

Case report

Systemic mastocytosis: variable manifestations can lead to a challenging diagnostic process

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SUMMARY

Systemic mastocytosis results from proliferation and activation of an abnormal mast cell clone. It is a heterogeneous disorder with clinical manifestations ranging from skin lesions alone to aggressive multi-organ infiltration and decreased survival. Given these varied manifestations, diagnosis can be difficult. We describe the case of a woman who presented with rash and diarrhoea and had a history of anaphylactic reactions. Over a protracted period, the patient's symptoms were investigated by a number of specialties including gastroenterology, dermatology, immunology and haematology. Morphological, immunohistochemical and molecular analysis of bone marrow samples ultimately led to a diagnosis of systemic mastocytosis. Management with leukotriene and histamine antagonists resulted in significant improvement in symptoms and quality of life. The case serves to highlight the protean manifestations of systemic mastocytosis, the tests available to diagnose it and the agents available to treat it.

BACKGROUND

Systemic mastocytosis is a rare disorder with an annual incidence of 0.89 per 100 000.¹ Normal mast cells develop from haematopoietic progenitors and have a role in immune function.² They are activated on binding to an antigen (allergen) which cross-links antigen-specific IgE on the mast cell surface. They can also be activated by non-specific triggers, including the physical stimuli of pressure and stress, and substances such as alcohol, aspirin, opioids, anticholinergics and radioactive dyes. Activation leads to secretion of vasoactive and proinflammatory mediators.

Symptoms in systemic mastocytosis can result from either release of mediators or infiltration of tissues by the mast cells. Organ-specific symptoms can involve the skin (rashes, flushing), gastrointestinal tract (diarrhoea, vomiting), heart (syncope, tachycardia), lungs (shortness of breath, wheeze), nervous system (concentration problems, migraines, depression) and musculoskeletal system (bone pain, osteopenia). Non-specific symptoms include fatigue, malaise and allergic reactions (anaphylactic reactions are more common in patients with mastocytosis compared with the general population).³

The most severe variant—aggressive systemic mastocytosis—is associated with decreased life expectancy. However, even in the indolent form (where life span is normal), systemic mastocytosis is a serious condition given the potential for

symptoms to have a profound effect on quality of life. Reaching the diagnosis of systemic mastocytosis is thus important but can be complicated by the wide variability in presenting symptoms.

This case exemplifies these diagnostic difficulties and illustrates the tools available to help reach the diagnosis. The case also provides context to describe available treatments, some of which have been recently developed.

CASE PRESENTATION

The patient, who is a retired consultant doctor, was referred to the haematology team in 2016 with a long-standing rash, flushing and diarrhoea. The rash was macular and pruritic and had first appeared 15 years earlier progressing to affect the torso, thighs and face. In 2013, the patient was reviewed by two dermatologists and an immunologist. Mast cell tryptase was mildly elevated and a diagnosis of mastocytosis was considered but skin biopsies demonstrated only non-specific changes. The diarrhoea had been investigated by gastroenterology in 2010 and had been attributed to coeliac disease following typical findings on endoscopic biopsy. In 2016, endoscopy was repeated given ongoing frequent bowel movements despite adherence to a gluten-free diet. This was reported as normal. Given persistence of all symptoms, further review by immunology took place in 2016 who referred to haematology for consideration of a bone marrow test to investigate further for systemic mastocytosis.

The patient's history was also notable for recurrent anaphylactic reactions to wasp stings which first manifested when she was 3 years old. She tested positive for IgE specific to common wasp venom, and aged 43 to 46 years she underwent de-sensitisation therapy to wasp stings, with good effect. The patient also had allergies to a number of medications. She had previously been diagnosed with asthma, hypothyroidism and osteopenia.

INVESTIGATIONS

Systemic mastocytosis is diagnosed in accordance with WHO criteria.⁴ WHO recognises three main subtypes:

- ▶ Cutaneous mastocytosis (including urticaria pigmentosa), which affects the skin only.
- ▶ Systemic mastocytosis, which involves mast-cell infiltration of organs in addition to, or other than, the skin.



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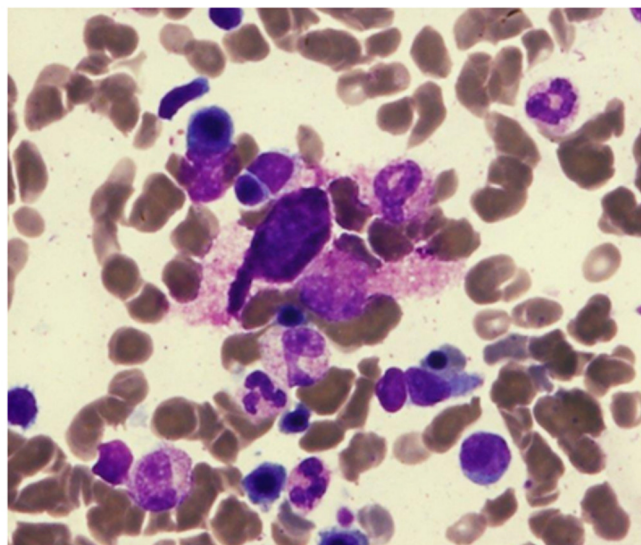


Figure 1 Bone marrow aspirate sample from the patient showing a mast cell of abnormal morphology (spindle-shaped cell in centre of picture).

- Mast cell sarcoma, which involves a unifocal mast cell tumour without evidence of systemic mastocytosis.

Diagnosis of systemic mastocytosis is based on the presence of a minimum number of WHO diagnostic criteria: either one major and one minor criterion, or three minor criteria, must be present. The major criterion is multifocal clustering of mast cells (>15 cells per cluster) in an extracutaneous organ, typically the bone marrow. The minor WHO criteria include: (1) basal serum tryptase of ≥ 20 ng/mL; (2) abnormal or spindle-shaped mast cell morphology in >25% of mast cells in an infiltrate; (3) aberrant expression on mast cells of the markers CD2 or CD25 or (4) presence of the D816V mutation in *KIT*, the gene which encodes the CD117 cell surface receptor.

In our patient, basal mast cell tryptase levels had been tested on a number of occasions but levels were consistently below 20 ng/mL and therefore did not fulfil this minor criterion. Skin biopsies performed in 2013 and 2014 did not show evidence of mastocytosis, nor did duodenal and colonic biopsies performed in 2010 and 2016. The bone marrow biopsy performed in 2017 was key in confirming the diagnosis: It demonstrated mast cells of abnormal morphology (see figure 1), which expressed CD25 on immunohistochemical analysis and *KIT* D816V on mutational analysis. These findings represented three of the WHO minor diagnostic criteria. Intestinal biopsy samples were subsequently re-reviewed in the light of this, and those from the 2016 colonoscopy were felt to be morphology from the colonoscopy was in keeping with mastocytosis. On the basis of the combination of clinical presentation and laboratory findings, a diagnosis of systemic mastocytosis was reached.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses included gastrointestinal conditions such as gluten enteropathy/inflammatory bowel disease; endocrinological conditions such as pheochromocytoma/carcinoid syndrome; autoimmune conditions including vasculitis; allergic conditions; angio-oedema; drug reactions and systemic mastocytosis. If investigation had not ultimately revealed a clonal mast cell population, a diagnosis of mast cell activation syndrome (MCAS) would have been considered. This syndrome presents with typical features of mast cell activation but without evidence

of a clonal mast cell disorder. No consensus diagnostic criteria exist for MCAS but proposed criteria have been published incorporating symptoms, measurement of a mast cell mediator such as mast cell tryptase and response of symptoms to antagonists of mast cells or their mediators.⁵

TREATMENT, OUTCOME AND FOLLOW-UP

General comments

Treatment of systemic mastocytosis depends on severity.³ Classification of severity is based on the presence or absence of particular clinical features referred to as B and C findings. The definitions of B and C findings are laid out in detail in the WHO criteria but key features are as follows⁴:

- B findings: include >30% infiltration of bone marrow by mast cells and serum tryptase level >200 ng/mL; dysplasia or myeloproliferation in non-mast cell lineages with normal or slightly abnormal blood counts; hepatomegaly without impaired liver function; palpable splenomegaly without hypersplenism and/or lymphadenopathy.
- C findings: include bone marrow dysfunction manifest by cytopenias; palpable hepatomegaly with impaired liver function, ascites and/or portal hypertension; skeletal involvement with osteolytic lesions and/or pathological fractures; palpable splenomegaly with hypersplenism or malabsorption with weight loss due to gastrointestinal mast cell infiltrates.

These definitions of B and C findings are then applied in the classification of severity. Put simply this is as follows (see WHO criteria for further detail):

- Indolent: Meets the general criteria for systemic mastocytosis; no more than one B finding; ; no C findings.
- Smouldering: Presence of two or more B findings; no C findings.
- Aggressive: Presence of at least one C finding.
- Mast cell leukaemia: Atypical mast cells accounting for >20% of total nucleated cells in bone marrow aspirate smears.

The management for indolent and smouldering systemic mastocytosis is primarily symptomatic plus monitoring for signs of progression. Pharmacological agents aim to antagonise the effects of mast cell mediators. Such agents include antihistamines (H1 and H2 antagonists), leukotriene antagonists (eg, montelukast), proton pump inhibitors, mast cell stabilisers (cromolyns), psoralen with ultraviolet light, steroids and monoclonal antibodies such as omalizumab. Patients with systemic mastocytosis should be aware of potential triggers of a symptomatic episode. Consideration should be given to provision of medical alert bracelets and epinephrine pens to use in case of anaphylaxis. Psychological well-being should be assessed.

For aggressive systemic mastocytosis, therapies that interfere with mast cell proliferation and survival can be considered. Traditionally agents such as the purine analogue, cladribine or interferon alpha have been used. Attempts are being made to employ more directed therapies, in particular, tyrosine kinase inhibitors (TKIs) which target the mutated *KIT* receptor. Midostaurin is one such agent and has been approved by both the European Medicines Agency and the United States Food and Drug Authority for use in systemic mastocytosis. A global phase 2 study is ongoing evaluating the efficacy and safety of avapritinib (BLU-285), a more selective *KIT* D816V inhibitor, in patients with advanced systemic mastocytosis.⁶ Stem cell allograft may be considered in selected patients with aggressive disease. In indolent mastocytosis another highly selective TKI, masatinib, was compared with best symptomatic management in a phase 3 trial

conducted in 2017.⁷ To date, masitinib has not been approved for use in indolent disease.

Management, follow-up and outcome for our patient

Our patient was concluded to have indolent systemic mastocytosis. Early in her workup, the leukotriene antagonist, montelukast, had been started empirically, which provided partial relief of the rash. Once the diagnosis of systemic mastocytosis was reached, the mast cell stabiliser cromoglycate was added but this worsened the patient's existing symptoms plus precipitated new symptoms (dizziness and flushing). Cromoglycate was thus ceased and the H2 antagonist, ranitidine, was started which resulted in marked improvement of all symptoms. Given

Patient's perspective

Originally, the visibility of the skin rash on my neck and face (having spread from my thighs and trunk) took me to a dermatologist. He queried systemic mastocytosis but thought the symptoms were not severe enough and treated me for an urticarial rash. A second dermatologist then took two biopsies (inconclusive) but did not request serum tryptase. Fortunately, I then saw an immunologist who found that I had a slightly raised tryptase level and referred me to haematology.

It has been a long journey but now I am feeling well, full of energy and enjoying retirement. 'Do not adjust your mind, there is fault in reality'.

Learning points

- Systemic mastocytosis may present with a variety of symptoms, many of which are non-specific. A low index of suspicion is required to facilitate appropriate investigation.
- WHO criteria for diagnosis include molecular, morphological, immunohistochemical and biochemical parameters. If there is clinical suspicion of systemic mastocytosis, comprehensive investigation using the WHO criteria should be performed by an appropriate specialist.
- Even in its indolent form, where lifespan is normal, mastocytosis can have a profound effect on quality of life including through debilitating symptoms and increased incidence of anaphylaxis.
- Indolent and smouldering mastocytosis can often be successfully managed symptomatically, using agents which antagonise the effects of mast cell mediators. Different agents may have variable efficacy and side effects in different patients, meaning that a trial of alternative agents is worthwhile if an initial regimen is not successful.
- A new era of targeted treatments is emerging in the form of tyrosine kinase inhibitors.

her history of anaphylaxis, the patient was already educated on trigger avoidance, carried epinephrine pens and wore a medicine alert bracelet. The patient is followed up 3–6 months in haematology clinic with input from other medical specialties as required. The patient's organ function remains normal.

DISCUSSION

This case exemplifies the diagnostic difficulties surrounding systemic mastocytosis, which are in part driven by its variable and non-specific manifestations. This point has been alluded to in previous case reports by rheumatologists and gastroenterologists.^{8,9} Our case illustrates the role of multiple specialities in diagnosis and the need for a low threshold for comprehensive investigation if there is clinical suspicion of systemic mastocytosis. Investigation should incorporate molecular, immunohistochemical and morphological techniques. Confirming the diagnosis facilitates comprehensive management and appropriate follow-up, leading to a transformative effect on the patient's quality of life.

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