Cholestasis in Crohn's disease: A diagnostic challenge

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N HILZENRAT, E LAMOUREUX, A SHERKER, A COHEN. Cholestasis in Crohn's disease: A diagnostic challenge. *Can J Gastroenterol* 1997;11(1):35-37. A 24-year-old male with Crohn's disease who developed three independent episodes of cholestatic liver disease over an eight-year period is described. The first episode was related to an idiosyncratic drug reaction while on sulfasalazine. The second episode, at the time of an exacerbation of his colitis, was characterized by moderate portal inflammation on liver biopsy and resolved quickly while he was on corticosteroid therapy. The most recent episode, occurring when the bowel disease was quiescent, was due to granulomatous hepatitis and resolved clinically with no specific therapy. Because numerous potentially serious hepatobiliary complications have been associated with inflammatory bowel disease, prompt and aggressive investigation in these instances is recommended.

Key Words: Cholestasis, Crohn's disease, Sulfasalazine

Choléstase dans la maladie de Crohn : un défi diagnostique

RÉSUMÉ : On décrit ici le cas d'un jeune patient de 24 ans atteint de maladie de Crohn qui a présenté trois épisodes distincts de maladie hépatique cholestatique. Le premier épisode avait rapport avec une réaction médicamenteuse idiosyncrasique associée à la sulfasalazine. Le deuxième épisode, survenu au moment d'une exacerbation de sa colite, a été caractérisé par une inflammation portale modérée à la biopsie hépatique et est rentré rapidement dans l'ordre avec la corticothérapie. L'épisode le plus récent, survenu alors que la maladie intestinale était quiescente, a été attribuable à une hépatite granulomateuse et est cliniquement rentré dans l'ordre sans traitement spécifique. À cause des nombreuses complications hépatobiliaires graves potentielles associées à la maladie inflammatoire de l'intestin, il est recommandé de procéder sans délais à des examens énergiques dans de tels cas.

Crohn's disease is a chronic inflammatory condition that may involve any part of the gastrointestinal tract and is often associated with numerous extra-intestinal manifestations. Although hepatobiliary disease is a known potential complication, it is not a frequent clinical occurrence. It may nonetheless lead to significant morbidity and mortality, including fatty liver, primary sclerosing cholangitis, cholangiocarcinoma, gallstones, hepatic abscesses, granulomas and drug reactions (1).

We report a case of a 24-year-old male with Crohn's colitis who presented with fever, chills and cholestasis.

CASE PRESENTATION

The patient, a 24-year-old Caucasian male, presented with a five-day history of fever and chills.

At age 16 he developed bloody diarrhea and fever, and had physical findings of erythema nodosum and a perianal fistula. The investigation confirmed Crohn's colitis. The patient responded to medical treatment with prednisone and metronidazole.

One year later he presented with an exacerbation of his illness and was treated with sulfasalazine. One month after initiation of this treatment, he developed fever, skin rash, jaundice and eosinophilia. These were attributed to an idio-

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Figure 1) Photomicrograph of liver biopsy. Numerous granulomas are scattered throughout the liver core (periodic acid-Schiff stain, $\times 19$)

syncratic reaction secondary to sulfasalazine, which was discontinued; his symptoms then resolved.

The following year the patient again developed bloody diarrhea, fever and jaundice, along with a rise in his liver transaminases. At presentation aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 1279 and 1225 U/L (normal for both 5 to 40), respectively, with an alkaline phosphatase of 874 U/L (normal 30 to 110). Within one week, the AST regressed to 68 U/L, ALT to 353 U/L and alkaline phosphatase to 447 U/L. These normalized completely within six weeks. Liver biopsy revealed mild to moderate inflammation of the portal zones with piecemeal necrosis. There was canalicular proliferation and fibrosis of one portal space.

A percutaneous transhepatic cholangiogram was normal. Viral serology and autoantibody studies were negative. The patient was diagnosed with idiopathic chronic active hepatitis. He was treated with a four-month course of oral prednisone for his bowel disease and experienced progressive improvement in his biochemical and clinical parameters, with resolution of fever and jaundice.

At age 22 he entered a phase of frequent recurrences of bowel disease and required treatment with various aminosalicylic acid preparations: metronidazole, prednisone and, eventually, 6-mercaptopurine. Immunosuppressive therapy was eventually discontinued after two years because of satisfactory, sustained remission.

Five days before the admission reported here, the patient presented with fever, chills and 'flu-like symptoms. He denied diarrhea, hematochezia or abdominal pain. Similarly, he denied any joint pain, ocular symptoms or buccal lesions. Physical examination was unremarkable.

Hemoglobin, white blood cell count and platelets were normal. Alkaline phosphatase was elevated at 593 U/L (normal 30 to 110), gamma-glutamyl transpeptidase was 220 U/L (normal 35 to 60), alanine transaminase was 66 U/L (normal 35 to 40) and total bilirubin was 7 $\mu\text{mol/L}$ (normal 33 to 17). All other biochemical parameters were normal. Serology for cytomegalovirus and hepatitis A, B and C viruses was nega-

Figure 2) Cluster of histiocytes admixed with multinucleated giant cell and lymphocytes forms the granulomas (periodic acid-Schiff stain, $\times 166$)

tive, as was serology for antimitochondrial antibodies, antismooth muscle antibodies, antinuclear antibodies and rheumatoid factor. Results from a chest x-ray and abdominal ultrasound were within normal limits. Because of persistent cholestasis, an endoscopic retrograde cholangiopancreatography (ERCP) was performed. It revealed a normal extrahepatic and intrahepatic biliary tree. A percutaneous biopsy of the liver revealed a globally normal architecture, with absence of active inflammation (Figures 1,2). Numerous non-necrotizing granulomas were seen throughout the hepatic lobules. Special stains were negative for mycobacteria and fungi.

Six days after initial presentation, the patient's symptoms resolved entirely without any specific therapy. He has remained asymptomatic in follow-up for over one year. During this period his treatment with mesalamine was maintained at 1.5 g/day.

DISCUSSION

The diagnosis of Crohn's disease in this patient was previously established endoscopically and histologically.

He manifested three independent episodes of cholestatic liver disease related to inflammatory bowel disease. The first was likely an idiosyncratic reaction to sulfasalazine, whereas the second and third were characterized by histological evi-

dence of mild portal inflammation and hepatic granulomas, respectively. The second episode resolved quickly while the patient was on corticosteroid therapy. The third episode was self-limited. This case illustrates several of the numerous potential causes of cholestatic liver disease associated with Crohn's disease enumerated in Table 1.

The diagnostic approach employed was to first rule out sepsis or a liver abscess. Although the biochemical abnormalities noted in this case could evoke these diagnoses (1,2), the negative blood cultures and ultrasound did not support this. The next diagnostic step was an ERCP to rule out large duct biliary disease, particularly primary sclerosing cholangitis, but no disease was found. The final diagnostic step was a liver biopsy to rule out conditions such as hepatic steatosis, chronic active hepatitis and small duct primary sclerosing cholangitis (1). The biopsy demonstrated hepatic granulomas in the absence of necroinflammatory disease.

A granuloma is a focal accumulation of macrophages that undergoes transformation to predominantly secretory cells in response to ingested antigens (3,4). Such granulomas may result from infections, immunological aberrations, enzyme defects, drugs and neoplasia, yet 13% are classified as idiopathic (3-5). The most common causes of hepatic granulomas include sarcoidosis, tuberculosis and histoplasmosis (4,5). Fever is a predominant feature of granulomatous hepatitis in up to 44% of patients (6). Abnormal laboratory tests are not diagnostic but serum alkaline phosphatase tends to be elevated out of proportion with serum transaminases, and elevation of erythrocyte sedimentation rate is common (3).

Although it is accepted that granulomas may be found in the liver in Crohn's disease, the prevalence, clinical manifestations and relationship to disease activity are not well established. Dordal et al (7) studied 27 patients with Crohn's disease and described five cases of liver granulomas. A second series by Eade and colleagues (8) followed 100 patients prospectively over 18 months; 49 liver biopsies were obtained and three demonstrated hepatic granulomas. Those authors also reviewed 20 liver biopsies in patients who underwent a colectomy for Crohn's colitis and found three cases of hepatic granulomas. Six- and 12-year follow-up on two of these three patients revealed a diminishing number of hepatic granulomas postoperatively (9). Maurer et al (10)

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TABLE 1

Major hepatobiliary complications of Crohn's disease

Biliary
Primary sclerosing cholangitis
Small bile ducts
Large bile ducts
Intrahepatic
Extrahepatic
Cholangiocarcinoma
Cholelithiasis
Hepatocellular
Hepatic steatosis
Chronic active hepatitis
Drug-induced liver disease
Granulomatous hepatitis
Hepatic abscesses

described a case of granulomatous hepatitis and regional enteritis in which the granulomas regressed after resection of the inflamed intestine.

Although these studies substantiate the coexistence of Crohn's disease and liver granulomas, no systematic search was undertaken to rule out other potential causes of granulomas. The incidence and prevalence of this hepatic complication in Crohn's disease remain unclear.

In the present case, the acute cholestatic liver disease associated with hepatic granulomas was not clearly correlated with disease activity and symptomatically resolved spontaneously.

CONCLUSIONS

This case illustrates several distinct hepatic complications of Crohn's disease occurring over the course of a single patient's illness. These individual manifestations were transient without any evidence of progressive liver disease.

In view of the numerous and potentially serious hepatobiliary complications of inflammatory bowel disease, the onset of cholestasis should warrant a prompt and aggressive investigation as outlined in this case report.

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