Gastrointestinal hemorrhage in mastocytosis

MICHAEL C. BELCON,* B SC, MD; STEPHEN M. COLLINS,† MB, BS, FRCP[C]; MARIO F. CASTELLI, MD, FRCP[C]; ALI H. QIZILBASH, MB, BS, FRCP[C]

In 1879 Ehrlich described and named mast cells (Mastzellen). Sézary[1] later applied the term mastocytosis to the systemic manifestations of the proliferation of mast cells in association with urticaria pigmentosa. Mastocytosis is a rare disease (accounting for 1 in 2500 new dermatologic consultations[2]) of unknown cause that occurs mainly in children. It has been reported in black and Japanese populations, but most cases described have been in white people.

This report describes a case of mastocytosis demonstrating many of the features found in the medical literature that ended fatally after repeated gastrointestinal hemorrhage.

Case report

A 19-year-old white man was admitted to hospital in acute distress with a 3-hour history of dyspepsia, general malaise and hematemesis. He was in shock and pyrexic, and his abdomen was protuberant. Fibreoptic endoscopy revealed esophageal varices and a small superficial ulcer near the esophagogastric junction; in neither location was there active bleeding. There was, however, active bleeding from the duodenal cap, which was partially stenosed and beyond which the endoscope could not be advanced.

Since infancy the patient had had urticaria pigmentosa, which had been diagnosed by skin biopsy. He had been treated with antihistamines and corticosteroids. A bone marrow biopsy done at age 4 years at another hospital had demonstrated mastocytosis. His developmental milestones had been delayed, and his language performance at 15 years of age was assessed as being at the level of 6 to 7 years. Chromosome analysis yielded normal results. Recently he had had intermittent diarrhea and skin eruptions, which had been successfully managed with the administration of disodium cromoglycate.[3] He was taking no other medication and was not an abuser of alcohol. Apart from a fracture of the right humerus there had been no other significant medical or surgical problems until the present illness.

Physical examination revealed a few spider nevi scattered over the anterior thorax, a diffuse macular, erythematous, nonurticarial eruption predominantly on the trunk and dermatographia. Minimal facial edema, cervical lymphadenopathy and marked hepatosplenomegaly were also noted.

The hemoglobin level was 10.6 g/dl, the leukocyte count 8.4 × 10^9/l (80% neutrophils, 8% band forms, 6% lymphocytes, 4% monocytes, 1% eosinophils and 1% basophils), the platelet count 295 × 10^9/l, the erythrocyte sedimentation rate 84 mm/h, the prothrombin time 18 s (control time 11 s), the partial thromboplastin time 43 s (control time 31 s), the 10-U thrombin time 12 s (control time 13 s) and the 2-U thrombin time 29 s (control time 30 s). The following serum concentrations were noted: fasting cholesterol 84 mg/dl, glutamic oxaloacetic transaminase 10 IU/l, γ-glutamyl transpeptidase 17 IU/l, glutamic pyruvic transaminase 10 IU/l, alkaline phosphatase 130 IU/l, total/direct bilirubin 29/5 μmol/l (1.7/0.3 mg/dl), calcium 2.3 mmol/l (9.1 mg/dl), albumin 2.9 g/dl, fasting histamine 3.7 ng/ml (normal less than 1.5 ng/ml), folate 21.5 nmol/l (9.5 ng/ml) and vitamin B_{12} 214 pmol/l (290 pg/ml). The chest roentgenogram was normal. Blood and urine cultures initially yielded no growth, but because the patient remained febrile and appeared ill intravenous therapy with gentamicin and aqueous penicillin G was started.

The patient's coagulogram returned to normal a few days after the initiation of parenteral therapy with vitamin K and fresh frozen

From the departments of gastroenterology and pathology, Henderson General Hospital and McMaster University, Hamilton

*Research fellow, Toronto Western Hospital, Toronto

†Associate in gastroenterology, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland

Reprint requests to: Dr. Mario F. Castelli, Mountain Medical Centre, 688 Concession St., Hamilton, Ont. L8V 4T1

plasma. It remained normal throughout his hospital course. Cimetidine, 300 mg, was given intravenously every 6 hours, but 48 hours after the start of this treatment bleeding increased. Selective celiac and superior mesenteric angiography showed extravasation of contrast material in the region of the duodenal bulb and dilatation of the splenic and portal veins on delayed films. Repeat endoscopy revealed fresh blood in the esophagus, stomach and duodenum. A Sengstaken–Blakemore tube was inserted and adequate esophageal tamponade obtained, with cessation of bleeding. The frequency of cimetidine administration was increased to once every 4 hours, and vasopressin, disodium cromoglycate and chlorpheniramine maleate were also administered intravenously, but subsequently the bleeding resumed. At laparotomy a large duodenal ulcer penetrating into the pancreas was undersewn. The liver and spleen were grossly enlarged, which made it technically impossible to establish a portacaval shunt. However, vagotomy, pyloroplasty and gastrostomy were performed together with jejunal and liver biopsies.

To ascertain the efficacy of cimetidine therapy in this patient, gastric secretions were obtained by means of continuous nasogastric aspiration. The collection was started 3 hours after the last dose of cimetidine was given, and another bolus of cimetidine was given 1 hour later. The results are shown in Fig. 1. Because the gastric output and acidity were elevated prior to administration of the last dose of cimetidine but were later effectively lowered for 1½ hours the frequency of administration of the drug was changed to once every 2 hours. Four days after the operation the patient suffered extensive loss of blood, which necessitated another laparotomy. No bleeding from the previously undersewn duodenal ulcer was observed; however, a large, actively bleeding varix on the lesser curvature of the stomach was ligated.

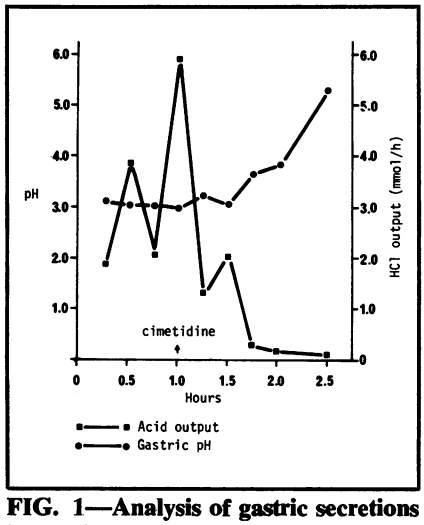

FIG. 1—Analysis of gastric secretions in patient with mastocytosis after vagotomy and intermittent intravenous administration of cimetidine. Previous dose of cimetidine was 3 hours prior to start of gastric aspiration.

Histologic examination of the jejunal biopsy specimen showed blunting of the villi, with edema, congestion and inflammation of the lamina propria (Fig. 2). In addition, a diffuse infiltrate of mast cells involving the deeper parts of the mucosa and the submucosa was noted (Fig. 3). The number of mast cells varied, but it was not unusual to find 20 or more per high power field in these areas.

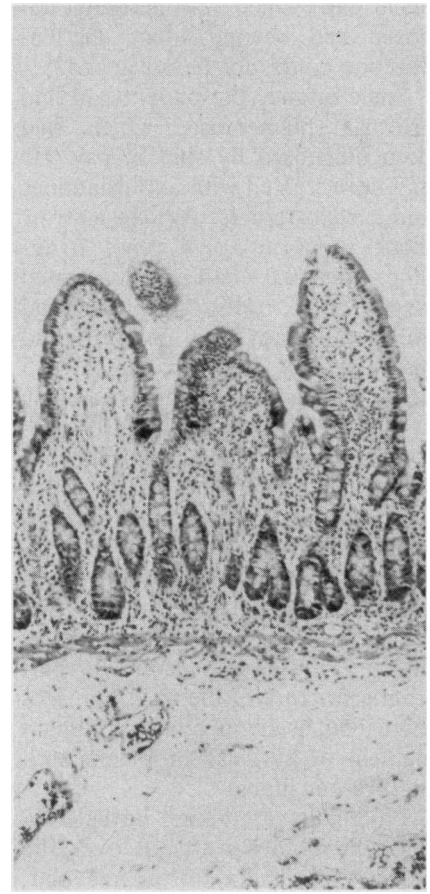

FIG. 2—Blunting and shortening of villi in jejunum (hematoxylin–eosin [H–E]; ×80).

The wedge biopsy specimen of the liver demonstrated extensive fibrosis with septa formation. The portal areas were enlarged and showed a piecemeal pattern of inflammation (Fig. 4); the inflammatory cells consisted of lymphocytes and a few plasma cells. In addition, numerous mast cells were noted, largely at the periphery of the portal areas and along the fibrous septa (Fig. 5). Despite the extensive fibrosis, nodules of regeneration were not present, and the appearance was not that of cirrhosis. The peripheral liver cell plate was disrupted in many places by the infiltration of inflammatory and mast cells and the swelling of hepatocytes. Branches of the hepatic artery and the portal vein were identified in the dense collagenous tissue of the portal areas and septa. The lymphatics were dilated. Small aggregates of mast cells were present randomly throughout the liver parenchyma and in the centrilobular zones, where they were associated with fibrosis of the terminal hepatic venules.

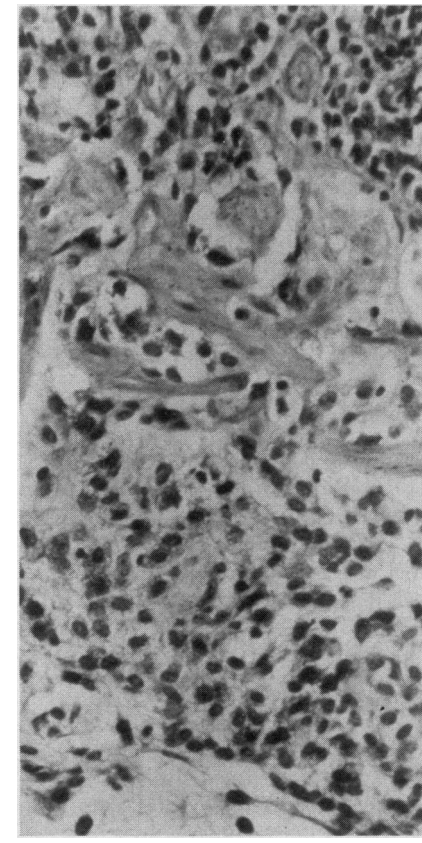

FIG. 3—Infiltration of mucosa and submucosa of jejunum by mast cells; muscularis mucosae separates mucosa above from submucosa below (toluidine blue; ×312).

A few larger sublobular veins also showed sclerosis, with thickening of the wall and marked narrowing of the lumen (Fig. 6). Although the patient's serum was not tested for the presence of hepatitis B surface antigen, the Shikata stain was negative.

The patient's course was complicated by pneumonitis, staphylococcal bacteremia, ascites and portal–systemic encephalopathy. Appropriate therapy was instituted, but the patient's level of consciousness and general condition deteriorated. He continued to bleed extensively, requiring approximately 24 units of blood and plasma over the course of his protracted illness and died 52 days after admission. Autopsy was refused.

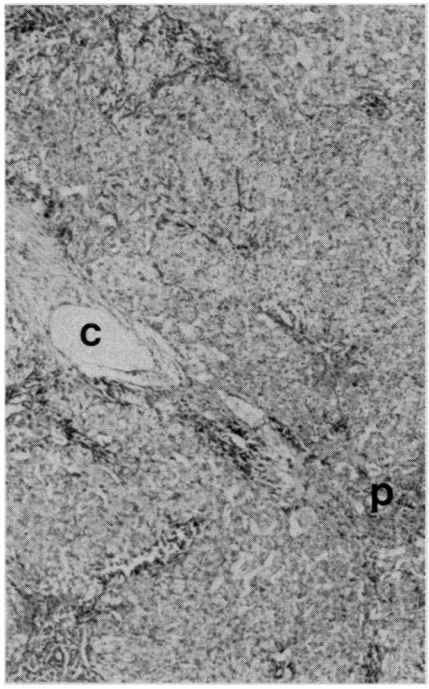

FIG. 4—Stellate portal fibrosis, with septum linking portal tract (p) and branch of sublobular hepatic vein (c), and absence of nodular regeneration (H–E; ×50).

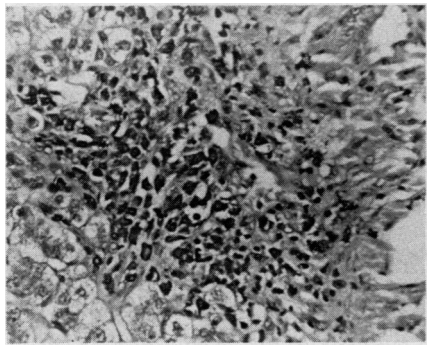

FIG. 5—Portal infiltrate: aggregates of mast cells disrupting peripheral liver cell plate (toluidine blue; ×156).

Discussion

Mastocytosis is a systemic disease reportedly involving almost every organ in the body. Its manifestations are legion and depend on the organ or tissue involved. However, mental retardation has not hitherto been described in association with mast cell disease, and, despite the widespread mast cell proliferation encountered in this disorder, direct central nervous system involvement is not a well documented feature.[4,5] With the normal chromosome configuration and no other known etiologic considerations in our patient, mental retardation could be a new manifestation of the disease.

In one review of 71 "proved" systemic cases the liver was involved in 72%, the spleen in 62%, the lymph nodes in 28%, the bone marrow in 90% and the peripheral blood in 16%. There was also roentgenographic evidence of bone and gastrointestinal tract involvement in 65% and 12% of the cases respectively.[6] In spite of this, cutaneous lesions are by far the most common manifestation of the disease, occurring in over 95% of the cases in most series.[7] Systemic involvement without cutaneous lesions, although rare, has been reported.[8,9] But, as in our case, the skin lesions are almost always the first clue to the diagnosis. The skin changes reported have included solitary mastocytomas and urticarial, bullous, telangiectatic, hemorrhagic and erythrodermic eruptions.[10]

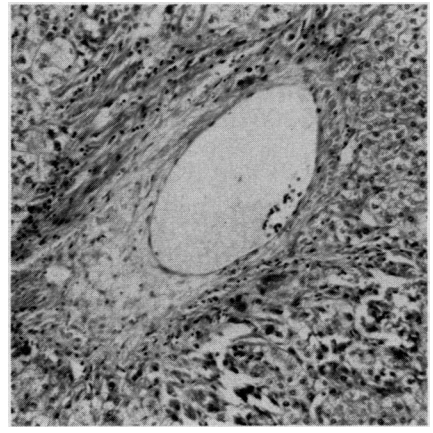

FIG. 6—Intimal fibrosis and narrowed lumen of sublobular hepatic vein (H–E; ×100).

Criteria for the diagnosis of mastocytosis from the histologic features of jejunal specimens have been proposed.[11,12] Our patient's mast cell count, 20 or more per high power field, surpassed the proposed criterion of 6 per high power field and, more important, was a measure of the extent of cellular proliferation.

With the 12% frequency of gastrointestinal tract involvement in one series[6] and the variety of gastrointestinal tract lesions identifiable radiologically in another,[13] gastrointestinal manifestations are assuming greater clinical importance in the natural history of mastocytosis. The many gastrointestinal symptoms in this disease — dyspepsia, flatulence and epigastric pain — are believed to be secondary to peptic ulcer disease or malabsorption or both. Hematemesis, however, is seldom reported in a case of mastocytosis. Four disease processes, which could occur simultaneously, may cause hematemesis in patients with mastocytosis:

- Peptic ulcer disease. This occurs in 4% to 10% of patients with mastocytosis.[6,7] Hyperhistaminemia and hyperchlorhydria have been observed, but a cause-and-effect relationship has not been satisfactorily demonstrated.[14] In our patient the serum histamine concentration was elevated, and frequent administration of cimetidine, a histamine H_2-receptor antagonist, was required to effectively lower the gastric output and acidity (Fig. 1). Although other histamine antagonists have been administered to patients with this disease,[15] this is the first reported instance of the use of cimetidine in such a case.
- Gastric erosions. Ammann and colleagues[14] described a patient with gastroduodenitis and mastocytosis. The gastroduodenitis apparently resolved spontaneously and did not cause hematemesis. Our patient had esophagogastric erosions, which should be considered a potential source of bleeding.
- Urticarial lesions. Endoscopic visualization of these lesions has previously been described.[13] The lesions are reportedly transient, resolving spontaneously. Similar lesions have produced bleeding in

animals after the administration of histamine and heparin.[16] However, because of the heavy bleeding in our patient they could not be ascertained at endoscopy.

● Varices. Portal hypertension must now be considered a rare complication of mastocytosis, as in the present case. Our patient exhibited esophageal and gastric varices, ascites and angiographic evidence of portal hypertension. Recently Capron and associates[17] described the first case to be reported of portal hypertension in a patient with systemic mastocytosis with raised wedged hepatic venous pressure. In our case the hepatic venous pressures were not determined, although the extensive fibrosis, especially the sclerosis of the outflow tract in the liver biopsy specimen, suggested a postsinusoidal block. That mast cells were prominent in the areas of fibrosis may imply a physiologic relation between mast cells and collagen deposition, the nature of which is unknown at this time.

Although any of the common causes of gastrointestinal bleeding could exist in cases of mastocytosis, the four disease processes outlined above should be borne in mind. Even more important, several of these entities may occur and cause bleeding simultaneously. This has important therapeutic implications.

A cure for systemic mastocytosis remains elusive. The mast cell has been shown to contain a number of biochemically active agents, including heparin,[18] histamine,[19] hyaluronic acid[20] and, in the rat, serotonin.[21] It is therefore not surprising that many researchers have implicated these powerful metabolites in the genesis of some of the constitutional symptoms and signs of this disease. It is also not surprising that the main thrust of therapy has been directed to offsetting the secretory activity of the mast cell. In our patient cimetidine, disodium cromoglycate and chlorpheniramine maleate were all employed in an attempt to reverse the systemic and gastrointestinal effects of mast cell secretion.

It is tempting to implicate the production of heparin by mast cells as contributing to the patient's continued bleeding, especially since hypocholesterolemia, a known effect of heparin, was observed. However, while the bleeding ensued the patient's coagulogram remained normal.

Presumably the outcome of this case could have been modified if surgical management of portal hypertension had not been hampered by technical difficulties. In spite of this, gastrointestinal hemorrhage should be considered a factor contributing to the overall prognosis of systemic mastocytosis. In the past this prognosis was thought to be uniformly favourable. There is evidence, however, that this is not the case; in a series of 25 cases of mastocytosis with a fatal outcome 48% of the patients died within 2 years of the onset of the disease.

Our case illustrates potentially lethal extensive tissue involvement in mastocytosis. Several factors with inherent diagnostic and therapeutic challenges appear to have contributed to the severe, recurrent gastrointestinal hemorrhage in our patient.

We thank Dr. Robert Goodacre, research fellow, department of medicine, McMaster University Medical Centre for performing the histamine analysis on the serum samples.

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