

Systemic Mastocytosis Involving the Gastrointestinal Tract

Case Report and Review

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• Mastocytosis is rare, and is actually a heterogeneous group of diseases that may only involve the skin (urticaria pigmentosa) or that may have a systemic presentation with multiorgan involvement. The gastrointestinal (GI) tract can be affected and symptoms related to GI involvement are often nonspecific. The diagnosis of systemic mastocytosis with primarily GI presentation can be challenging and requires familiarity with this entity and a high index of suspicion. We report a case of systemic mastocytosis primarily diagnosed by the recognition of small intestinal and colonic involvement and review the diagnostic criteria, histopathology, and recent developments regarding this entity.

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A 32-year-old woman presented to her primary physician with complaints of intermittent abdominal pain and diarrhea. The symptoms began 3 months before presentation and she was referred to a gastroenterologist for further evaluation. Upper gastrointestinal endoscopy and colonoscopy were recommended, as the differential diagnosis included inflammatory bowel disease. The upper endoscopy findings were unremarkable, but colonoscopy revealed nodular mucosal irregularities with decreased vascular pattern throughout the colon. The findings were not endoscopically typical for Crohn disease or ulcerative colitis, but these entities remained in the clinical differential diagnosis, as did some type of diffuse infiltrative process, given the nodular appearance of the mucosa. Biopsy specimens were obtained from the small intestine and colon to investigate the subtle mucosal abnormalities seen endoscopically.

PATHOLOGIC FINDINGS

Histologically, both the enteric and colonic biopsy specimens contained a lamina propria infiltrate of mixed inflammatory cells including lymphocytes, some plasma cells, and conspicuous eosinophils. These cells expanded the lamina propria, spreading apart the crypts and expanding the enteric villi. In addition to the lamina propria expansion, there was some minimal architectural distortion of the intestinal crypts, with a few branched and irregular profiles. A rare focus of active cryptitis was present. These findings were initially interpreted as possibly consistent with inflammatory bowel disease, perhaps in a relatively quiescent phase, and were sent to our institution for a second opinion. In our histologic evaluation, within the inflammatory infiltrate and particularly just beneath the surface epithelium, we noted a population of spindled cells with oblong, ovate nuclei, inconspicuous nucleoli, and pale cytoplasm (Figure, A and B). These cells stained strongly with a c-KIT immunohistochemical stain, confirming the morphologic impression of mast cells (MCs; Figure, C). Additionally, the MCs were immunohistochemically positive for tryptase and aberrantly expressed CD25 (Figure, D).

COMMENT

Mastocytosis is recognized as a myeloproliferative neoplasm by the 2008 WHO (World Health Organization) *Classification of Tumours of Haematopoietic and Lymphoid Tissues*¹ and is defined as an accumulation of clonal MCs in 1 or more organs. The skin is involved in most patients (80%) and may be the only organ involved. Skin involvement most commonly presents as urticaria pigmentosa^{2,3} with red or pigmented macules that produce hives and itch intensely when stimulated, owing to release of histamine by the collections of MCs. Elicitation of this reaction by stroking the skin of a patient with mastocytosis underlies the Darier sign, which can aid in diagnosis. Isolated cutaneous mastocytosis occurs most commonly in children and may regress spontaneously, typically by puberty. Systemic mastocytosis (SM) is characterized by clonal MC accumulation in bone marrow and other extracutaneous organs such as liver, spleen, lymph nodes, and the gastrointestinal (GI) tract. Organomegaly is possible when the spleen and/or liver are involved. While the diagnosis of SM depends on extracutaneous involvement, the skin can be involved as well. The bone marrow is the most common extracutaneous organ involved. Systemic mastocytosis is

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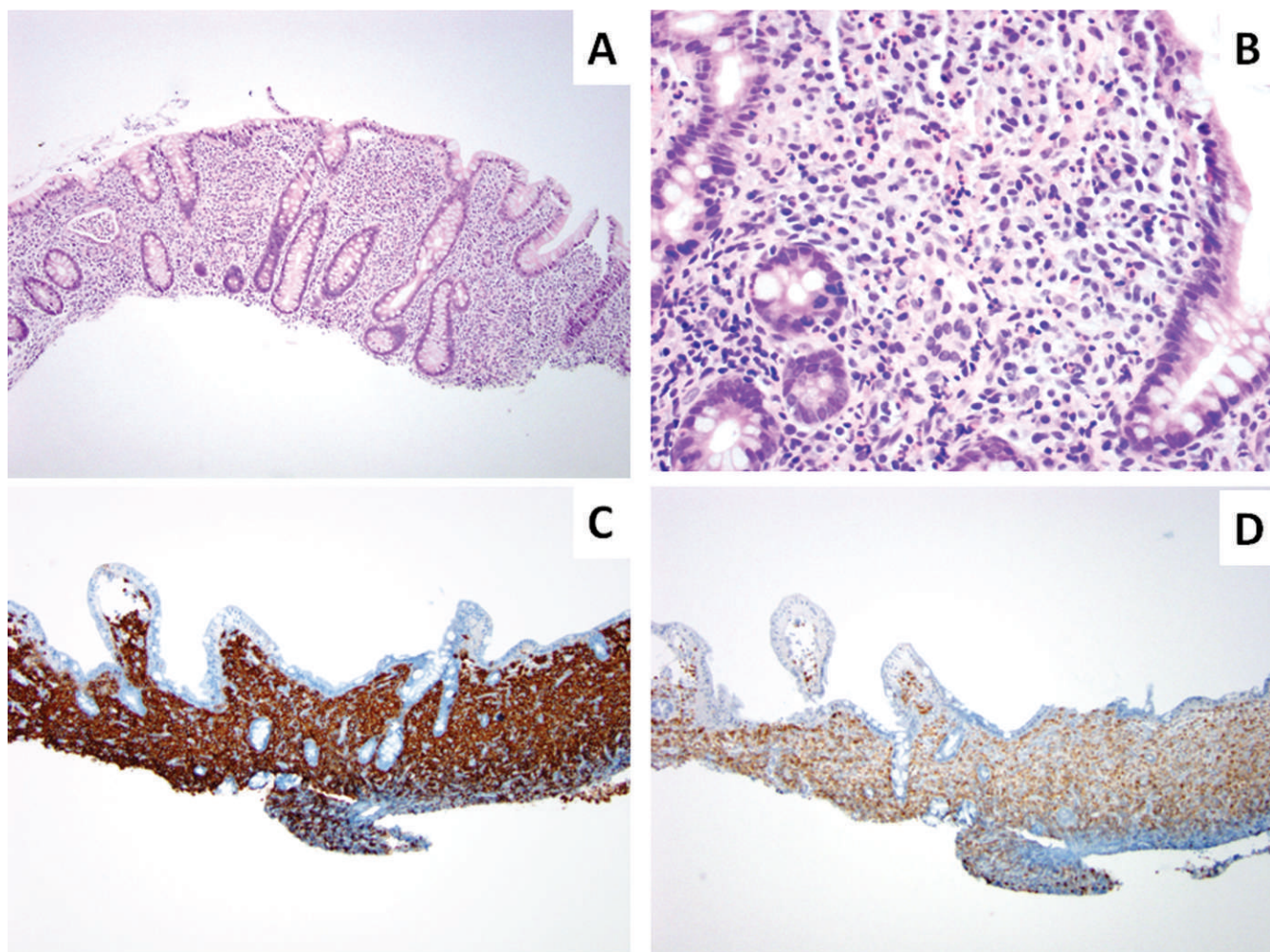


Figure Low-power (A) and high-power (B) hematoxylin-eosin (H&E) sections of colonic mucosa. Note expansion of lamina propria and vague mucosal distortion. There appears to be a mixed population of inflammatory cells, but the degree to which atypical mast cells make up the lamina propria is demonstrated by using immunohistochemistry with anti-CD117 (C) and anti-CD25 (D) antibodies (H&E, original magnifications $\times 4$ [A] and $\times 40$ [B]; original magnifications $\times 4$ [C] and $\times 4$ [D] H&E not used).

more common in adults and, unlike cutaneous mastocytosis, does not regress spontaneously.

The clinical presentation of SM can range from asymptomatic to multiorgan dysfunction and/or failure in aggressive cases. Most of the symptoms can be attributed to the release of vasoactive substances and other inflammatory mediators and include flushing, hypotension, dyspepsia, diarrhea, abdominal pain, or musculoskeletal pain. Other vague constitutional symptoms such as fever and weight loss are also possible. The course of disease is variable and can be indolent or associated with life-threatening reactions.

Diagnostic Criteria for Systemic Mastocytosis

The bone marrow is frequently involved in SM and a bone marrow biopsy is indicated in all adult cases with suspected SM. Similar diagnostic criteria are used in any extracutaneous organ to render the diagnosis of SM. The diagnosis is based on a combination of morphologic, immunohistochemical, serologic, and molecular findings. The WHO defines minor and major criteria for diagnosis and requires the presence of either 1 major criterion and 1 minor

criterion, or 3 minor criteria to diagnose SM. These criteria are summarized in the Table.

Morphologic examination and immunophenotyping play important roles in diagnosis of mastocytosis. Nonneoplastic

World Health Organization Diagnostic Criteria for Systemic Mastocytosis

Major criterion

Multifocal compact infiltrates of mast cells (>15) in extracutaneous organ(s)

Minor criteria

1. Presence of $>25\%$ atypical or spindle-shaped mast cells in extracutaneous organ(s)
2. Detection of *KIT* mutation D816V in extracutaneous organ(s)
3. Expression of CD2 or/and CD25 in extracutaneous mast cells
4. Serum tryptase concentration >20 ng/mL (with the exception of cases with associated clonal myeloid neoplasm)

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MCs have round to ovoid nuclei, abundant metachromatic or basophilic granules, and are generally individually dispersed in tissue. Neoplastic MCs, on the other hand, have atypical features such as elongated and spindle morphology and reduced or absent granularity.⁴ In addition, they often occur in clusters in tissue, and this in combination with their spindle morphology may lead to their misinterpretation as fibroblasts, such as those seen in a healing injury. Tryptase and CD117 (c-KIT) are expressed in normal as well as neoplastic MCs and can be used to help identify and quantify the MCs in the tissue by immunohistochemistry or in the blood or bone marrow by flow cytometry. These stains are particularly helpful in proving the presence of compact clusters of more than 15 mast cells (the major diagnostic criterion) in cases where there is a mixed inflammatory background, and the utility of these immunostains was apparent in this case. Additionally, expression of CD2 or CD25 by the MCs in SM is considered aberrant and is a minor criterion for the diagnosis. Although clustering of MCs is typically seen only in mastocytosis, increased numbers of scattered MCs can be seen in nonneoplastic conditions; therefore, the strict identification of true clusters is necessary to fulfill the major criterion.⁴ In such conditions it is also important to ensure the absence of atypical MC morphology and/or aberrant expression of CD2 or CD25 to exclude true SM. One potential diagnostic pitfall is the expression by MCs of CD68 and other markers traditionally associated with macrophages. In combination with abnormal MC morphology, such expression can prove diagnostically confusing.

Similar to other myeloproliferative diseases, abnormal tyrosine kinase activity is at the center of the pathogenesis of systemic mastocytosis.⁵ Activating somatic point mutations of the *KIT* gene are associated with mastocytosis^{6–9} and are encountered in most (>80%) sporadic cases.^{10,11} Irrespective of the WHO subtype, the *KIT* D816V mutation, resulting from substitution of a valine for an aspartic acid in exon 17, is the most frequently detected *KIT* mutation in SM and is another minor diagnostic criterion.^{6,8,12} Other activating mutations of exon 17 such as D816Y, D816H, and D816F are uncommon and are not included in screening for SM. New allele-specific polymerase chain reaction assays can successfully detect the D816V mutation in paraffin-embedded tissue.¹³ It is important to note that mastocytosis can be a component of “myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*.” Hence, screening for the *FIP1L1*-*PDGFRA* fusion is necessary in cases with significant peripheral blood eosinophilia.¹

Gastrointestinal Manifestations

Gastrointestinal involvement is seen in 70% to 80% of patients with SM.^{14,15} Abdominal pain and diarrhea, as encountered in our patient, are the most common GI complaints, but SM can involve any of the GI organs and generate a variety of site-specific symptoms such as gastroesophageal reflux, peptic ulcer disease, steatorrhea, malabsorption, and diarrhea.¹⁶ The precise pathogenesis of the symptoms is not well understood but they are thought to be secondary to mediator release by MCs.¹⁵

Gastrointestinal involvement by SM is often quickly suspected in patients with a previously established diagnosis of mastocytosis who present with GI symptoms. These patients should be screened by endoscopy and undergo multiple biopsies to investigate GI involvement. On

endoscopic examination, the mucosa may have nodules, pigmented areas, or thickened folds, or may appear normal. Even in the absence of MCs in mucosal biopsy specimens, a patient's GI symptoms may still be explained by the systemic effects of released mediators in SM.¹⁶ On the other hand, given the low prevalence of SM and the nonspecific nature of the symptoms, cases with isolated GI symptoms may be underdiagnosed and often managed as irritable bowel syndrome. It is important for the pathologists to have a high index of suspicion for this diagnosis, particularly in GI biopsies of patients with prolonged, unexplained symptoms. As exemplified in our case, immunohistochemical stains for c-KIT (CD117), tryptase, and CD25 can help establishing the diagnosis. Additionally, if available, correlation with serum tryptase and molecular studies for the *KIT* D816V mutation may be necessary.

So-called mastocytic enterocolitis is a recently described entity that may be considered in patients with diarrhea and that could enter the differential diagnosis of GI involvement by SM. This entity is reportedly characterized by an increased number of MCs in the endoscopically normal colonic mucosa of patients with intractable diarrhea.¹⁷ This controversial entity, however, has not been well characterized and does not have consistent clinical or histologic criteria. We do not currently make this diagnosis in our practice and would caution against the possibility of misinterpreting the finding of prominent MCs in mucosal biopsy specimens and missing a potential true case of GI involvement by SM.

CONCLUSION

The diagnosis of GI involvement by SM should be considered in GI biopsies of patients with prolonged, unexplained symptoms of pain and diarrhea, particularly in the setting of subtle endoscopic findings such as nodularity and pigmentation. Morphologic assessment with a high index of suspicion is at the heart of this diagnosis and in suspected cases it should be augmented with ancillary studies including immunohistochemical stains, serum tryptase levels, and molecular assay for the *KIT* D816V mutation. Additionally, correlation with other symptoms, especially dermatologic signs, is important.

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