cutaneous and systemic forms of mastocytosis, and accordingly have been implicated in its pathogenesis. The most common mutation occurs in codon 816, with a substitution of valine for aspartate (D816V).³

To date, therapy has generally been symptomatic, aimed at controlling pruritus, flushing, nausea, vomiting, abdominal pain and diarrhoea. We report prolonged clinically beneficial response to cladribine in a patient with SM who had severely symptomatic cutaneous disease.

Report

A 62-year-old white woman presented with a 4-year history of a pruritic rash affecting her limbs and torso. She had osteoporosis but no other medical conditions.

Physical examination revealed multiple brown-red maculopapular lesions on the chest, lower back, groin

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and dorsal surfaces of both feet, with thick plaques in the axillae. Individual lesions urticated on rubbing, displaying a positive Darier sign. An incisional biopsy from a lesion in the submammary area showed features consistent with urticaria pigmentosa (Fig. 1).

At presentation, full blood count, liver and renal function tests were normal. The patient's pruritus responded poorly to potent topical steroids, and to oral fexofenadine 180 mg twice daily, both alone, and in combination with ranitidine 150 mg twice daily and oral sodium cromoglycate 200 mg four times daily. Photochemotherapy (bath psoralen ultraviolet UVA 16 treatments, total dose 10.1 J/cm²) and narrowband UVB phototherapy (20 treatments, total dose 17.41 J/cm²) was ineffective.

The patient later developed intermittent nausea, vomiting, diarrhoea and bloating. An upper gastrointestinal endoscopy and histology of small bowel biopsies were normal. The serum tryptase level was found to be high at 95 µg/L (normal range 2–11.4 µg/L).

Histological examination of a bone marrow biopsy revealed hypercellular bone marrow, with myeloid

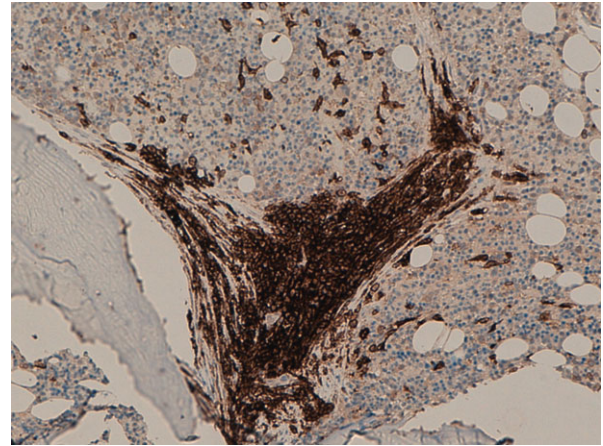


Figure 2 Immunohistochemistry for CD117 (KIT) revealed mast cells (brown) with spindle-shaped nuclei (original magnification × 200).

hyperplasia, abnormal mast cells, eosinophilia, and paratrabecular fibrosis. Immunohistochemistry confirmed peritrabecular aggregates of CD25, CD117 and

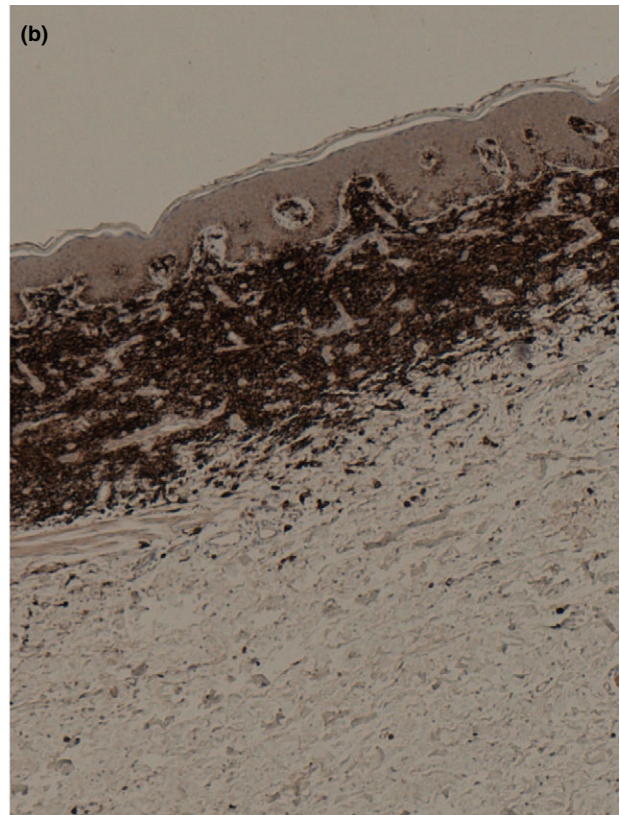
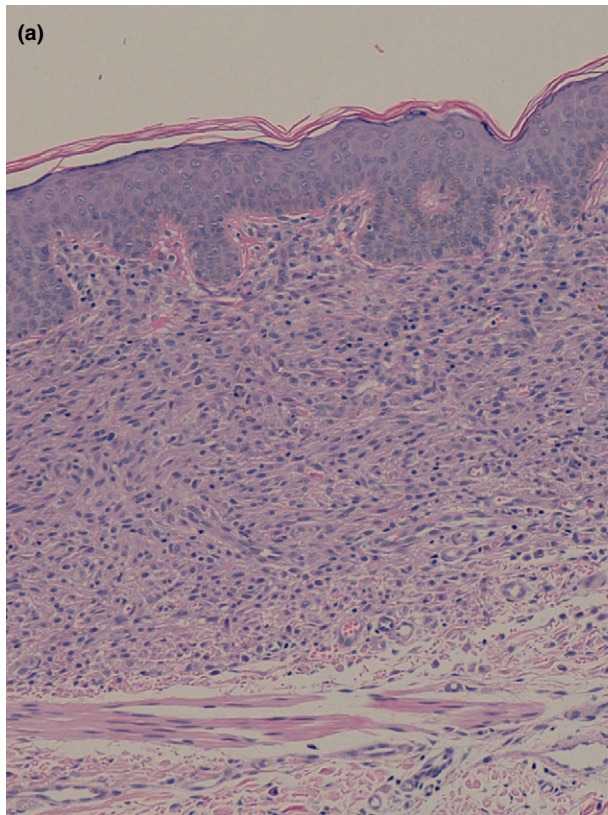


Figure 1 Skin biopsy from submammary area, showing (a) an upper dermal and perivascular inflammatory cell infiltrate, mainly composed of round and spindle-shaped cells with granular cytoplasm (haematoxylin and eosin, original magnification × 200). (b) Immunohistochemistry for CD117 (KIT) revealed these to be mast cells (brown) (original magnification × 200).

mast cell tryptase-positive cells, with spindle-shaped nuclei, consistent with SM (Fig. 2). Genetic analysis identified a D816V mutation in *KIT*.

In view of the severity of the patient's symptoms, she was treated with interferon- α (1.5×10^6 U subcutaneously once daily). This was discontinued after 4 weeks because of intolerable nausea and flushing. There was no response to thalidomide (up to 100 mg orally once daily for 8 weeks). The patient was very keen to avoid chemotherapy if possible. The tyrosine kinase inhibitor nilotinib, administered at 400 mg orally twice daily gave no improvement after 3 months, and was discontinued. Owing to the continuing severity of the patient's symptoms, cytoreductive therapy with cladribine was initiated [five cycles of a 5-day course of intravenous (IV) cladribine 0.13 mg/kg once daily, over 5 months]. During her first cycle, she developed watery diarrhoea and erythematous plaques over her limbs and trunk, probably due to release of mediators from destroyed mast cells. Subsequent courses were better tolerated with IV pirarcton and hydrocortisone administered pre-dose. Prophylactic antimicrobials (oral itraconazole 200 mg twice daily, oral aciclovir 400 mg twice daily and nebulized pentamidine 300 mg monthly) were given throughout the treatment.

At follow-up 4 years later, the patient had only mild pruritus controlled with loratadine (10 mg twice daily) and improvement in her gastrointestinal symptoms. She had postinflammatory hyperpigmentation in previously affected areas (Fig. 3). Her serum tryptase fell

from an initial level of 64.7–15.7 $\mu\text{g/L}$ after cladribine therapy, and is 32.4 $\mu\text{g/L}$ 4 years later.

Most adults with SM have ISM, with no significant symptoms and a stable clinical course, carrying a good prognosis.⁴ There is no curative treatment for CM or SM, with management being aimed at controlling symptoms. Antihistamines, antileucotriene agents and mast cell stabilizers are the mainstay of treatment.⁵ Some patients appear to be at increased risk of osteopenia and osteoporosis,⁶ and should be investigated appropriately.

Other therapies can also be used in the management of SM. Interferon- α , starting at 1–3 MU subcutaneously three times/week can be used,³ but its side effects are poorly tolerated. Thalidomide has been used successfully to treat two patients with advanced SM, but additional efficacy and safety data is lacking.⁷ Cytoreductive therapy with cladribine is usually restricted to ASM or MCL, owing to the paucity of evidence for its use and potential side effects. Some evidence suggests that it has therapeutic activity in all SM subtypes.¹ One study followed 26 patients with SM treated with IV cladribine 0.13–0.17 mg/kg for 5 days, for a median of three cycles. They showed overall response rates of 55%, with a median duration of response of 11 months.⁸ However, side effects include fever, headaches, nausea and diarrhoea. Other side effects include myelosuppression, lymphopenia and the risk of opportunistic infections. The risks and benefits should be weighed and discussed in detail with the patient.

More novel treatments for refractory or aggressive SM are tyrosine kinase inhibitors (e.g. nilotinib,



Figure 3 Right axilla of patient (a) before and (b) after treatment with cladribine.

imatinib, dasatinib, midostaurin and masitinib mesylate). Nilotinib has shown promise in a phase II study (60 patients, overall response rate 20%) in patients with SM. Although tolerated well by our patient, reported adverse effects included headaches, diarrhoea and thrombocytopenia.⁹ Imatinib mesylate, masitinib mesylate and dasatinib have all shown some clinical benefit to patients in several studies.¹ Midostaurin (PKC412) has shown benefit in SM, including in a patient with the D816V mutation.¹⁰

In conclusion, we report a case of a 62-year-old woman with SM, associated with osteoporosis, gastrointestinal symptoms and intolerable pruritus, which was refractory to most treatments but responded to cladribine.

Learning points

- Dermatological symptoms in mastocytosis can be treated with oral antihistamines, potent topical steroids, mast cell stabilizers and phototherapy.
- Mediator-induced symptoms of systemic mastocytosis can be severely debilitating and have a huge effect on a patient's quality of life.
- Nonresponders may benefit from cytoreductive therapy with cladribine.
- Serum tryptase levels should be performed regularly in adults and children, and patients should be referred for a haematology opinion if this is > 20 µg/L on at least two occasions.
- Patients should be investigated for osteoporosis and gastrointestinal involvement.
- Patients with the common D816V mutation in *KIT* have been shown to be resistant to the tyrosine kinase inhibitor imatinib, therefore mutational analysis may prove helpful when considering therapy.

References

- 1 Pardanani A. Systemic mastocytosis in adults: 2012 update on diagnosis, risk stratification, and management. *Am J Hematol* 2012; **87**: 401.
- 2 Horny HP, Metcalfe DD, Bennett JM *et al.* Mastocytosis. In: *WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues*, 4th edn (Swerdlow SH, Campo E, Harris NL *et al.*, eds). Lyon, France: International Agency for Research and Cancer (IARC), 2008; 54–63.
- 3 Akin C. Clonality and molecular pathogenesis of mastocytosis. *Acta Haematol* 2005; **114**: 61–9.
- 4 Lim KH, Tefferi A, Lasho TL *et al.* Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood* 2009; **113**: 5727–36.
- 5 Bologna JL, Jorizzo JL, Schaffer JV *et al.* (eds). *Dermatology*. 3rd edn. Vol. 2. Beijing, China: Elsevier Saunders, 2012; 1993–2002.
- 6 Brumsen C, Papapoulos S, Lentjes E *et al.* A potential role for the mast cell in the pathogenesis of idiopathic osteoporosis in men. *Bone* 2002; **31**: 556–61.
- 7 Damaj G, Bernit E, Ghez D *et al.* Thalidomide in advanced mastocytosis. *Br J Haematol* 2008; **141**: 249–53.
- 8 Lim KH, Pardanani A, Butterfield JH *et al.* Cytoreductive therapy in 108 adults with systemic mastocytosis: outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. *Am J Hematol* 2009; **84**: 790–4.
- 9 Hochhaus A, Ottmann OG, Lauber S *et al.* A phase II study of nilotinib, a novel inhibitor of c-Kit, PDGFR, and Bcr-Abl, administered to patients with systemic mastocytosis. *Blood* 2006; **108**: Abstract 2703.
- 10 Gotlib J, DeAngelo DJ, George TI *et al.* KIT inhibitor midostaurin exhibits a high rate of clinically meaningful and durable responses in advanced systemic mastocytosis: report of a fully accrued phase II trial. ASH Annual Meeting Abstracts. *Blood* 2010; **116**: Abstract 316.