Recurrent Gastrointestinal Bleeding Associated With Myelofibrosis and Diffuse Intestinal Telangiectasias

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Case Report

A 70-year-old retired nurse was admitted in November 1986 with hematochezia and early satiety followed by recurrent gastrointestinal bleeding.

Fifteen years earlier, she had been admitted with abdominal pain, bloody diarrhea, and severe dehydration. At that time, the rectum was normal at sigmoidoscopy; a barium radiograph study of the colon showed ulceration and thumbprinting in the ascending and proximal transverse colon; results of barium studies of the upper gastrointestinal tract and small intestine as well as a visceral arteriogram were normal. A presumptive diagnosis of ischemic colitis was made, and the patient's acute illness resolved without specific therapy.

Ten years before admission, the patient developed symmetric polyarticular arthralgias and a normochromic, normocytic anemia. She began aspirin therapy for presumed seronegative rheumatoid arthritis. One year later she had a month-long episode of fevers and leukopenia (white blood cell count, 3100) with marked leftward shift. A bone marrow aspiration and biopsy were nondiagnostic. Despite extensive evaluation, a specific etiology was not discovered, and the patient's signs and symptoms resolved spontaneously.

Four years before admission, she developed a chronic nonproductive cough. Wheezing was intermittently noted, and an allergist diagnosed "pollen asthma." Despite weekly inoculations of "mixed allergens" and oral aminophylline, her dry cough persisted. A chest radiograph was interpreted as normal with the exception of calcified granulomas in the upper lobes. Results of pulmonary function tests were otherwise normal.

During the 2 months before admission, she noted progressive fatigue and a 20-lb weight loss associated with early satiety. On admission for hematochezia, her medications included 12 buffered aspirin tablets per day for arthritis, thyroid hormone supplement for hypothyroidism, and hydrochlorothiazide for hypertension.

On physical examination she was tachycardic but normotensive. Physical examination was also remarkable for a spleen tip palpated 3 cm below the left costal margin and bright red blood on rectal examination.

Laboratory studies showed a hematocrit of 0.23 (23%) with a mean corpuscular volume of 80 fL, a white blood cell count of 5900, and a platelet count of 256,000. The peripheral smear showed microcytic and hypochromic red blood cells with occasional tear drops, acanthocytes, elliptocytes, and nucleated red blood cells; occasional metamyelocytes and myelocytes were present. An elevated partial thromboplastin time (PTT) of 39.3 seconds (control, 29.4 seconds) was attributed to heterozygous factor XI (FXI) deficiency with an FXI level of 38%; prothrombin and bleeding times were normal. A leukocyte alkaline phosphatase score was normal, as were serum electrolyte, blood urea nitrogen, creatinine, aminotransferase, and lactate dehydrogenase levels. Alkaline phosphatase concentration was elevated at 205 U/L (normal, ≥120 U/L), and γ-glutamyl transferase level was normal. Except for diffusely sclerotic vertebrae and humeri, a chest radiograph was unremarkable.

Management included red blood cell transfusions, ranitidine, and aggressive treatment of symptoms associated with myelofibrosis and telangiectasias.

Abbreviations used in this paper: AVM, arteriovenous malformation; FXI, Factor XI; PTT, partial thromboplastin time; SMCD, systemic mast cell disease.

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dine, and sucralfate; treatment for mild FXI deficiency was not indicated. Colonoscopic examination showed several left-sided diverticula and focal erythema in the sigmoid colon, but no bleeding site. Esophagogastroduodenoscopy revealed numerous variably raised, red lesions 2–10 mm in diameter on edematous folds located primarily in the distal body of the stomach. Several similar lesions were found scattered throughout the duodenum to its third portion, but no varices were seen. Biopsies of the gastric lesions were interpreted as showing chronic gastritis. Results of a small bowel barium study were normal. By ultrasonography, the spleen appeared homogeneous and measured 15 cm in its greatest dimension. Bone marrow aspirate and biopsy showed moderate fibrosis; areas not involved by fibrosis were markedly hypercellular (90%) with a mildly increased myeloid-to-erythroid ratio and increased megakaryocytes with clustering.

A diagnosis of idiopathic myelofibrosis (agnogenic myeloid metaplasia) with associated congestive gastropathy was made. Within 2 months of institution of hydroxyurea, early satiety and palpable splenomegaly abated. Red blood cell microcytosis and hypochromia resolved on oral iron supplements. Stools remained intermittently positive for occult blood despite withdrawal of aspirin and other nonsteroidal antiinflammatory agents and initiation of ranitidine and sucralfate therapy. The patient required transfusion of packed red blood cells approximately every 3 months during the 2 years.

In June 1988, the patient complained of fatigue, bloating, and a decreased attention span. Blood counts remained unchanged with a hematocrit of .33 (32.5%). Thyroid-stimulating hormone level was 61 mIU/L. On an increased dose of levothyroxine, 0.225 mg daily, her symptoms abated. In September 1988, she was hospitalized because of weakness and melena. Physical examination now revealed liver and spleen edges palpable 3 cm below the right and left costal margins, respectively. There was no lymphadenopathy. The hematocrit was 0.19 (19%). The white blood cell count was 5300 and, except for 18% eosinophils and 3% basophils, the differential was normal. Other laboratory test results were unchanged, except the alkaline phosphatase concentration was now 334. She received packed red blood cell transfusions. Ranitidine and sucralfate therapy were continued. Esophagogastroduodenoscopy again revealed the gastric and duodenal lesions seen during the November 1986 study, but none of these were bleeding. Serum cortisol levels increased normally in response to parenterally administered adrenocorticotropic hormone. Her melena abated, and she was discharged on her former medical regimen.

In November 1988, she was readmitted for recurrent melena associated with profound anemia. Results of physical and laboratory examinations remained the same except for a blood urea nitrogen concentration of 12.5 mmol/L and an alkaline phosphatase of 500 U/L. Colonoscopy revealed focal telangiectatic-appearing lesions scattered throughout the entire colon (Figure 1), some of which were oozing blood. The lesions resembled those previously seen in the stomach and duodenum except that the colonic lesions were flat, not raised. There was no surrounding edema or erythema. Biopsies were nondiagnostic. In view of the patient's splenomegaly and presumptive myeloproliferative disorder, the possibility was again raised that the telangiectatic lesions in the stomach, duodenum, and colon were a manifestation of portal hypertension. Despite the institution of propranolol therapy of 10 mg three times daily, intermittent melena continued following discharge with an increased transfusion requirement of 1.5 U of packed red blood cells per week. A second bone marrow biopsy revealed extensive myelofibrosis, markedly increased compared with that in the bone marrow specimen obtained 2 years previously. In view of the patient's increasing dependence on transfused red blood cells, hydroxyurea was discontinued in an effort to promote erythropoiesis. However, abdominal distention, early satiety, and dyspnea recurred. A chest radiograph revealed a diffuse interstitial infiltrate, which in retrospect was appreciated on chest films obtained 1 year earlier. Hydroxyurea was re instituted with improvement in the patient's symptoms. Because of its inefficacy, propranolol therapy was discontinued.

In January 1989, the hematocrit decreased to 0.16 (16%), prompting readmission. Results of another small bowel barium study was normal. Esophagogastroduodenoscopy confirmed the previous visual and pathological findings. Following discharge, she required approximately 3 U of packed red blood cells per week to compensate for her continued blood loss. A diagnostic procedure was performed.

### Differential Diagnosis

**Dr. Reed E. Drews (Hematology):** This patient presented with gastrointestinal bleeding in the setting of moderate splenomegaly and early satiety. The presence of occasional tear drops, acanthocytes, nucleated red blood cells, and early precursors of polymorphonuclear leukocytes on the peripheral blood smear suggested leukoerythroblastosis from a myelophthisic process. Consequently, we were not surprised to find myelofibrosis on biopsy of the patient's bone marrow. Although the leukoerythroblastastic findings were surprisingly mild for the degree of observed myelofibrosis, we felt that the diagnosis of idiopathic myelofibrosis, alias agnogenic myeloid metaplasia, was most likely. The additional marrow findings of hypercellularity with leftward-shifted granulopoiesis and megakaryocyte clustering supported the diagnosis of this myeloproliferative disorder as well. An incidental finding was heterozygous FXI deficiency. Because the heterozygous state is not associated with a hemorrhagic diathesis, correction of the prolonged partial thromboplastin time (PTT) was not indicated. Treatment for idiopathic myelofibrosis is generally symptomatic and palliative, and thus hydroxyurea was used in this patient for early satiety secondary to splenomegaly.

**Dr. Steven D. Freedman (Gastroenterology):** The search for the etiology and treatment of recurrent and progressive gastrointestinal bleeding in this patient with myeloid metaplasia presented us with quite a challenge. Multiple red, variably raised lesions had been seen throughout the stomach, duodenum, and...
Figure 1. Endoscopic image of the colon. Numerous friable telangiectatic lesions are present in this representative view of the colonic mucosa obtained in November 1988.

colon. We speculated that the hemorrhage was occurring in both the upper and lower tracts and that, moreover, if we could assess the remainder of the small intestine endoscopically, these same abnormalities would be found there as well.

At this point, two issues confronted us: we had to discover the nature of the intestinal lesions, and we had to determine the best method for treating them. Although the gastric biopsies revealed chronic gastritis, the endoscopic appearance was more consistent with a vascular etiology. Vasculitis seemed unlikely because of the lack of abdominal pain and the absence of multisystemic involvement. Large hemangiomas, which rarely involve the bowel, are usually solitary and frequently associated with cutaneous lesions (1,2). Although the bleeding is generally chronic and painless, as in our patient, the diffuse nature of the endoscopic findings would not favor this diagnosis.

One of the more common causes of hemorrhage that was most consistent with the endoscopic findings in this patient is arteriovenous malformations (AVMs). Such lesions can be hereditary in origin, as seen in the Osler-Weber-Rendu syndrome (3,4), von Willebrand's disease (5), and Turner's syndrome (6); they may also be secondary to acquired disease, as in scleroderma with CREST syndrome (calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia), renal failure, and possibly aortic stenosis (6–10). This patient had no evidence of any of these disorders.

The findings of red lesions on edematous gastric folds also suggested an entity termed "congestive gastropathy," which is associated with portal hypertension and cirrhosis (11–13). The gastric biopsy showing a mononuclear infiltrate, although not specifically supporting the diagnosis of congestive gastropathy, does not rule it out, because such infiltrates have been reported in cases of this disorder (13). Portal hypertension has been described in agnogenic myeloid metaplasia (14–18), with hemorrhage usually occurring from esophageal and/or gastric varices. Despite the lack of association of AVMs or congestive gastropathy with myeloid metaplasia, we wondered whether the latter had produced portal hypertension leading to the vascular abnormalities seen throughout the gastrointestinal tract. One other consideration was bleeding because of direct involvement of the bowel by extramedullary hematopoiesis. However, our patient had no cessation of bleeding on hydroxyurea treatment in contrast to a case reported recently (19).

Propranolol has been efficacious in the treatment of hypertensive gastropathy (20), thus the use, albeit unsuccessful, in our patient. Other options such as endoscopic cautery or laser therapy were considered but felt not realistic because of the diffuse nature of the lesions. On the other hand, the patient's rate of bleeding had increased to the point that more invasive diagnostic and therapeutic intervention clearly seemed warranted. We thought that angiography was indicated to exclude or establish the presence of portal hypertension, to exclude venous thromboses, and to visualize any large hemangiomas, AVMs, or varices.

Dr. Donald J. Glotzer (Surgery): I first heard about this patient in the fall of 1988. We discussed the possibility of portal hypertension secondary to her presumed myeloid metaplasia as the underlying pathogenic mechanism. We speculated that the lesions in the colon conceivably might represent a congestive "colopathy" variant of colonic varices (21,22). We made the analogy to patients with cirrhotic portal hypertension, 5% of whom bleed from congestive portal hypertension. However, this patient did not fit that profile.
gastropathy (12), although this figure maybe as high as 50% if gastric erosions are included (23). I realized that these thoughts were at least moderately far-fetched and indicative of a “think-tank” approach to the problem. However, this approach was perhaps not unwarranted in view of the desperate nature of her situation, which so far had eluded definitive diagnosis and effective treatment. I suspected that the spleen was not sufficiently enlarged to produce portal hypertension solely on the basis of its contribution to the portal blood flow, but liver infiltration, nonneoplastic sinusoidal abnormalities, and portal venous thrombosis were reasonable possibilities. Therefore, I concurred with the recommendation for an angiographic study.

Diagnostic Studies

Angiographic Findings

Dr. Ducksoo Kim (Radiology): In the arterial phase, the superior mesenteric and celiac arteries were normal. In the venous phase, portal, splenic, and superior mesenteric veins were all widely patent with centripetal flow. However, there was retrograde flow into the central portion of the inferior mesenteric vein, which was moderately dilated. Moderate splenomegaly was noted, but there were no vascular abnormalities of the viscera such as varices, arteriovenous malformations, or hemangiomata. The hepatic vein wedge pressure measured 143 mm Hg (normal, <120 mm Hg).

Dr. Drews: We were skeptical that this mild degree of portal hypertension could produce a “congestive enteropathy,” although the entity could not be totally excluded. A splenectomy and, if possible, splenorenal shunt might ameliorate bleeding by decreasing her portal pressure. At the very least, a splenectomy would allow us to discontinue the hydroxyurea therapy, which had been effective in controlling symptoms of splenomegaly but was inhibiting effective erythropoiesis, a problem that was only certain to worsen with advancing myelofibrosis. However, at the very worst splenectomy might result in one or more potentially ominous complications: (a) life-threatening pancytopenia as a consequence of removing a major site of extramedullary hematopoiesis; (b) an enhanced thrombotic diathesis with risk for thrombotic complications; (c) symptomatic hepatomegaly and hepatic dysfunction as a consequence of compensatory expansion of hepatic hematopoietic elements; or (d) marked ascites as a result of presinusoidal obstruction and increased presinusoidal resistance from these same expanding hepatic islands of extramedullary hematopoiesis (24–26). Although these complications can carry a high fatality rate, we felt that the patient was otherwise healthy and had no adverse predictors for an immediate decreased survival from the idiopathic myelofibrosis.

Operative Findings

Dr. Glotzer: During surgery, which was performed through an abdominal incision, the spleen was found to be several times enlarged, measuring about 25 cm in maximum diameter, and considerable perisplenitis was present. The liver was enlarged, had an irregular surface, and felt quite firm. I was rather surprised at the time to find that the hilum of the spleen contained very large lymph nodes that were intimately adherent to the splenic vein and the pancreas, which itself had a wooden, fibrotic consistency. Moreover, multiple large nodes were found in the small bowel mesentery measuring up to 3 cm in diameter. The stomach, small bowel, and colon were carefully inspected and found to be normal externally. A modest amount of ascites (about 500 mL) was found. A splenectomy was performed along with removal of local lymph nodes. An end-to-side splenorenal shunt was constructed to the anterior surface of the renal vein. The postoperative course was uncomplicated but slow, and the patient was discharged on the 12th postoperative day.

Pathology of the Surgical Specimens

Drs. Humphrey Gardner and Stephen J. Galli (Pathology): The spleen weighed 145 g and was firm but lacked discrete masses. A lymph node measuring 1 × 1 × 1 cm was also received. Microscopic examination of H&E-stained sections of the spleen revealed aggregates of mononuclear cells in paratrabecular and parafollicular locations associated with trabecular fibrosis and infiltrates of eosinophils and other acute and chronic inflammatory cells. The lymph node also showed acute and chronic inflammatory cell infiltration with many eosinophils, as well as aggregates of mononuclear cells similar to those in the spleen. Many of these mononuclear cells could be identified as mast cells because they contained fine cytoplasmic granules that reacted strongly with the Giemsa or chloroacetate esterase stains. They also showed variably metachromasia when stained with toluidine blue (Figure 2).

The growth pattern of the mast cells in the spleen and lymph node, the distribution of fibrosis in these organs, and the accompanying leukocyte infiltrate including many eosinophils were all typical of the condition referred to as systemic mastocytosis or, more recently, systemic mast cell disease (SMCD) (27–29). Mononuclear cells similar to those in the spleen and lymph node were seen when the bone marrow biopsy specimen from 1986 was reviewed.
Although sections from decalcified specimens generally are not suitable for cytochemical stains, the bone marrow fibrosis, eosinophilia, and myeloid hyperplasia present in the biopsy from 1986 are characteristic of SMCD (27–29). Review of the gastric and colonic biopsies did not reveal increased numbers of mast cells or eosinophils.

Discussion

Dr. Drews: Needless to say, the clinicians caring for the patient were surprised by the findings. This is an unusual presentation of SMCD, a disorder of mast cells that may or may not involve the skin. Cutaneous mastocytosis, a more common and readily diagnosed manifestation of mast cell disease, usually presents with urticaria pigmentosa. It is characterized by multiple hyperpigmented macules and papules that become urticarial when stroked (30,31). Only 10%–30% of patients with cutaneous mastocytosis will show some degree of systemic infiltration by mast cells, typically of bone, spleen, and lymph nodes, but also of liver, bowel, and lung. Symptoms, when present, are attributable to secreted mast cell products, which may produce flushing, headache, pruritus, wheezing, abdominal cramps, or diarrhea (32,33).

Fortunately, the majority of these patients enjoy a benign course, warranting the appellation “benign” systemic mastocytosis. However, one third of these patients will progress to an aggressive variety, characterized by extensive mast cell proliferation and fibrosis involving the previously mentioned organs.

Dr. Freedman: Gastrointestinal symptoms have been reported to occur in 25%–80% of patients with SMCD (34–37). Frequently, there will be complaints of abdominal pain that may be characterized as dyspepsia. On endoscopic evaluation, peptic ulceration, duodenitis, or gastricis can be found.

One third of patients may have small bowel malabsorption as determined by d-xylose, fecal fat, or Schilling tests, although steatorrhea is uncommon (37). Severe malabsorption has been reported, with small bowel biopsies showing a wide spectrum of pathological findings, from atrophy and loss of villi to frank mast cell infiltration of mucosa and submucosa to normal architecture despite severe steatorrhea (36–43). This last discrepancy may be the result of sampling error. When atrophy is present, it may be confused with sprue. In fact, response to a gluten-free diet has been documented (38). It is interesting that our patient developed clinical and chemical evidence of hypothyroidism on a long-standing stable dose of thyroid hormone supplement, suggesting that malabsorption to some degree may have been present.

Diarrhea is common and, if associated with flushing, can be indistinguishable clinically from carcinoid. Unlike carcinoid, in which urinary 5-hydroxyindoleacetic acid level is generally elevated, the pathophysiology in mast cell disease is attributed to increased levels of certain mediators including histamine and prostaglandin D2. This may also result in gastric hypersecretion. Isolated instances in which aspirin has induced complete resolution of diarrhea that had not responded to H2 and H3 blockers have been reported, suggesting that in some circumstances prostaglandins may play a significant role (44).

Bleeding is less commonly encountered and can arise from various entities. These include peptic ulcer disease, gastritis, duodenitis, and possibly cutaneous lesions, which have been reported to occur in the stomach, duodenum, and rectum (39,45–47). Whether or not local release of heparin from mast cells potentiates bleeding is unknown.

Portal hypertension in mast cell disease can manifest itself with variceal bleeding and/or ascites (48–50). If there is intraabdominal or retroperitoneal lymph node invasion by mast cells, an exudative rather than transudative ascites may develop (38). Splenomegaly from mast cell infiltration is common in this setting, whereas liver involvement is less predictable. When splenomegaly is present, arteriovenous shunting because of mast cell–derived vasodilators may contribute to increased portal pressures. However, a moderate increase in intrahepatic resistance may be secondary to extramedullary hematopoiesis, as in the myeloproliferative disorders, or secondary to mast cell infiltration and fibrosis, as in aggressive mastocytosis. If cirrhosis is not present, splenectomy alone may sufficiently decrease portal hypertension; otherwise, some type of shunt is required in addition to splenectomy (48,49).

Finally, fibrosis is commonly seen in organs in which there is mast cell proliferation. Mast cell products, such as heparin, which inhibits collagenase activity, or perhaps even fibrogenic cytokines, may contribute to this process.

During the 7 months following surgery, the patient's stools were brown and only intermittently positive for occult blood. Colonoscopy was electively performed and showed a normal-appearing mucosa with complete resolution of the telangiectatic lesions. A magnetic resonance image of the abdominal vessels showed persistent reverse flow in the inferior mesenteric vein despite a patent splenorenal shunt. This suggested that no significant reduction in portal pressures had occurred, and it argued against a congestive enteropathy from portal hypertension as the primary cause of her intestinal bleeding.

An alternative explanation is that the telangiectatic lesions of the stomach and bowel were related to mast cell secretory products. In retrospect, the erythema-
tous lesions with surrounding edema seen in the stomach could have represented an urticaria-like reaction. Vasoactive products from mast cells may contribute to the arteriovenous shunting observed in the spleens of patients with SMCD. In addition, the lesions of some patients with urticaria pigmentosa show prominent telangiectatic patterns (33), suggesting that mast cell products might also have contributed to the development of the telangiectasias seen in the colon of our patient. Although no one has described this type of lesion in the mastocytosis syndrome, it is intriguing to speculate that the telangiectasias involving the bowel in our patient were secondary to SMCD and that one of the benefits of splenectomy was to significantly decrease the levels of vasoactive factors in the circulation. However, the absence of increased numbers of mast cells in the lesions precludes a definitive association, although, as will be discussed, biopsy specimens from the gastrointestinal tract rarely show increased numbers of mast cells, even in the setting of florid gastrointestinal symptoms (51).

Dr. Drews: Over the ensuing months the patient developed intermittent melena, requiring blood transfusion support every 4–6 weeks. This was associated with worsening dyspnea and dry cough. Physical examination now showed a liver edge extending 6 cm below the right costal margin. Her alkaline phosphatase level was >1200 U/L with persistently normal aminotransferase levels.

Treatment with hydroxyurea as well as H₁- and H₂-receptor antagonists was resumed. Over the next several months, the patient’s lymph nodes and liver decreased in size, and her cough improved. However, hepatic dysfunction worsened as manifested by a decrease in albumin concentration and an increase in prothrombin time.

In the 12th month following surgery, the patient developed increasing somnolence and forgetfulness despite discontinuation of the H₁- and H₂-receptor blockers. Concomitant with an episode of melena and an associated decrease in hematocrit, she developed frank encephalopathy. Magnetic resonance imaging and correlative Doppler ultrasound studies of the abdominal vasculature showed absent flow in the portal vein and the splenorenal shunt. A presumptive diagnosis of portal vein thrombosis was made, but because of persistent gastrointestinal bleeding, she was not deemed a candidate for anticoagulant or thrombolytic therapy. Surprisingly, she did not develop progressive ascites, edema, or worsening intestinal hemorrhage, and on lactulose therapy and a low-protein diet, her mental status and asterixis markedly improved. Despite this, she died after an episode of dyspnea, 6 weeks after the onset of frank encephalopathy. A postmortem examination was performed.

Autopsy Findings

Drs. Humphrey Gardner and Stephen J. Galli:

The most notable gross finding at autopsy was marked enlargement of the mediastinal, perportal, and mesenteric lymph nodes. Microscopically, these showed fibrosis and extensive aggregates of mast cells and eosinophils in the paracortical and parafollicular distribution typical of SMCD. Infiltrates of mast cells and eosinophils were also present in the bone marrow, in association with extensive paratrabeicular fibrosis and hypercellularity of all three hematopoietic cell lineages. The liver showed moderate to severe periportal fibrosis with associated infiltrates of lymphocytes and eosinophils. Although only scattered mast cells were present in the portal areas, the pattern of other changes is consistent with previous involvement by SMCD. Detailed gross examination and microscopic sampling of the gastrointestinal tract revealed neither a source for this patient’s gastrointestinal bleeding nor evidence for involvement by SMCD. Additional findings included an intact splenorenal shunt and a patent hepatic portal venous system. In retrospect, it is likely that all of this patient’s hematologic and bone marrow findings, as well as many of her other clinical problems, resulted from aggressive systemic mast cell disease. However, the autopsy did not reveal a specific acute cause of death.

This case clearly illustrates that SMCD can have protean manifestations and quite variable clinical presentations, often without evidence of cutaneous involvement. Moreover, mast cells can be extremely difficult to identify in formalin-fixed, H&E-stained specimens. Indeed, biopsies of the gastrointestinal tract are rarely diagnostic in systemic mast cell disease, even when the specimens are processed and stained to reveal mast cells and the biopsies are performed in patients with florid gastrointestinal manifestations of this disorder (51). In short, establishing the diagnosis can require a high index of suspicion. Properly processed and interpreted bone marrow biopsies represent an important means for diagnosing systemic mast cell disease (33,51,52). In one series of 66 patients with SMCD (51), roughly half lacked urticaria pigmentosa and/or skin symptoms. However, half of the patients had radiographic evidence of bone involvement and a third had a second hematologic condition, most frequently a dysmyelopietic or myeloproliferative disorder (51). Given the frequent failure of gastrointestinal biopsies to establish the diagnosis of systemic mast cell disease, bone marrow biopsies should be reevaluated or performed to identify mast cells in any patient with unusual gastrointestinal problems, portal hypertension, and a diagnosis of “myelofibrosis.”

The clinical course of SMCD may be indolent or
aggressive (52). Our patient had several of the poor prognostic factors of SMCD, including hepatosplenomegaly, ascites, bone marrow hypercellularity, constitutional symptoms, anemia, and lack of skin involvement (52). Other factors associated with an aggressive course are cytological atypia of the mast cells, thrombocytopenia, and abnormal results of liver function tests.

Systemic mast cell disease represents only part of a broad spectrum of mast cell disorders, none of which are understood at the molecular level (reviewed in references 53 and 54). However, as illustrated by this case, much of the clinically important pathology associated with SMCD is not due to the infiltration of tissues with large numbers of mast cells per se, but rather appears to reflect the diverse actions of biologically active mast cell products. The effects of histamine and other classical mast cell mediators on vascular tone or permeability and gastrointestinal functions have already been mentioned, and recent work indicates that appropriately stimulated mouse mast cells can produce a variety of multifunctional cytokines with many important effects in hematopoiesis, inflammation, and the development of fibrosis (55–63). These include granulocyte/macrophage colony–stimulating factor, interleukin-5 (a major eosinophil growth factor), interleukin-3, and interleukin-4 (which have important effects on mouse mast cell proliferation or maturation), transforming growth factor β (TGF-β), and tumor necrosis factor α (TNF-α) (55–63). Both TGF-β and TNF-α, among their diverse bioactivities, can promote fibrosis and angiogenesis and may influence bone remodelling (reviewed in references 61 and 64–67). In light of these findings, it will be important to define the types of cytokines that can be produced by various populations of normal or neoplastic human mast cells and to investigate the possibility that mast cell cytokine production contributes to the pathogenesis of many of the clinical and pathological manifestations of SMCD.

Final Diagnosis

The final diagnosis was systemic mastocytosis with aggressive clinical course.

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