REVIEW

Systemic mastocytosis: a gastroenterological perspective

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Abstract

A 53 year old woman presented with abnormal liver function tests and subsequently developed intermittent abdominal pain, vomiting and diarrhoea. There were no rash or anaphylactoid reactions. Endoscopic biopsies showed excessive density of eosinophils and immunohistochemical staining for tryptase revealed a florid mast cell infiltrate. A diagnosis of systemic mastocytosis was made by bone marrow biopsy. Systemic mastocytosis is a rare myeloid neoplasm often associated with gastrointestinal symptoms due usually to mediator release but may rarely represent organ infiltration. While endoscopic and routine biopsy appearances are non-specific, suggestive features should lead to staining for mast cell tryptase or CD 117. However, diagnose generally requires bone marrow biopsy. The prognosis in the majority of patients is good and supportive management only is required. For patients with aggressive disease, cytoreductive therapy may be needed.

Case history

A previously healthy 53-year-old woman was first reviewed by a gastroenterologist in 2007 for abnormal liver function tests (LFTs). The alkaline phosphatase was 112 g/l (normal 30–90 g/l), γ -glutamyl transferase 126 U/l (normal <38 U/l) and alanine aminotransferase 57 U/l (normal <47 U/l). Clinical examination was unremarkable. Abdominal imaging with an ultrasound and subsequent CT scans was considered normal as were the remainder of the blood tests including the viral serology. The patient declined a liver biopsy. A presumptive diagnosis of non-alcoholic steatosis was made and lifestyle modification, exercise and weight loss were recommended.

In October 2010, the patient was once again reviewed by her gastroenterologist.

The abnormal LFTs persisted, and she described intermittent abdominal pain, vomiting and diarrhoea. A colonoscopy was performed (see figures 1 and 2).

Q1. What is your differential diagnosis based on the endoscopic and microscopic appearances?

Q2. What additional investigations would you order to refine your diagnosis?

Background and clinical manifestations

Systemic mastocytosis is characterised by the abnormal growth and proliferation of mast cells in one or more visceral organs and is classified as a myeloproliferative neoplasm.¹ More than 90% of cases of systemic mastocytosis can be explained by a gain-of-function mutation in the tyrosine kinase receptor CD117 on the mast cell surface leading to deregulated replication and accumulation.² Due to its rarity, the incidence has not been determined but case reports and aetiological surveys suggest a prevalence of between 1/300 000 and 1 000 000 people.¹ The condition occurs with equal frequency in men and women with a mean age at diagnosis of 50 years.¹ Gastrointestinal symptoms are common, with more than 60% of patients complaining of abdominal pain, nausea, diarrhoea or vomiting.¹ The symptoms are thought to be secondary to mediator release (such as histamine, leukotrienes, prostaglandins) although infiltration of the gut does occur in an unknown percentage of cases and can result in endoscopically definable lesions (see below).^{3–4} Other common features are a history of itch and skin rash (present in 50% of cases and appearing in several forms including urticaria pigmentosa), hepatosplenomegaly (30%), idiopathic and recurrent anaphylactoid reactions (15%), weight loss and fatigue.⁵

Figure 1 Views at colonoscopy of the sigmoid colon showing non-specific nodularity, oedema and ulceration.

Investigations and diagnosis

The diagnosis of systemic mastocytosis is based on a bone marrow and/or visceral organ biopsy according to WHO criteria.⁶ In practice, a bone marrow trephine biopsy is almost always performed to allow accurate cell counts, immunocytochemistry and genetic investigations for c-KIT mutations. A definitive diagnosis is based on finding one major plus one minor criterion or three minor criteria. The major criteria are the presence of multiple dense infiltrates of more than 15 mast cells in the bone marrow or in other extracutaneous organs detected by immunohistochemical stains. Minor criteria are an abnormal mast cell morphology, c-KIT mutation at codon 816, an aberrant CD25+ and/or CD2+ mast cell immunophenotype and/or serum total tryptase of >20 ng/ml.⁶ Confirmed cases are then subclassified according to WHO criteria (see table 1).

Investigation involves a combination of blood tests, endoscopy, imaging, bone marrow biopsy and genetic characterisation as outlined in table 2. A key investigation that may give a clue to the presence of systemic mastocytosis is an elevated serum tryptase (> 11.5 ng/ml), since this was found in 90% of patients in the largest case series to date.¹ Performing mast cell tryptase at least twice—ideally one when the patient is symptomatic and one when the patient is well—may improve the diagnostic yield particularly as it remains elevated independently of the symptoms.¹ Other common findings include a mixed disturbance in LFTs—30% had elevations in two or more of alanine aminotransferase, alkaline phosphatase and γ -glutamyl transferase—and eosinophilia (15%).⁷

Figure 2 Histology from biopsies of the sigmoid colon. A florid mast cell infiltrate is demonstrated with the use of the mast cell tryptase immunohistochemical stain.

Intestinal infiltration of mast cells in cases of systemic mastocytosis has been well documented, but its prevalence is unknown due to the rarity of the condition and the variable availability and need for endoscopy.⁸ Endoscopic features are non-specific but include nodularity of the mucosa in the stomach or intestines as well as erythematous and ulcerative lesions resembling more common disease processes such as enteropathy secondary to non-steroidal anti-inflammatory drugs or inflammatory bowel disease.⁴

The histological findings in cases of systemic mastocytosis are also non-specific using standard H&E stains; a mixed inflammatory infiltrate including mast cells may be seen in a variety of intestinal conditions including inflammatory bowel disease and even possibly irritable bowel syndrome.³ Hence, given the apparent lack of specific diagnostic markers, the ordering of further, non-routine diagnostic techniques may occur when systemic manifestations are present to alert the astute clinician to this potential albeit very rare diagnosis, or on occasion when the changes on H&E are very florid and arouse suspicion. Histopathological features particularly suggestive but not diagnostic for systemic mastocytosis include expansion and distortion of the lamina propria, abnormal mast cells sometimes resembling histiocytes and coexistent abundant eosinophilic infiltrates.⁹ Visualisation of mast cells is greatly enhanced by the use of stains including giemsa, toluidine blue, mast cell tryptase and CD117 (c-KIT).⁹ The astute clinician and/or pathologist hence need to order alternative stains and usually a bone marrow biopsy in suspected cases.

Prognosis

The prognosis varies according to the disease subtype (see table 1). Patients with *indolent systemic mastocytosis* have a good prognosis and their life expectancy is the same as that of healthy controls.¹⁰ Patients with dense mast cell infiltrates and organ infiltration

Table 1 Modified WHO classification of systemic mastocytosis subtypes (adapted from Lim *et al*)¹

Disease	Subtype	Manifestations	Prognosis
Cutaneous mastocytosis		Urticaria pigmentosa. No organ infiltration	Excellent
Systemic mastocytosis	Indolent systemic mastocytosis	Organ infiltration. No organ dysfunction	Good, no effect on mortality
	Smouldering systemic mastocytosis	Organ infiltration. No organ dysfunction. Dense mast cell infiltrate $\pm$ appearance of myelodysplasia	Intermediate, often live for decades
	Associated haematological non-mast cell lineage disease		Variable, often determined by associated haematological disorder
	Aggressive systemic mastocytosis	Organ infiltration and organ dysfunction, eg, abnormal liver function tests, cytopenias	Poor
Mast cell leukaemia		High numbers of circulating mast cells. Dense organ infiltration. Organ dysfunction	Very poor

Table 2 Investigations for systemic mastocytosis

Investigation	Key findings	Significance
Blood tests	Serum tryptase will be elevated in approximately 90% (cut-off 11.5 ng/ml) Liver function tests mixed abnormalities, eg, elevation GGT, ALP and ALT. Full blood examination	Common in aggressive systemic mastocytosis (ASM). Poor prognosis. Cytopenias are common in ASM. Also found in associated haematological non-mast cell lineage disease (AHNMD) Eosinophilia ($>1.5 \times 10^9/l$) Approximately 30% of ASM, rare in indolent disease Mast cell leukaemia is very rare but should be excluded, $>10\%$ abnormal mast cells
Imaging (CT or other)	Hepatosplenomegaly, lymphadenopathy	Can be associated with organ dysfunction (ASM) and poor prognosis
Gastrointestinal endoscopy	The oesophagus, stomach, small and large intestine can be involved. Findings include nodularity, granularity and ulceration. May require special stains and immunohistochemistry to delineate mast cells. Often accompanied by eosinophilic infiltrate	Macroscopic appearance is non-specific. Helps to distinguish between disease caused by mediator release and organ infiltration; the latter may require cytoreductive therapy and portends a poor prognosis
Bone marrow biopsy	Dense mast cell aggregates (15 or more mast cells). Abnormal mast cell morphology in 25% or more	Usually needed for a diagnosis (see text). Also can help diagnosed AHNMD and mast cell leukaemia.
Genetic test	Codon 816 c-kit mutation in blood, marrow or tissue biopsy	Found in 90% of cases. Helpful diagnostically. Defines imatinib resistance

ALP, alkaline phosphatase; ALT, alanine aminotransferase; GGT, γ -glutamyl transferase.

in the absence of organ dysfunction (*smouldering mastocytosis*) have a variable prognosis but often live for decades.¹¹ Together, these two subtypes account for approximately two-thirds of cases. Organ infiltration *with* evidence of organ dysfunction such as abnormal LFTs or cytopenias (*aggressive systemic mastocytosis*) is associated with a relatively poor prognosis.¹² Systemic mastocytosis can be associated with haematological clonal non-mast cell disorders (usually myelodysplasia) and have a variable prognosis, or more rarely represent or transform to mast cell leukaemia and have a very poor prognosis.¹² Some patients who have a persistently elevated serum mast cell tryptase but do not satisfy the criteria for a diagnosis of systemic mastocytosis on bone marrow biopsy may be classified as having a 'clonal mast cell activation syndrome'.¹³

Case progress and commentary

The patient did not have any history or clinical examination findings specific for systemic mastocytosis,

such as a skin rash or anaphylactoid reaction, but did have gastrointestinal symptoms presumably related to localised disease (see figures 1 and 2) and possibly systemic mediator release. The first clue that the patient had systemic mastocytosis was following histological assessment of the endoscopic biopsies, where a florid eosinophilic infiltrate was noted and mast cell tryptase stains performed (see figure 2). The serum tryptase was 14 ng/ml (upper limit of normal <8 ng/ml). A bone marrow biopsy was subsequently performed that was consistent with a diagnosis of systemic mastocytosis and the patient was treated according to the principles outlined in table 3.

Treatment

Diagnosis and co-ordination of management is usually by a haematologist or specialist in clinical allergy and immunology. A treatment approach according to the disease subtype is summarised in table 3. Supportive treatment to alleviate gastrointestinal and cutaneous

Table 3 Treatment of systemic mastocytosis

Symptoms	Medication	Patient instructions	Practical tips/rationale
Gastrointestinal (GI), eg, nausea, diarrhoea, pain	H ₁ antagonist	Regular orally (PO), eg, cetirizine 10 mg PO BD	Larger than standard doses may be needed
	H ₂ antagonist	Regular PO, eg, ranitidine 150 mg PO BD	Gastric ulceration is reported in systemic mastocytosis, possibly related to H ₂ stimulation
	Mast cell stabiliser	Regularly PO Sodium cromoglycate 200 mg QID	
	Proton pump inhibitor	Regular PO, eg, esomeprazole 40 mg daily	Add-on treatment when antihistamines ineffective
Systemic mediator release (eg, flushing, sweating, GI)	H ₁ antagonist	As for GI	As for GI
Refractory GI or systemic mediator release symptoms	Corticosteroids	Regular PO, eg, prednisolone 40 mg PO daily	May be a bridge to cytoreductive therapy in ASM
Anaphylactoid reactions	Adrenaline auto-injector	To be carried on person and/or stored nearby	Careful instruction needed. Patient to wear medical alert bracelet or similar
Anaphylaxis to insect bite	Allergen immunotherapy	Lifelong	Use adrenaline auto-injector medical alert bracelet
Organ dysfunction (eg, cytopenias, massive hepatomegaly, abnormal liver function)	Consider cytoreductive therapy		Various agents being trialled (see text)

ASM, aggressive systemic mastocytosis; BD, twice daily; QID, four times a day.

symptoms can be used for all disease subtypes. H₁ and H₂ antagonists and mast cell stabilisers are routinely recommended, and proton pump inhibitors may be needed as add-on therapy.¹² Patients with a history of anaphylaxis should carry and be instructed on the use of an adrenaline auto-injector. If the episode was associated with an insect sting, ongoing desensitisation could be recommended.¹² For severe refractory symptoms such as recurrent anaphylaxis, case reports suggest a role for omalizumab, a biological agent that blocks immunoglobulin E attachment to mast cells and eosinophils.¹⁴

Cytoreductive therapy may be advocated in cases of systemic mastocytosis with associated haematological non-mast cell lineage disease or aggressive systemic mastocytosis when organ dysfunction is symptomatic (eg, cytopenias, massive hepatosplenomegaly).¹² No therapy has been shown to alter the natural history of systemic mastocytosis: cure is not possible.¹² Given the rarity of the disorder, only a small number of treatment studies have been undertaken.¹ Most cases of systemic mastocytosis involve mutation D816V in the cell surface tyrosine kinase receptor (c-KIT). Since this mutation differs from that often found in gastrointestinal stromal tumours (the K551-E560 mutation), imatinib (a tyrosine kinase inhibitor used with great success in chronic myeloid leukaemia and gastrointestinal stromal tumours) is relatively ineffective.¹² Alternative agents, including combination chemotherapy regimens, are currently being trialled.¹²

Summary

Systemic mastocytosis is a very rare myeloid neoplasm. Gastrointestinal symptoms are common and often result from mediator release, but more rarely represent organ infiltration. As the gastrointestinal

manifestations and endoscopic findings are non-specific, the coexistence of associated clinical features, such as a rash, a history of anaphylactoid reactions or the histological finding of a florid eosinophilia at endoscopy and biopsy, may be the first clues to prompt further diagnostic techniques such as stains for mast cell tryptase or for CD117. A definitive diagnosis usually relies on a bone marrow trephine biopsy. Referral to a haematologist is essential. The prognosis for the majority of patients is good, and for many supportive management only is required. For patients with aggressive disease, cytoreductive therapy may be needed.

Competing interests None.

Patient consent Obtained.

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