Case History

A 73-year-old male with history of ulcerative colitis and diet-controlled type 2 diabetes mellitus presented for surveillance colonoscopy. On endoscopic examination, the colonic mucosa appeared normal. Random biopsies were taken every 10 cm. Histologically, all colon biopsies showed similar findings. Upon inquiry, the patient denied weight loss, flushing, pruritis, nausea, bloating, diarrhea, dyspepsia, peptic ulcers, abdominal pain, vomiting, musculoskeletal pain, fatigue, rash, or prior episodes of anaphylaxis. A PET scan revealed no lesions suspicious for malignancy.

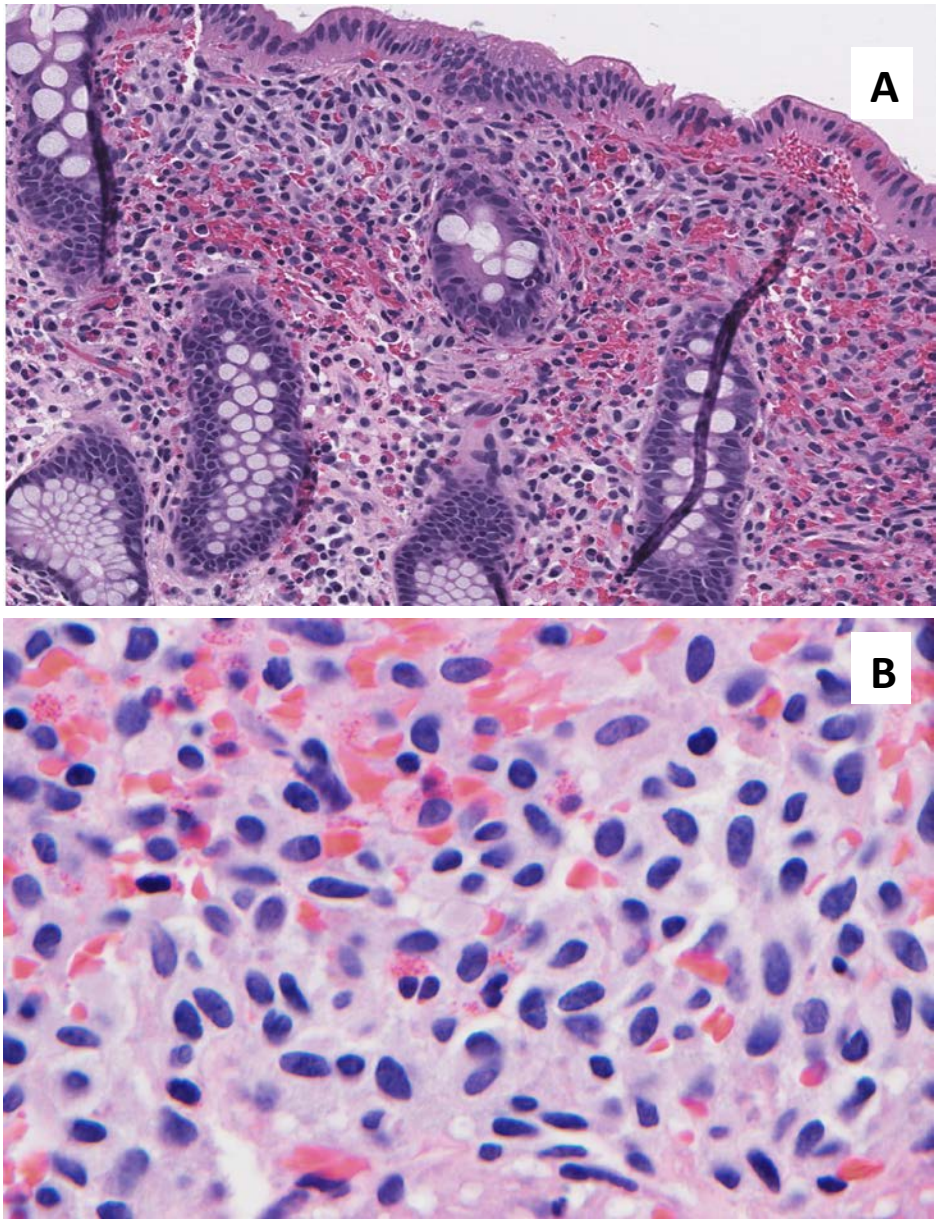

Figure 1: Colonoscopy biopsy. A. H&E (20X). B. H&E 100X (oil immersion).

Q1. What immunostains would you perform to confirm the diagnosis?

A. CD20, CD5, CD43, and BCL1
B. CD68 and CD163
C. CD117, CD25
D. S100, CD1a, and langerin

The following immunostains were performed:

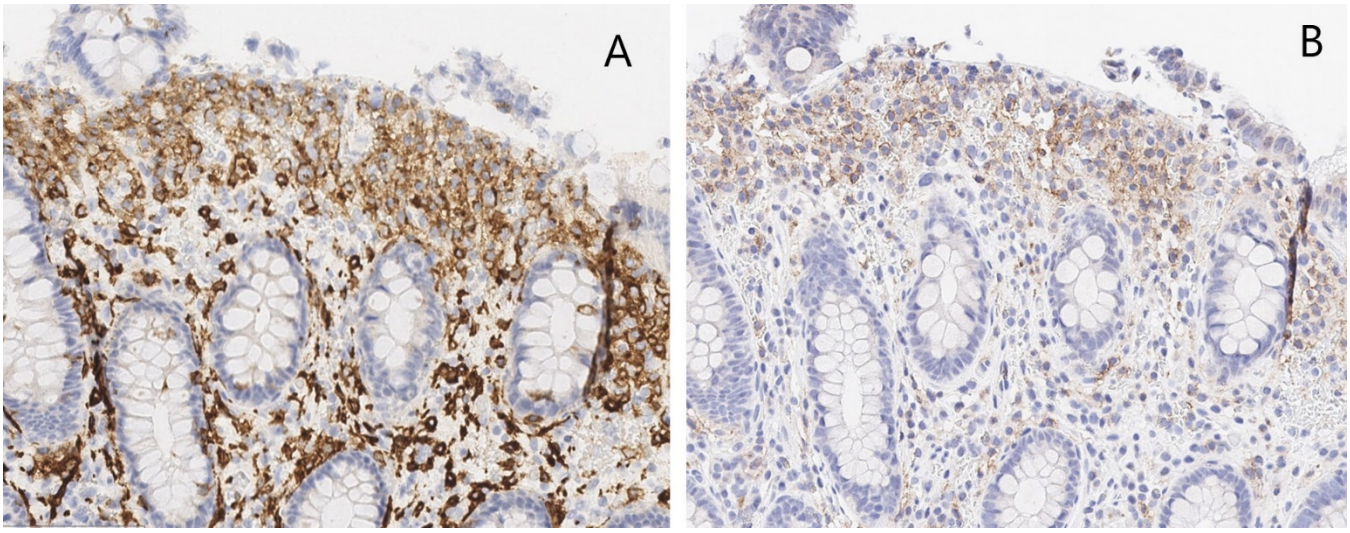

Figure 2: Colonoscopy biopsy. A. CD117 immunostain (10X). B. CD25 immunostain (10X).

Additional laboratory testing revealed the following:

Serum tryptase	15.5 ug/L (normal range <10.9ug/L)
KIT D816V mutation	Positive in blood; negative in the bone marrow

Q2: What is the most likely diagnosis?

A. Systemic mastocytosis
B. Mast cell sarcoma
C. Lymphoplasmacytic lymphoma
D. Langerhans cell histiocytosis

Correct answer for Q2: (A) Systemic mastocytosis.

The predominantly superficial colonic lamina propria is expanded by a cellular infiltrate with elongate nuclei, dark, even chromatin, and a moderate amount of pale cytoplasm. Background eosinophils are abundant. The atypical cells are highlighted by CD117 and CD25 expression. In addition, the patient was subsequently found to have the *KIT* D816V mutation in blood. These findings are consistent with systemic mastocytosis (choice A). Upon further work up the patient was found to have a lambda-restricted population of plasma cells within bone marrow, comprising 20% of the cellularity. Lambda light chains were found in serum and urine. In the absence of myeloma-related organ or tissue impairment or myeloma-related symptoms, the latter findings are those of asymptomatic (smouldering) plasma cell myeloma (Fig 3).(2) However, in the setting of concurrent systemic mastocytosis, the patient's hematologic disease is classified as systemic mastocytosis with associated hematologic neoplasm (SM-AHN).(2) The accompanying hematologic disorder is usually a myelodysplastic syndrome, a myeloproliferative neoplasm, or an acute myeloid leukemia; however, other non-myeloid disorders such as myeloma have rarely been described in association with this disease category.

Although a proliferation of atypical mast cells was present in the colonic mucosa, the mast cells did not form a mass lesion nor did they cause destruction of the normal glandular architecture, thus excluding mast cell sarcoma (**choice B**). Lymphoplasmacytic lymphoma (**choice C**) is a neoplasm of small B cells demonstrating plasmacytic differentiation. In the current case, the morphology of the cells (e.g., ovoid nuclei, abundant pale cytoplasm) along with the CD117 positivity confirm the identity of the cells as mast cells; no neoplastic proliferation of B cells is present in the colonic mucosa. Although Langerhans cell histiocytosis (LCH) (**choice D**) also frequently presents in a background of abundant eosinophils, the neoplastic cells of LCH have characteristic grooved nuclei and are immunopositive for S100, CD1a, and langerin.

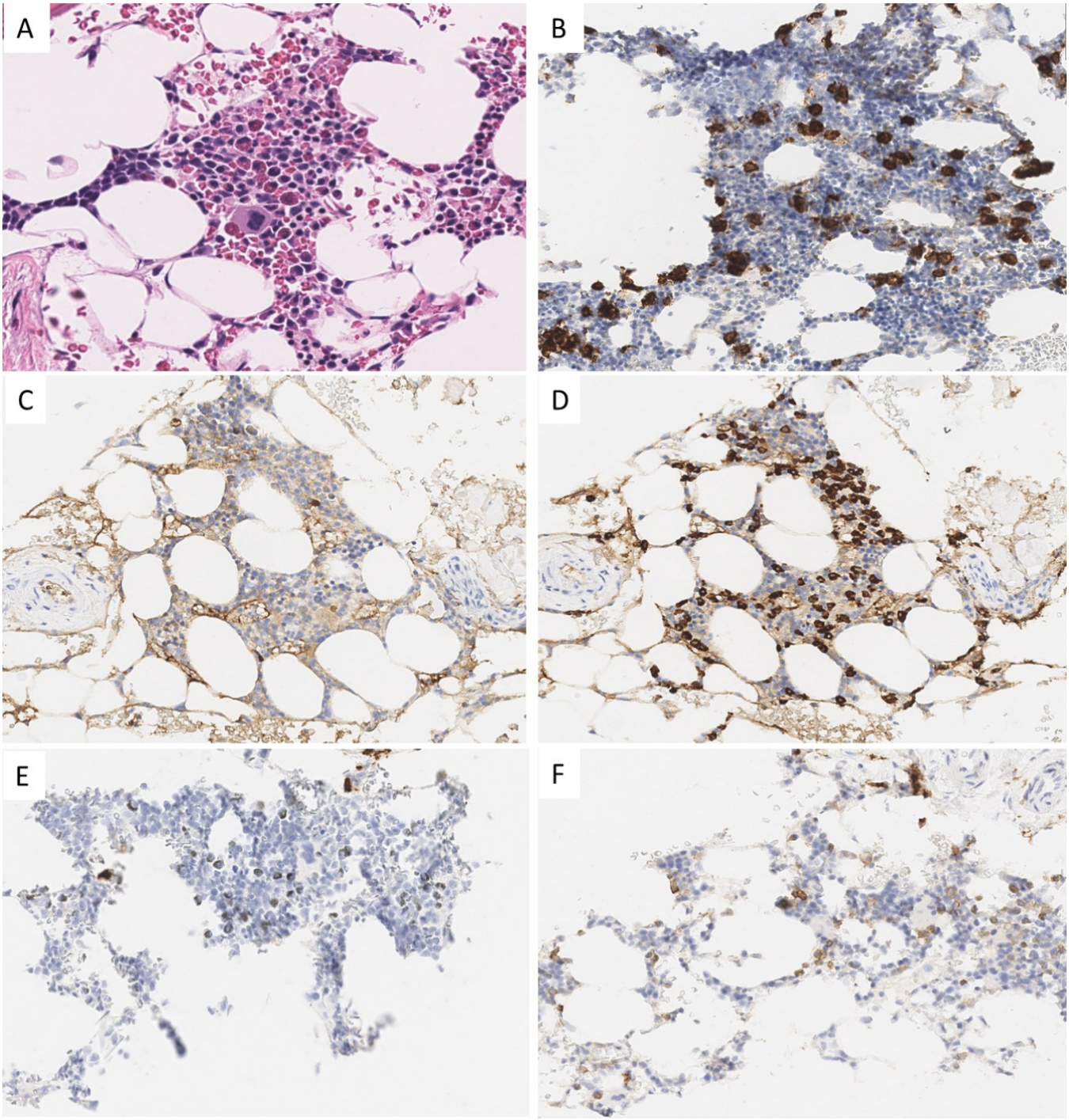

Figure 3: Bone marrow core biopsy. A. H&E (20X). B. CD138 immunostain (20X). C. Kappa immunostain. (10X). D. Lambda immunostain (10X). E. Tryptase immunostain (10X). F. CD117 immunostain (10X).

Additional laboratory testing revealed the following:

Serum immunofixation electrophoresis	Monoclonal protein identified (lambda light chains only)
Urine immunofixation electrophoresis	Lambda light chains, consistent with Bence-Jones proteins

Lambda free light chains (serum)	60.40 mg/dL (normal 0.33-1.94 mg/dL)
Kappa free light chains (serum)	1.07 mg/dL (normal 0.33-1.94 mg/dL)
Hemoglobin	14.6 g/dL
Hematocrit	41.8%
Creatinine	0.99 g/dL
Calcium	8.9 mg/dL

Discussion of systemic mastocytosis

Mastocytosis encompasses a group of related disorders characterized by accumulation of clonal mast cells in one or more organs. Depending on the site of involvement, mastocytosis has two forms: (1) cutaneous – in which mast cell infiltrates are confined to the skin, and (2) systemic – in which mast cell infiltrates involve extracutaneous sites such as bone marrow, spleen, liver and the gastrointestinal tract (GIT). Presenting symptoms are highly variable due to the wide range of organs that may be involved, as well as the effects of inflammatory mediators released from the mast cells. Extracutaneous manifestations include diaphoresis, fever, fatigue, nausea, vomiting, abdominal pain, diarrhea, bone pain, myalgias, and arthralgias. Prognosis of systemic mastocytosis is also highly variable, ranging from an indolent condition with normal life expectancy to aggressive mast cell leukemia.

Mast cells are typically highlighted using CD117 (KIT) and/or mast cell tryptase immunohistochemistry. Since CD117 is not specific for mast cells, mast cell tryptase immunostain may also be warranted. According to the current World Health Organization (WHO) guidelines, the diagnosis of systemic mastocytosis requires the presence of the major criterion (i.e., multifocal dense infiltrates of mast cells consisting of at least 15 mast cells per aggregate in any non-cutaneous organ, along with at least one minor criterion; *OR* the presence of 3 or more minor criteria: (1) mast cells with spindled or atypical morphology on biopsy, or immature or atypical morphology on bone marrow aspirate (must involve >25% of mast cells in biopsy or aspirate), (2) aberrant expression of CD25 and/or CD2, (3) presence of an activating *KIT* mutation at codon 816 in any extracutaneous organ, and (4) persistent elevation of serum tryptase >20 ng/mL. The WHO classification system further defines different forms of the disease based on extent of tissue involvement and clinical signs and symptoms: indolent systemic mastocytosis, smouldering systemic mastocytosis, systemic mastocytosis with associated hematologic neoplasm, aggressive systemic mastocytosis, and mast cell leukemia.(1)

The atypical/spindled mast cells of systemic mastocytosis are characterized by ovoid to elongate nuclei, dark, even chromatin, and a moderate amount of optically clear to pale cytoplasm that sets the individual mast cell nuclei apart from one another. In the colon, the mast cells frequently aggregate in the superficial lamina propria where they may be mistaken for histiocytes. In this location, however, histiocytes have slightly paler chromatin and cytoplasm that is typically more eosinophilic than that of atypical mast cells. In systemic mastocytosis, background eosinophils are usually abundant and may raise the differential diagnosis of eosinophilic colitis. If the atypical mast cell aggregates are numerous or large, they can push apart crypts, suggesting mild architectural distortion. In such cases, the combination of increased eosinophils and crypt distortion may raise the differential diagnosis of inflammatory bowel disease.(3)

In the GIT, mast cells typically comprise 2–5% of the mononuclear cells in the lamina propria. The reported average number of mast cells per high power field ranges from 13 to 26 per high power field in the colonic mucosa of asymptomatic patients.(2-4) Interestingly, prior studies have noted increased numbers of mast cells in the GIT of patients with irritable bowel syndrome(4-6) and inflammatory bowel disease (IBD)(7-10) compared to healthy controls. Mast cells in IBD patients are more frequently activated, with increased release of mast cell mediators, compared to controls.(11, 12) Whether these observations are indicative of a specific role for mast cells in the pathogenesis of IBD or reflect a secondary response to inflammation in the mucosa is yet to be determined.

Whereas histologic evidence of GIT involvement is well known in (at least a subset of) patients with established systemic mastocytosis,(3, 4) separate reports also document the presence of abnormal mast cells in the GI mucosa of patients presenting for routine screening or non-specific symptoms and in whom no evidence of progressive systemic disease is found on follow-up or further diagnostic evaluation.(13, 14) These latter cases highlight the existence of a group of cases in which atypical mast cell aggregates may not have the same clinical import as symptomatic or molecularly confirmed systemic mastocytosis, and as such, may ultimately benefit from separate classification.(13)

For the gastrointestinal pathologist, recognition of the atypical mast cell aggregates is essential in order to identify systemic mastocytosis involving the GIT. Additionally, when considering the diagnosis of an eosinophil-rich process such as eosinophilic colitis and inflammatory bowel disease, systemic mastocytosis should be kept in mind.

Comments for Q1

Choice A is a panel of stains used for diagnosis of B cell lymphomas. CD20 is a B cell marker. BCL1 (marker for cyclin D1) is positive in cases of mantle cell lymphoma. CD5 and CD43 are T cell markers; however, both are aberrantly expressed in small lymphocytic lymphoma and mantle cell lymphoma.

Choice B. CD68 and CD163 are markers of macrophage/monocyte lineage. The hemoglobin scavenger receptor CD163 is a macrophage-specific protein and is overexpressed in macrophages in response to inflammation. CD68 is a transmembrane glycoprotein highly expressed by monocytes, circulating macrophages and tissue macrophages. In the current biopsy, the lesional cells have dark, even chromatin and pale cytoplasm. In comparison, macrophages in the superficial lamina propria of colonic mucosa typically have less dense chromatin and more abundant eosinophilic cytoplasm.

Choice C (the correct answer). CD117, also known as c-kit, highlights mast cells (both benign and neoplastic) as well as interstitial cells of Cajal (ICC) and a few other cell types. By tissue location and morphology, ICC and the other cell types are not a consideration, however CD25 is the alpha chain of the interleukin 2 receptor and is a marker of regulatory T cells. It is not expressed in normal mast cells but is aberrantly expressed in neoplastic mast cells. Thus, the morphology in combination with expression of CD117 and CD25 identifies the cells as neoplastic mast cells.

Choice D. S100, CD1a and langerin are markers for Langerhans cell histiocytosis (LCH). LCH is typically positive for all three of these immunostains, and this panel is used to distinguish LCH from

other lymphohistocytic processes. In this biopsy, although there are increased eosinophils, no classic Langerhans cells with grooved nuclei are present.

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