

Cholestatic jaundice and bone lesions in an elderly woman

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SUMMARY

Background A 74-year-old Caucasian female presented with jaundice, clay-colored stools, diarrhea, and fatigue of 3 months' duration, accompanied by a weight loss of 6.8 kg. Physical examination demonstrated mild hepatomegaly. Initial blood work revealed abnormal liver biochemistries with a cholestatic pattern. An abdominal CT scan showed intrahepatic bile-duct dilatation without masses but with multiple lytic and blastic bone lesions. A sacral bone biopsy established the diagnosis.

Investigations Endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, CT scan, bone biopsy and liver biopsy.

Diagnosis Systemic mastocytosis affecting the biliary system resulting in a primary-sclerosing-cholangitis-like picture combined with diffuse blastic and lytic bone lesions.

Management Biliary stenting, histamine 1- and 2-receptor blockers, and chemotherapy (cladribine).

KEYWORDS Blastic bone lesions, cholangiopathy, lytic bone lesions, primary sclerosing cholangitis, systemic mastocytosis

CME

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

THE CASE

A 74-year-old Caucasian female presented to her primary care physician with jaundice and fatigue. The patient was well until 3 months earlier, when she developed clay-colored stools and yellow discoloration of her skin accompanied by fatigue and weight loss. Initial blood work revealed abnormal liver function tests, predominantly elevated levels of alkaline phosphatase and gamma glutamyltransferase. An abdominal CT scan showed intrahepatic bile-duct dilatation and a prominent pancreatic head. The patient was referred to the University of Pittsburgh Medical Center, PA, for further work-up of possible pancreatic cancer. On presentation, she reported a weight loss of 6.8 kg. She did not experience fever, chills, abdominal pain or other symptoms.

Past medical history was remarkable for hypertension and chronic diarrhea. The patient had been taking FOSINOPRIL for many years, did not smoke and rarely consumed alcohol. Family history was remarkable for a mother with gastric cancer and a maternal aunt with colorectal cancer.

Physical examination revealed an ICTERIC elderly female in no distress. Heart and lung examinations were normal. The abdomen was soft, with normoactive bowel sounds and mild hepatomegaly. The spleen was not palpable. There were no lymphadenopathy or skin changes detected. Laboratory test results are presented in Table 1.

Endoscopic ultrasound revealed diffuse hypo-echoic homogenous parenchymal changes involving the entire pancreas (hepatization), which appeared inflamed. No pancreatic masses were seen. Fine needle aspiration of the pancreatic head revealed normal pancreatic cells. An endoscopic retrograde cholangiopancreatography (ERCP) showed a common bile duct (CBD) stricture and diffuse intrahepatic bile-duct dilations and

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Table 1 Laboratory test results at presentation.

Test	Patient's results	Normal range
Hematocrit	27.5%	34.1–43.0%
Mean corpuscular volume	95 fl	82.6–97.4 fl
White blood cell count	$12.6 \times 10^9/l$	$3.8\text{--}10.6 \times 10^9/l$
White blood cell differential		
Polymorphs	48%	44–77%
Lymphocytes	18%	13–44%
Bands	6%	0–5%
Monocytes	26%	4–13%
Eosinophils	2%	0–2%
Platelet count	$211 \times 10^9/l$	$156\text{--}369 \times 10^9/l$
Prothrombin time	11.5 s	10.0–12.8 s
Partial thromboplastin time	31.2 s	24.4–33.2 s
Total bilirubin ^a	3.1 mg/dl	0.3–1.5 mg/dl
Alkaline phosphatase ^b	906 IU/l	40–125 IU/l
Gamma glutamyltransferase ^c	784 IU/l	<65 IU/l
Aspartate aminotransferase ^d	38 IU/l	<40 IU/l
Alanine aminotransferase ^e	40 IU/l	<40 IU/l

^aA chemical present in the blood, which is taken and excreted by the liver and used as a measure of liver function. ^bA group of isoenzymes that are derived from the liver, bone and the placenta; increased levels are a sensitive marker of impaired bile excretion (cholestasis). ^cAn enzyme present in the liver, pancreas and kidney; it constitutes a marker of liver and biliary diseases. ^dA transaminase present in the heart, skeletal muscle, brain, kidney and liver, and is a sensitive marker of liver injury. ^eA transaminase found primarily in liver cells that is a sensitive and specific indicator of liver injury.

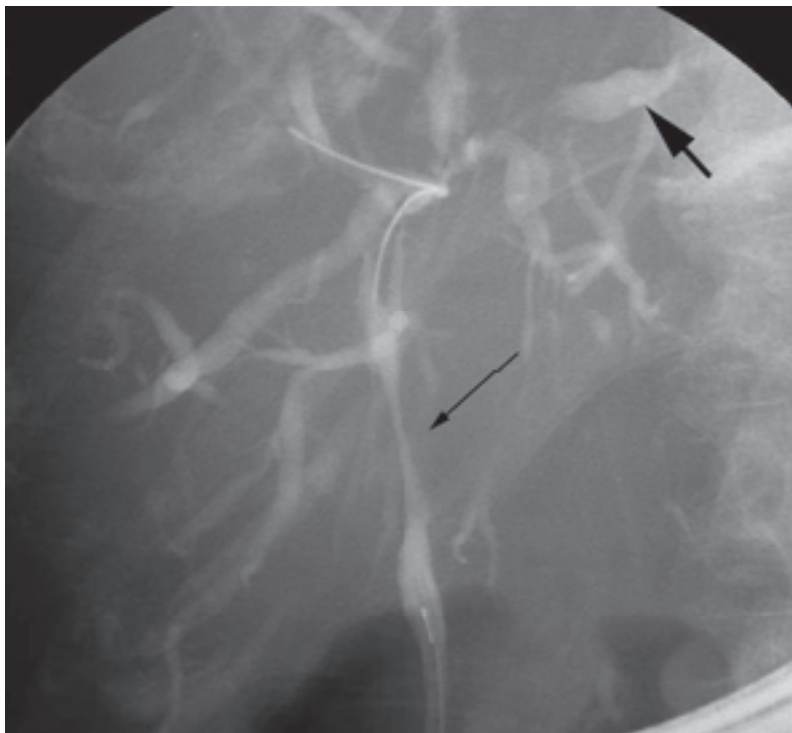


Figure 1 An endoscopic retrograde cholangiopancreatography image. Endoscopic retrograde cholangiopancreatography of the patient showed intra- and extrahepatic bile-duct strictures (thin arrow) and dilations (thick arrow). These abnormalities are associated with primary sclerosing cholangitis.

strictures (Figure 1). These abnormalities were initially interpreted as primary sclerosing cholangitis (PSC). BRUSH CYTOLOGY of the CBD revealed normal biliary cells. Because of the dominant stricture in the CBD, a biliary stent was placed.

A repeat CT scan confirmed the presence of biliary irregularities, intrahepatic biliary dilatation, thickening of the common-hepatic-duct wall and enlarged portocaval lymph nodes. It also showed hepatosplenomegaly, as well as multiple bony lesions that were both lytic and blastic (Figure 2). A bone scan was normal. Levels of the serum CA19-9 and carcinoembryonic antigen tumor markers were normal.

A subsequent sacral bone biopsy showed the presence of hypercellular bone marrow with increased trilineage hematopoiesis, with orderly maturation and several large aggregates of small cells with abundant clear cytoplasm (Figure 3). These clear cells had round to oval nuclei and some were spindle shaped. There were scattered admixed eosinophils. The above findings did not meet the diagnostic criteria for a co-existing chronic myeloproliferative disorder. Immunohistochemical stains for CD117 and tryptase confirmed that these clear cells were mast cells. Aberrant mast cells with positive staining for CD25 were also present. These histologic features met the WHO criteria for aggressive systemic mastocytosis (one major and one minor criteria) as described in a recent consensus clinical classification.¹

A subsequent percutaneous liver biopsy revealed portal-to-portal bridging fibrosis (evolving biliary-type fibrosis), with an increase in the number of peribiliary mast cells. The portal tracts were expanded by a ductular reaction, fibrosis and mild mononuclear inflammation, which are typical of biliary-tract obstruction. The peribiliary mast cells were seen on light microscopy and confirmed by staining for c-Kit and mast-cell-specific tryptase. This highlighted a greater number of mast cells than could be appreciated on hematoxylin and eosin staining (Figure 4). The 24-hour urinary histamine and serum tryptase levels were elevated at 118 ng (normal 13–62 ng) and 94 ng/ml (normal 2–10 ng/ml), respectively.

DISCUSSION OF DIAGNOSIS

The four most likely causes of cholangiopathy of the type seen in the patient are, in an ascending order, obstruction (e.g. choledocholithiasis,

benign biliary stricture), autoimmunity (e.g. PSC), neoplasms involving the bile duct (e.g. cholangiocarcinoma, metastatic carcinoma) and infiltrative processes (e.g. sarcoidosis, histiocytosis X). Other minor potential causes are ischemic and inflammatory processes (e.g. inflammatory pseudotumor). Determining the etiology of cholangiopathy is usually a challenge and may affect therapy and prognosis.

DIFFERENTIAL DIAGNOSIS

Cholelithiasis

Gallstones originating in the gallbladder may migrate into the CBD and give rise to biliary colic, bacterial cholangitis, acute pancreatitis and biliary cirrhosis. In the case presented, there was no history of biliary colic, fever or chills to suggest bacterial cholangitis and also no clinical or laboratory evidence of acute pancreatitis. The liver biopsy, however, suggested the involvement of an obstructive process. Eventually, the ERCP, which did not show the presence of any calculi in the biliary system, revealed diffuse biliary strictures, and this excluded the diagnosis of cholelithiasis.

Primary sclerosing cholangitis

PSC is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the intra- and extrahepatic bile ducts. A close association between PSC and inflammatory bowel disease has been established. Among northern Europeans, 70–80% of PSC patients have ulcerative colitis.^{2,3}

A typical PSC patient presents with either asymptomatic elevation of liver biochemistries or with symptoms of fatigue and pruritus. Jaundice and weight loss develop later in the course of the disease.

Diagnosis of PSC is based on cholangiography, which usually shows multifocal strictures with intervening saccular dilation (beads-on-a-string appearance) of both intra- and extrahepatic bile ducts. Periductal fibrosis with inflammation, bile-duct proliferation and ductopenia constitute the main histological findings.

The two major PSC-related complications are recurrent bacterial cholangitis and cholangiocarcinoma, with a prevalence of 10–15%.² Disease progression is slow and may result in biliary cirrhosis and hepatic failure.

In this case, given the cholangiographic findings on ERCP, PSC was considered as a possible diagnosis. The absence of associated inflammatory bowel disease and the presence



Figure 2 Results of an abdominal CT scan. The CT scan showed that the patient had hepatosplenomegaly, intrahepatic bile-duct dilations (thin arrow), and vertebral lytic and blastic lesions (thick arrow).

of diffuse blastic and lytic bone lesions on CT scan, combined with normal findings on bone scan, however, pointed towards a neoplastic or an infiltrative process rather than PSC.

Cholangiocarcinoma

Cholangiocarcinoma is a primary malignancy of the biliary epithelium. It may arise from intra- or extrahepatic bile ducts and tends to spread along the bile duct. Cholangiocarcinoma is more common in the presence of PSC, parasitic infestation with liver flukes, which is endemic in Southeast Asia, and congenital anomalies such as choledochal cysts. The average age at diagnosis is 60–65 years, with a male:female ratio of 3:1.⁴

The clinical features of cholangiocarcinoma depend on the tumor location. Approximately 60–70% occur at the hepatic ducts bifurcation, with the remainder in the distal CBD (20–30%) or the liver (5–15%).⁴ Most subjects with extrahepatic bile-duct or hilar tumors present with jaundice and features of biliary obstruction (dark urine and clay-colored stools). Nonspecific symptoms such as anorexia and nausea, weight loss and fatigue are also common. Cholangitis is uncommon

GLOSSARY

FOSINOPRIL

An angiotensin-converting enzyme inhibitor prescribed for cardiovascular diseases and hypertension

ICTERIC

Yellow discoloration of the skin and mucosal membranes, which is indicative of excess bilirubin

BRUSH CYTOLOGY

Tissue cell sampling for cytologic examination

CD117

(Tyrosine kinase Kit.) A cell-surface antigen involved in the signaling of tyrosine kinase, which is expressed on mast cell precursors

CD25

A cell-surface antigen, acting as an interleukin-2 receptor, which is aberrantly expressed on mast cells

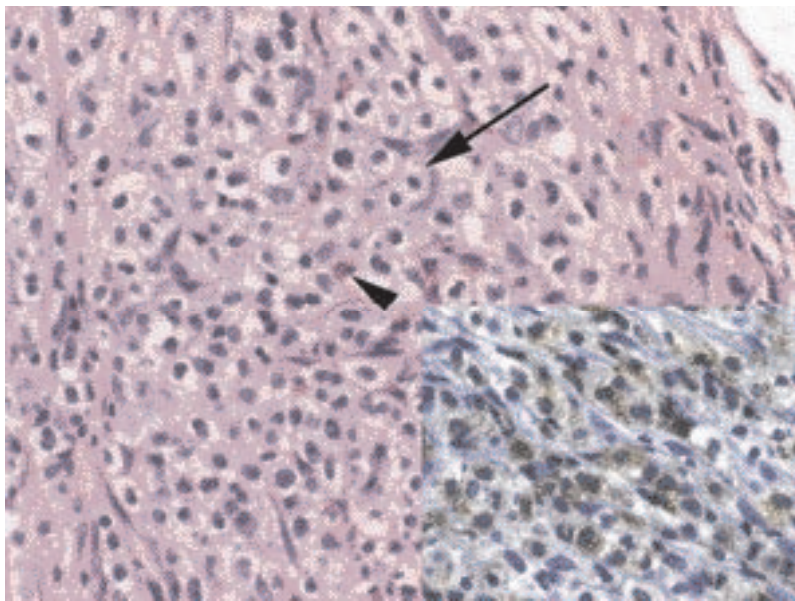


Figure 3 Hematoxylin and eosin staining of a sacral bone biopsy revealing a large mast-cell aggregate. The arrow points to a typical mast cell with abundant pale-staining cytoplasm and a central, round to oval nucleus. The arrowhead points to an eosinophil with the typical bi-lobed nucleus and red granules. Scattered reactive eosinophils are typical of mast-cell disease. Eosinophils usually accompany the mast-cell infiltrates in systemic mastocytosis. The inset shows strong histochemical staining for tryptase, levels of which are elevated in most cases of systemic mastocytosis (magnification $\times 200$).

unless the biliary tree is instrumented. Subjects with intrahepatic cholangiocarcinomas usually present with nonspecific right upper quadrant pain but jaundice is less common. Serum carcinoembryonic antigen and CA19-9 concentrations can be elevated. Diagnosis is made by using a combination of imaging studies and histology.

In this case, given the patient's age, the presenting symptoms of obstructive jaundice, fatigue, weight loss and the presence of bone lesions, a diagnosis of metastatic cholangiocarcinoma was considered likely. The patient did not, however, have any of the associated risk factors for cholangiocarcinoma, and bile-duct brush cytology and tumor marker concentrations were repeatedly normal. In addition, diffuse bone metastases are rarely seen in patients with cholangiocarcinoma.

Systemic mastocytosis

Systemic mastocytosis is a clonal neoplastic disease of the hematopoietic system. It is a rare disorder that is characterized by mast-cell infiltration of the skin, bone marrow, gastrointestinal tract, liver, spleen and lymph nodes.⁵ The

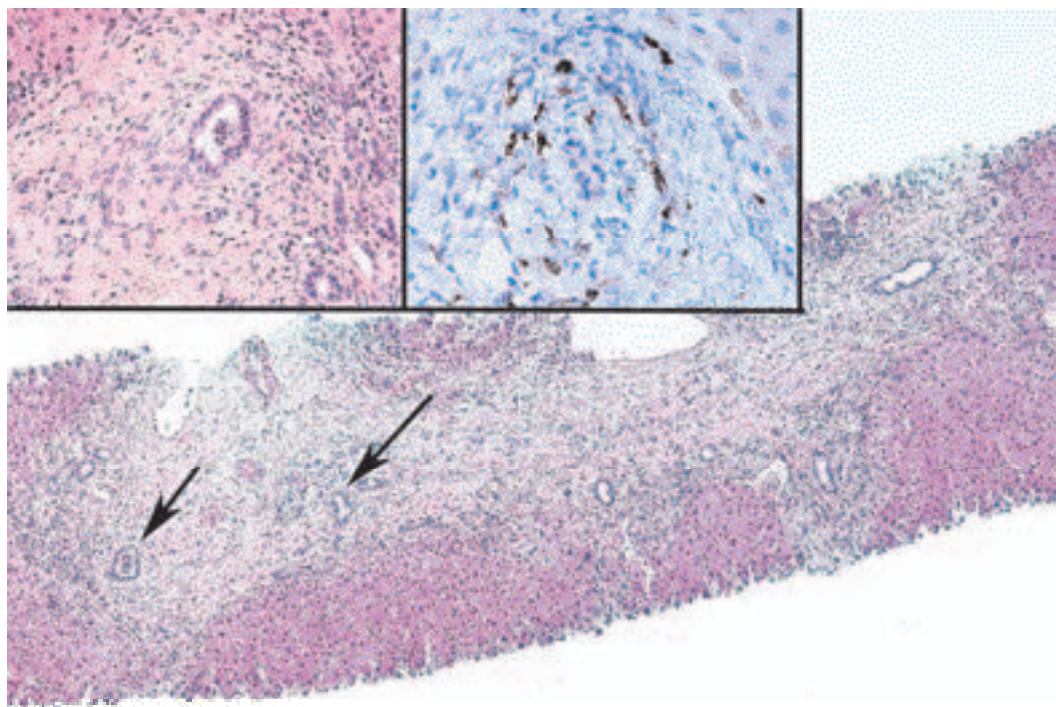
typical symptoms of systemic mastocytosis are caused by the release of mast-cell mediators and include dizziness, flushing, palpitations, wheezing, nausea, vomiting, diarrhea, headache, pruritus or cutaneous lesions (urticaria pigmentosa). Hepatomegaly is found in 40–70% and abnormal liver tests in ~50% of adults with systemic mastocytosis.^{5,6}

In the patient, the findings of mast-cell infiltration on bone and liver biopsies combined with the PSC-like cholangiogram established the diagnosis of aggressive systemic mastocytosis. Notably, however, the patient did not have typical urticaria pigmentosa skin lesions.

Urinary histamine levels are elevated in most cases of systemic mastocytosis, but there is a poor correlation between the level of urinary histamine and the severity of symptoms. The serum tryptase level is elevated in >80% of patients and is highly specific for this disorder.⁷ Bone-marrow biopsy is often diagnostic, as it was in our case (Figure 3). Immunohistochemical analysis with monoclonal antibodies against tryptase and CD117 confirms the diagnosis.

TREATMENT AND MANAGEMENT

Treatment for systemic mastocytosis targets either the symptoms (histamine 1- and 2-receptor blockers and cromolyn sodium) or the disease progression (interferon- $\alpha 2b$, imatinib mesylate [an inhibitor of c-Kit tyrosine kinase; effective in only those patients who do not have a mutation in the tyrosine kinase domain of c-Kit] and cladribine [a purine analogue]).⁸ In this case, the patient was started on histamine 1- and 2-receptor blockers, which resulted in a marked improvement in her diarrhea. Over the following several months, she reported increasing fatigue and pruritus. Repeat ERCP demonstrated an irregular but patent CBD, therefore a new biliary stent was not placed. Subsequently, the patient was started on cladribine. The rationale behind the use of cladribine was based on the evidence that mast cells share a common progenitor with monocytes, combined with the knowledge that the drug is particularly toxic to monocytes.⁹ The first cycle of cladribine therapy (0.13 mg/kg body weight once daily for 5 days) was well tolerated and her pruritus subsided. Although a decline in the levels of alkaline phosphatase (to 553 IU/l) was noted, there was no change in the total serum bilirubin level (4.5 mg/dl).

**Competing interests**

The authors declared they have no competing interests.

Figure 4 Liver biopsy and staining for peribiliary mast cells. The main figure is of a liver biopsy showing portal-to-portal bridging fibrosis with peribiliary mast-cell infiltration. The upper left inset highlights a duct, indicated in the main picture by a short arrow, showing periductal lamellar edema. The upper right inset shows the c-Kit stain of a duct, highlighted by the long arrow in the main picture. Note the numerous c-Kit-positive mast cells, which surround most of the bile ducts and comprise a significant proportion of the portal inflammation.

CONCLUSION

To our knowledge, mast-cell cholangiopathy has been described only once in the literature, and, in contrast to our case, it was a late manifestation of long-standing systemic mastocytosis.¹⁰ An unusual manifestation of 'PSC' should raise the suspicion of a different disease entity because, as illustrated by this case, mast-cell biliary infiltration with a cholangiographic PSC-like picture can be the presenting feature of systemic mastocytosis.

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