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Case Report

Gastrointestinal Ulceration in Systemic Mastocytosis

Hugh J Freeman*

Department of Medicine Gastroenterology, University of British Columbia, Vancouver, BC, Canada

***Corresponding Author:** Hugh J Freeman, Department of Medicine Gastroenterology, University of British Columbia, Vancouver, BC, Canada

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Abstract

An elderly woman presented with abdominal pain and a long-standing history of involvement of multiple organs with systemic mastocytosis. A Gastric ulcer was detected and responsive to proton pump inhibitor therapy. Although rare mast cells were detected in gastric biopsies, the ulcer was likely related to a circulating mast cell mediator, her treatment medications, or both, and not her advanced systemic mastocytosis. After resolution of her pain and complete endoscopic healing of her ulcer, ongoing anti-secretory drug therapy was provided. This report adds further evidence that gastric ulcer disease, reported in up to 50% of patients with systemic mastocytosis, may not be directly to due to the disease, but indirectly due to a circulating mast cell mediator or drug treatment for an associated clinical disorder.

Keywords: Systemic Mastocytosis; Gastric Ulceration and Gastric Involvement; Sprue-Like Intestinal Disease; Mastocytic Enterocolitis

Mastocytosis is a rare myeloid neoplasm defined by cutaneous and systemic clinical features that may be explained by either direct mast cell infiltration, a mast cell mediator, or both [1,2]. Gastrointestinal symptoms may be present in up to 85% of patients, second only to pruritus from skin involvement, and may be an important determinant to the quality of life [1-3]. In systemic mastocytosis (in contrast to cutaneous mastocytosis, mainly recorded in children), mast cell proliferation occurs most commonly in bone marrow as well as spleen, liver and kidney. Gastric or duodenal ulceration is common in systemic mastocytosis, occurring in up to 50% [1,4]., often with bleeding apparently sustained by mast cells [5]. In addition, unusual giant ulcers may occur [6]. Here, a well-defined case of systemic mastocytosis, initially involved skin biopsies, but later after a long and indolent course developed in numerous organs including bone as well as spleen, liver, kidney, lymph nodes. During the course of her disease, discrete duodenal and gastric ulcers developed in the absence of prominent gastric or intestinal infiltrative disease. In spite of extensive systemic disease, her ulcers were completely responsive to anti-secretory treatment using proton pump inhibitors with complete endoscopic mucosal healing.

Case review

A 71-yr old female was referred for epigastric abdominal pain, intermittently present for 6 years and, more recently, with progressive weight loss over the past year.

Her past history revealed a pruritic urticarial skin rash that first developed in 1956. At that time, a skin biopsy confirmed a diagnosis of mastocytosis. Because of periodic intense flushing and swelling over the face and ears, she was eventually treated with oral sodium cromoglycate 200 mg tid providing good control. In 1989, she developed splenomegaly and had a splenectomy showing massive infiltration with mast cells. No other treatment for mastocytosis was provided. Upper endoscopy in 1999 for abdominal pain showed a “punched out” 1 cm duodenal bulbar ulcer leading to treatment with a 2 month course of oral omeprazole 20 mg daily.

Gastric biopsies showed superficial gastric body and antral gastritis without *Helicobacter pylori*. No mast cell infiltrates were seen, abdominal pain lessened and eventually disappeared over the next 2 months.

Over the next 3 years, she developed progressive arthritis of the lumbosacral spine, knees and ankles with osteoporosis. This led to marked disability with walking, height loss and a tibial "fragility fracture". Treatment with alendronate and daily calcium, vitamin D, and magnesium along with arthrotec (diclofenac/misoprostol) and prednisone were provided. Eventually, a total knee replacement was done that partially improved her impaired mobility.

In 2003, she was reviewed because of persistent iron deficiency anemia and worsening skin eruptions associated with biopsies showing increased dermal mast cells. A sigmoidoscopy and gastroscopy were normal in a rural hospital. She was referred by her family physician to a separate teaching hospital. A CT scan of chest, abdomen and pelvis showed extensive lymphadenopathy in both axillae, mediastinum, retro-crural and retroperitoneal areas, abdomen and pelvis. A mass was noted in the right renal hilum. Hepatomegaly was seen with nodular changes and ascites. Diffuse sclerotic appearance of the skeleton was shown with central lytic areas in the hips and spine consistent with diffuse mastiocytic

osseous disease. Enhancing soft tissue surrounding the thoracic spine was believed to be due to extra-medullary hematopoiesis. A colonoscopy and biopsies were normal. Treatment with oral iron provided a partial hematologic response.

In 2005, she was first referred to our hospital by her hematologist. Exam revealed a very debilitated woman with wasting. Her liver was readily palpable and enlarged. Her hemoglobin was 92 g per L (normal, 115 to 160) with an elevated platelet count of 570,000 (normal, 150,000 to 400,000) and normal white count. Peripheral blood smear showed typical post-splenectomy findings with Howell-Jolly bodies. She was iron deficient. Serum albumin was depressed to 27 g per L (normal, 35 to 50). Alkaline phosphatase was 255 U per L (normal, 50 to 200) with fractionation showing increased liver and biliary alkaline phosphatase isoenzymes. Serum gastrin was normal. Upper endoscopy showed prominent gastric body folds with a slight mammillated surface appearance (Figures 1 and 2) along with a single, linear circumferential prepyloric antral ulcer, a likely source of blood loss. Gastric mucosal biopsies showed reactive inflammatory features with prominent eosinophils and rare spindle-shaped mast cells that stained positive with Giemsa. No *Helicobacter pylori* organisms were identified. Duodenal biopsies were normal. Changes were thought to be due to anti-inflammatory drugs, not directly from mastocytosis. Treatment with omeprazole led to resolution of abdominal pain and repeat endoscopic evaluation of the upper gastrointestinal tract showed completely healed gastric ulceration; gastric biopsies were normal. Given her overall medical state with an advanced malignancy involving multiple organs, further investigations were not pursued. It was elected to prescribe ongoing omeprazole treatment after discharge from hospital.

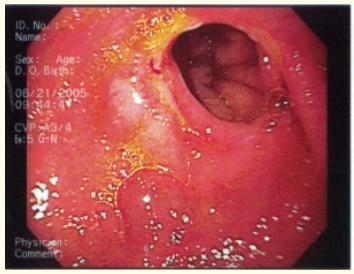

Figure 1: Gastroscopy showing linear and circumferential prepyloric gastric antral ulcer with diffuse hyperemia of gastric antral mucosa. A focal red spot in the ulcer likely source of bleeding. Normal duodenum. Gastric biopsies showed only reactive inflammatory changes with normal duodenal mucosa.

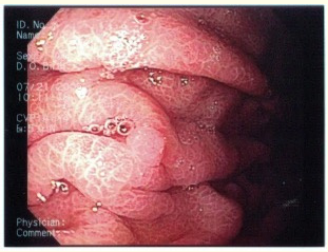

Figure 2: Gastroscopy showing prominent gastric body folds but gastric biopsies showed only reactive inflammatory changes with rare mucosal mast cells.

Discussion

Mastocytosis is a clonal proliferation of neoplastic mast cells that involves several different organs. The disorder is clinically heterogeneous, most commonly affecting one or more of: skin and other sites, including bone marrow, liver and spleen as well as lymph nodes. Although direct infiltration of the gastrointestinal tract may occur, most believe that the explanation for gastrointestinal symptoms in mastocytosis is related to chemical mediator release from mast cells including histamines, leukotrienes, heparin and proteases [1,2]. As in the present case, only rare mast cells are often seen in biopsies from gastric and intestinal tissues. Here, gastric and duodenal ulceration was documented in a patient with systemic mastocytosis and the ulceration responded readily to cessation of anti-inflammatory medications and administration of proton pump inhibitors. This case serves as a reminder that even patients with aggressive and advanced systemic mastocytosis affecting multiple organs may benefit from limited investigations, if a readily treatable disorder is evident. For the future, empirical ongoing treatment with anti-secretory therapy would appear to be reasonable.

This patient was initially referred with an already well established diagnosis of systemic mastocytosis involving multiple organs. The disease was clearly advanced and so further extensive evaluation was deemed to be inappropriate. Moreover, controversy is evident in the literature regarding the histopathological evaluation of gastric and intestinal biopsies for mast cells and their significance in order to explain common symptoms, such as abdominal pain and diarrhea. For some pathologists, a major diagnostic criterion for systemic mastocytosis has included counting of mast cell aggregates for skin, bone marrow or other involved tissues (eg. over 20 mast cells per high power field in the lamina propria) [1,5,6]. This may be less important in an established case of systemic mastocytosis with mast cell infiltrates evaluated using special methods, such as Giemsa stains or c-kit (CD 117) immunoperoxidase labeling [7,8]. However, quantitation of mast cells may produce mixed results with increased, decreased or normal numbers of mast cells even in patients with well established systemic mastocytosis compared to controls [9].

Definition of mastocytosis in the gastrointestinal tract, however, may be more difficult in a number of non-neoplastic clinical settings with gastrointestinal symptoms, particularly, diarrhea, including sprue-like intestinal disease [10], diarrhea-predominant irritable bowel syndrome [1,2]. and so-called "mastocytic enterocolitis" [12]. Indeed, it is unclear what constitutes normal numbers of mast cells even in routine luminal mucosal biopsies. Mast cell enumeration of endoscopic screening biopsies may be irrelevant since there are no clearly established and agreed upon guidelines in those without an already established diagnosis of systemic mastocytosis [13-15]. Indeed, a prior clinicopathologic study compared mast cell density in 24 patients with systemic mastocytosis (including the gastrointestinal tract) to100 asymptomatic patients as well as 100 patients with diarrhea-predominant irritable bowel syndrome. In the investigator's view, the degree of overlap in mast cell density was too large to permit a clinically-useful method for differentiation [9].

In summary, a patient with long-standing systemic mastocytosis presented with abdominal pain. Limited studies revealed a gastric ulcer that responded to proton pump inhibitor treatment.

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