CASE REPORT

Diagnostic Challenges of Systemic Mastocytosis With Gastrointestinal Involvement.

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ABSTRACT

Systemic mastocytosis is a rare disorder defined by an abnormal proliferation of atypical mast cells within extracutaneous organs. The diagnosis of this neoplasm can be challenging because of its nonspecific clinical presentation. We report a case of systemic mastocytosis presenting with gastrointestinal symptoms, reflecting the complexities of making the diagnosis. A 49-year-old male initially thought to have eosinophilic colitis continued to have chronic diarrhoea. Serial biopsies of the terminal ileum and colon showed mastocytosis. Further investigations revealed atypical mast cells within bone marrow with aberrant CD25 expression. Molecular studies showed a D816V mutation in the c-KIT gene which supported the diagnosis of systemic mastocytosis. Gastrointestinal symptoms are seen in about 60% to 80% of patients with systemic mastocytosis. Therefore, this neoplasm should be considered as a differential diagnosis in patients presenting with non-specific symptoms such as abdominal pain, diarrhoea, bloating and vomiting in the absence of common causes.
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Keywords: Systemic mastocytosis, Gastrointestinal manifestation, Chronic diarrhoea, D816V mutation, Eosinophilia.

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INTRODUCTION

Mast cells are mononuclear cells of haematopoietic lineage which play an important role in the immune response (1). They were first identified and reported by Paul Ehrlich in 1878 (1). Mast cells originate from haematopoietic pluripotent stem cells in the bone marrow and reach the peripheral blood circulation as mast cell precursors (1). Once these precursor cells reach various tissues in response to several cytokines and growth factors, they differentiate into mature mast cells (1). Consequently, mature mast cells are only seen in tissues and not in peripheral blood circulation. Mastocytosis is defined as a heterogeneous group of disorders attributed to abnormal proliferation and accumulation of mast cells within cutaneous and/or extracutaneous tissues (1). It is a rare disease with an estimated annual incidence of 6.6 per 1 million persons (1). According to the 2022 World Health Organization (WHO) classification system, mastocytosis can be broadly divided into three groups: cutaneous mastocytosis, systemic mastocytosis and mast cell sarcoma (2). The clinical symptoms of systemic mastocytosis depend on the type of mediators released from its granules and the organ system affected. If the gastrointestinal system is involved, the diagnosis of systemic mastocytosis can be challenging due to its non-specific manifestations. In this case, we will address the challenges of detecting systemic mastocytosis with gastrointestinal involvement, emphasising the complexity that hinder proper diagnosis.

CASE REPORT

A 49-year-old man initially presented with upper abdominal pain and diarrhea for three months. Upper gastrointestinal endoscopy showed peptic ulcer disease while colonoscopy showed colitis with a small internal haemorrhoid. Initial biopsies of the colon favoured eosinophilic colitis, but clinically there was no associated atopy or parasitic infestation identified. The patient continued to have diarrhoea with 1-2 episodes of loose stools per day (Bristol Stool Chart Type 6) over the subsequent 12 months. He had no fever, dysphagia, abdominal pain, nausea, vomiting, constitutional symptoms, or cutaneous manifestations throughout. There was no history of recent travelling and there was no intake of either over-the-counter or traditional medications. He did not exhibit any weight loss,

steatorrhea, or electrolyte imbalances. Laboratory tests, such as renal profile and liver function test including albumin were within range. Physical examination showed no ascites or hepatosplenomegaly. Full blood count and anaemia profile revealed mild iron deficiency anaemia with reactive thrombocytosis. He also had persistent mild eosinophilia since February 2023, ranging between 0.58x109/L - 0.79x109/L. Repeated upper gastrointestinal endoscopy showed features of gastritis and duodenitis while colonoscopy showed only loss of normal mucosal folds at the caecum. Reviewed alongside the first biopsy, repeat biopsies of the terminal ileum, cecum, ascending, transverse, and descending colon revealed infiltration of atypical mast cells, most prominently in the superficial lamina propria and rimming crypts which were admixed with eosinophils, lymphocytes, histiocytes, and plasma cells (Figure 1). These atypical mast cells were medium-sized cells with ovoid nuclei, inconspicuous nucleoli and pale cytoplasm that co-expressed CD117 and CD25 (Figure 2) with very focal expression of Tryptase. A subsequent full blood picture showed no circulating blast or mast cells while a bone marrow aspirate showed normocellular marrow with about 2% mast cells. There was no evidence of leukaemia or lymphomatous infiltration. A trephine biopsy showed infiltration of mast cells forming multifocal aggregates of more than fifteen mast cells per aggregate (Figure 3a). Most of these mast cells were of atypical immature forms (promastocytes) while others were medium sized, rounded to spindle shaped cells with elongated nuclei, inconspicuous nucleoli, and ample pale agranular cytoplasm. These mast cells were positive for CD117 (KIT) and tryptase with aberrant CD25 expression as shown by figures 3b, 3c and 3d respectively. Serum Tryptase level was not available. Molecular study of bone marrow aspirate sample using quantitative real time polymerase chain reaction (PCR) showed the presence of a D816V mutation in the c-KIT gene which favoured the diagnosis of systemic mastocytosis. The patient was initially prescribed 30mg of oral prednisolone for five months, gradually reduced to 5mg daily, with no other intervention.

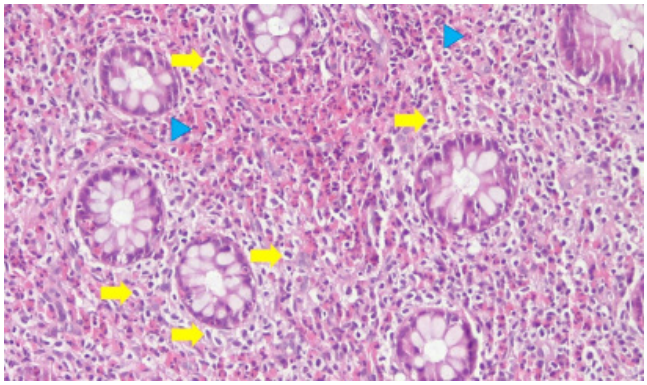

Figure 1: Diffuse infiltration of atypical mast cells (yellow arrow) admixed with prominent eosinophils (blue arrowhead), lymphocytes and plasma cells within the intestinal mucosa (H&E, original magnification 200x)

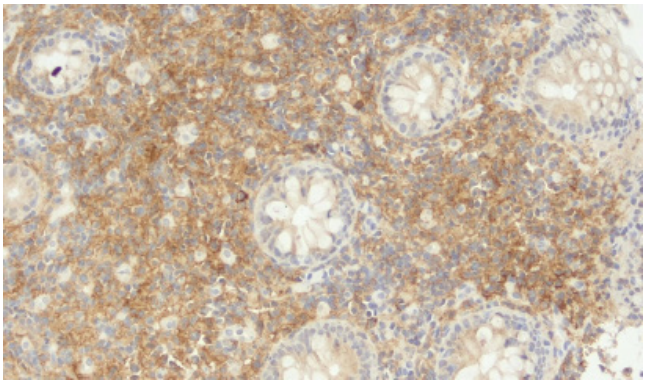

Figure 2: The atypical mast cells express CD25 (Immunohistochemistry, original magnification 200x)

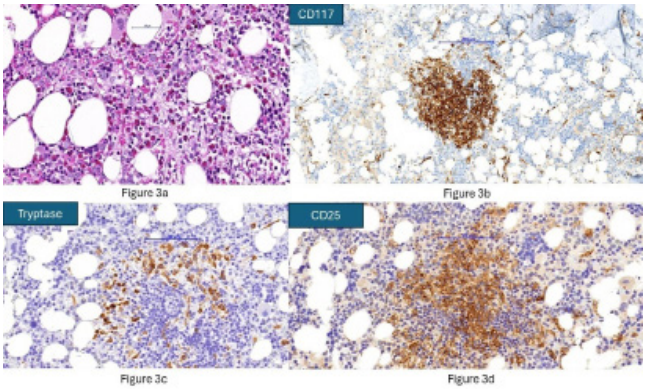

Figure 3a – 3d: (3a) The trephine biopsy shows infiltration of atypical mast cells intermixed with a significant population of eosinophils (H&E, original magnification 400x). (3b, 3c, 3d) Immunohistochemistry analysis shows atypical mast cells positive for CD117 (original magnification 200x), tryptase (original magnification 400x), and aberrant CD25 expression (original magnification 400x), respectively.

DISCUSSION

Systemic mastocytosis is a heterogeneous disease defined by abnormal proliferation and accumulation of atypical mast cells in extracutaneous organs (1). Morphologically, progenitor mast cells are agranular mononuclear cells with CD34 and CD117 surface receptors (3). As these progenitor cells enter peripheral tissues, they gain complete morphological and functional maturation. During this maturation process, some surface molecules are downregulated while others are retained or upregulated (e.g., CD117) (3). The progenitor mast cells exhibit tyrosine kinase-type receptors encoded by the KIT proto-oncogene (3). These receptors are specific for stem cell factor (SCF). Under normal circumstances, the interaction between SCF and the SCF receptor KIT leads to the proliferation and differentiation of mast cells (3). When there is an activating mutation involving KIT, a clonal proliferation of mast cells is seen (3). Although the molecular pathology of mastocytosis is not completely understood, an activating mutation involving codon 816 in KIT is reported to be the most common mutation seen in systemic mastocytosis (3).

There were several challenges encountered in this case before reaching the final diagnosis of systemic mastocytosis. Firstly, chronic diarrhoea is not specific for systemic mastocytosis and is seen in many other conditions. Gastrointestinal symptoms are reported in about 60-80% of patients with systemic mastocytosis (4). Diarrhoea and bloating are the most frequently reported symptoms followed by nausea, abdominal pain, and vomiting (4). The exact mechanism of diarrhoea in mastocytosis is poorly understood but gastric hypersecretion due to overproduction of histamine could be a possible cause (5). According to a study by Sokol et al, an inverse relationship between D816V mutations and a high diarrhoea score was observed concluding that D816V mutations are not associated with diarrhoea. In addition, this study also suggested that other KIT mutations cause more local invasion resulting in diarrhoea when compared to patients with D816V KIT mutations (5). Interestingly in this case, the patient had a D816V mutation, while his predominant complaint was chronic diarrhoea.

Secondly, the patient was thought to have chronic eosinophilic colitis based on the initial colon biopsy findings. Dense eosinophilic infiltration of the small bowel and colon could potentially mask underlying mast cell proliferations, making the diagnosis of mastocytosis difficult (4). Additionally, an increased number of both mast cells and eosinophils may be seen in non-neoplastic conditions such as allergic reactions as well as neoplastic disorders such as Hodgkin Lymphoma, systemic mastocytosis and chronic eosinophilic leukaemia. Both systemic mastocytosis and chronic eosinophilic leukaemia share molecular defects involving the tyrosine kinase gene whereby gain of function D816V KIT mutations are seen in systemic mastocytosis while FIP1L1-PDGFRA fusion is associated with Chronic Eosinophilic Leukaemia (1). In this case, the patient was not investigated for FIP1L1-PDGFRA fusion gene mutation as his eosinophil count was persistently less than 1.5x109/L.

Another challenge in this case, is that mast cell infiltration in the gastrointestinal tract shows nonspecific findings in endoscopy examination. Nodularity, erythema, erosions, and loss of mucosal folds comprise about 60% of gastrointestinal endoscopy findings in systemic mastocytosis while no significant findings were reported in approximately 30%-40% of cases (4). In this case, the patient's upper gastrointestinal endoscopy showed features of gastritis and duodenitis while colonoscopy findings showed loss of normal mucosa at the caecum. Histopathological examination of serial small bowel and colonic biopsies were required to make the diagnosis of mastocytosis.

Tyrosine kinase inhibitors such as Imatinib and Nilotinib have been reported to show less response against systemic mastocytosis with KIT D816V mutation (4). In this case, the patient was started on corticosteroid therapy with the aim of reducing the occurrence of malabsorption.

CONCLUSION

Although rare, systemic mastocytosis should be considered in patients with persistent, nonspecific symptoms like prolonged diarrhea when other common causes are excluded. Accurate diagnosis needs a comprehensive evaluation, including tissue biopsy with relevant stains such as tryptase and CD117 as well as molecular testing. A high level of suspicion from both physicians and pathologists is key to overcoming diagnostic challenges.

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