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Association of Crohn's Disease and Hepatic Cirrhosis Post-Primary Sclerosing Cholangitis: A Case Report

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Abstract **Case Report**

Primary sclerosing cholangitis (PSC) is a distinct entity associated with inflammatory bowel disease (IBD). We report the case of a 49-year-old patient with ileocecal Crohn's disease of the stenosing phenotype, presenting with perianal lesions in the form of fistulas, who was diagnosed with PSC complicated by hepatic cirrhosis following the development of clinical and biological cholestasis, as well as his first ascitic decompensation. After initiating treatment with azathioprine for Crohn's, he experienced significant abdominal pain, ascites, and jaundice, leading to further investigations. MRI revealed bile duct stenosis, and endoscopic procedures confirmed portal hypertension. After excluding secondary causes, a diagnosis of PSC was made. Treatment with methotrexate and ursodeoxycholic acid resulted in clinical improvement. The discussion emphasizes the rare but notable association between Crohn's disease and PSC, outlining diagnostic challenges and management strategies. It highlights the poor prognosis linked to PSC, including risks of cirrhosis and colorectal cancer, with recommendations for regular monitoring and surveillance for dysplasia in patients with both conditions. Overall, the study underscores the need for careful management and ongoing research into effective treatments for this challenging dual diagnosis.

Keywords: Chronic inflammatory bowel disease - Crohn's disease - Primary sclerosing cholangitis.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease characterized by transmural inflammation that can be associated with perianal and extra-digestive manifestations. Primary sclerosing cholangitis (PSC) is an inflammatory disease of the bile ducts with an unknown precise cause but suspected to involve an autoimmune mechanism. It is a rare condition most commonly occurring in men (male-to-female ratio of 2:1), with a median age of diagnosis at 40 years. PSC is characterized by fibrous-inflammatory stenosing lesions of the bile ducts.

OBSERVATION

Mr. M.M., a 49-year-old patient, has a medical history that includes intestinal tuberculosis, treated in 2013 with anti-tuberculosis agents for six months. He underwent an appendectomy in 2014 and later an ileocecal resection, involving an 8 cm ileal segment and a 7 cm colonic segment, due to an obstructive syndrome. A colostomy was performed, which was subsequently restored after three months.

He was a chronic smoker (20 pack-years) who quit 17 years ago and had a history of chronic alcoholism, also abstinent for 17 years. He was followed for ileocecal Crohn's disease of the stenosing phenotype, classified as A3L1B2p according to the Montreal classification, with perianal fistulas classified UOF1aSO according to Cardiff classification. He was intolerant to immunosuppressors (hematological toxicity), experiencing moderate flares with liquid, sometimes mucoid diarrhea, 3-4 times a day, without blood, diurnal and nocturnal, associated with a Koenig syndrome but without rectal syndrome. He was put on immunosuppressive therapy upon discovering a Rutgeerts i4 appearance during a control colonoscopy. The patient was initially placed on Azathioprine 2.5 mg/kg/day with a good initial clinical response.

Two years later, he developed chronic right upper quadrant pain. Clinical examination revealed a conscious patient, hemodynamically and respiratory stable, with: BMI: 24 kg/m², WHO score of 2, conjunctival jaundice, and digital clubbing. Abdominal examination showed: Abdominal tenderness in the right

upper quadrant and epigastric region, presence of ascitic fluid with a palpable mass in the flanks and a concave upper limit.

Exploratory paracentesis revealed ascitic fluid with low protein content, which was managed with antibiotic therapy and albumin infusion. Hepatic function tests showed cholestasis with elevated GGT (3 times normal), ALP (2 times normal), and total bilirubin (17.8 mg/dL) predominantly conjugated. MRI showed a segmental stenosis of the bile ducts without upstream dilation or endoluminal obstruction, with peri-portal and peri-biliary infiltration.

Endoscopic examination included an esophagogastroduodenoscopy (EGD) revealing features of portal hypertensive gastropathy, grade III esophageal varices with red signs, which were band ligated without incident. Additionally, a total colonoscopy with catheterization of the last ileal loop showed a Rutgeerts I0 appearance, with biopsies indicating a slight subacute and chronic non-specific colitis. The patient was maintained on the same treatment.

The diagnosis of primary sclerosing cholangitis was established following the exclusion of secondary causes via immunological tests (anti-nuclear antibodies, IgG4), viral serologies (HIV), and the elimination of bacterial or ischemic cholangitis. The therapeutic decision involved the continuation of the existing treatment (Methotrexate) as background therapy, with the addition of ursodeoxycholic acid at a dosage of 13 mg/kg/day. The clinical outcome demonstrated significant improvement, characterized by the resolution of abdominal pain, enhanced overall condition, and regression of cholestasis.

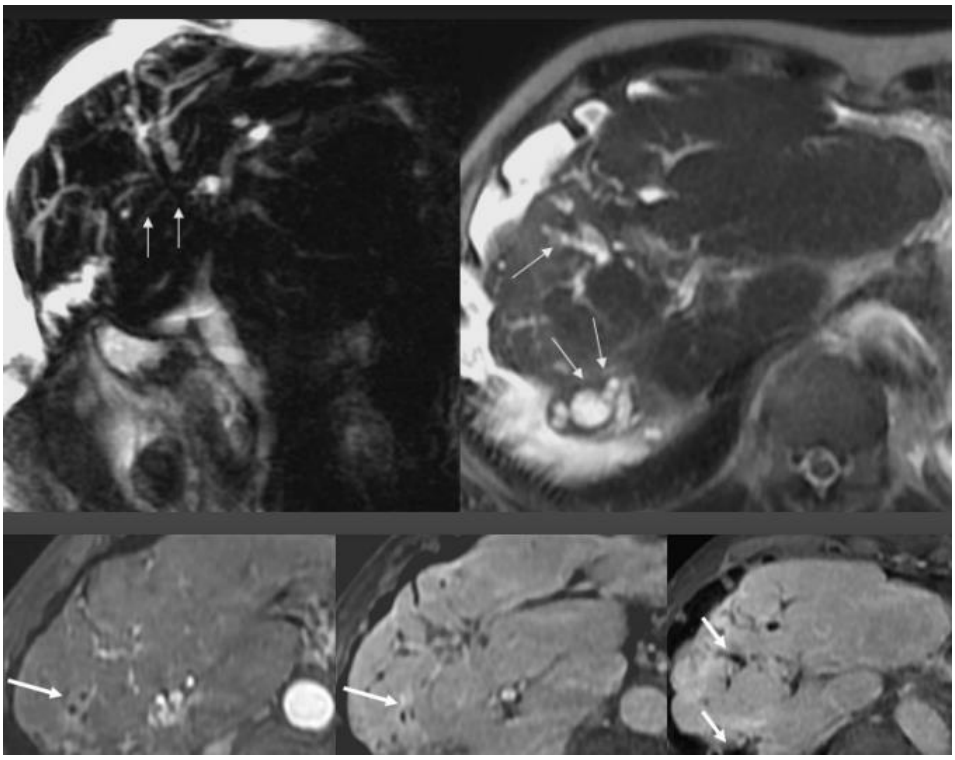

Figure 1: Liver of chronic hepatopathy, associated with segmental stenosis of the biliary tree

DISCUSSION

The association between Crohn's disease (CD) and primary sclerosing cholangitis (PSC) is a very rare entity. PSC involves an inflammatory and fibrotic condition of the intrahepatic and/or extrahepatic bile ducts that can progress to cirrhosis. It is the most specific hepatic-biliary manifestation associated with inflammatory bowel diseases (IBD). It predominantly affects young men (under 40 years old) and can present in various ways, ranging from cholangitis to subtle hepatic biochemical disturbances. It can also precede the crohn disease.

Diagnosis can be challenging and relies on at least two of the following four criteria (including at least the radiological or histological criteria): – Abnormal liver biochemical tests indicating fluctuating and moderate cholestasis; – Radiological abnormalities of the intrahepatic and/or extrahepatic bile ducts detected via MR cholangiography; – Histopathological signs compatible with chronic cholestatic hepatopathy, including pure intrahepatic forms (ranging from the classic but rare fibrous and obliterative cholangitis, which is pathognomonic, to portal peri-biliary inflammation, bile duct atrophy, or simple ductular proliferation or ductopenia); – Association with IBD. Diagnostic difficulties mainly arise in children and adults

with normal cholangiograms. Alkaline phosphatase is the most commonly elevated serum hepatic enzyme, often significantly (3 to 5 times the normal level). Aminotransferases (AST and ALT) are rarely more than 5 times the normal level. MR cholangiopancreatography (MRCP) and endoscopic cholangiography are diagnostic, showing diffuse multifocal stenoses and dilations, which give a characteristic "beaded" appearance.

Medical management of CD associated with PSC remains inadequate. Methotrexate, corticosteroids, cyclosporine, azathioprine, and 6-mercaptopurine have not demonstrated proven benefits. Ursodeoxycholic acid (UDCA) has shown improvements in hepatic biochemistry and histology but has not demonstrated an effect on disease progression. In a randomized, placebo-controlled clinical trial, patients receiving ursodeoxycholic acid had reduced serum liver enzyme levels, but they did not show higher survival rates compared to those receiving placebo. In another randomized, placebo-controlled trial, the risk of the primary endpoint (death, liver transplantation, minimal criteria for liver transplant listing, cirrhosis, esophageal or gastric varices, and cholangiocarcinoma) was 2.3 times higher in patients receiving a high dose of ursodeoxycholic acid (25 mg per kilogram of body weight) compared to those receiving placebo ($P<0.01$). Therefore, treatment recommendations for PSC are conflicting: the American Association for the Study of Liver Diseases and the American College of Gastroenterology do not support the use of ursodeoxycholic acid, while the European Association for the Study of the Liver recommends its use at moderate doses (13 to 15 mg per kilogram). Given these conflicting guidelines, it may be reasonable, to prescribe ursodeoxycholic acid (at a dose of 13 to 15 mg per kilogram) for 6 months and monitor the patient's liver enzyme levels. If no decrease in alkaline phosphatase levels is observed within this time frame, we would suggest discontinuing the treatment and continuing to monitor the patient. Infliximab therapy could be effective. Siemanowski and Regueiro reported using infliximab in two patients with CD and PSC. Their serum liver tests improved one month after the first infliximab infusion. However, its effect was not proven by histopathology, and further evidence is needed to support its routine use. Additionally, several new treatments are being evaluated in ongoing clinical trials. For instance, obeticholic acid is a semi-synthetic analogue of chenodeoxycholic acid and a potent ligand for the farnesoid X receptor, with antifibrotic effects. Another trial involves the use of simtuzumab, a monoclonal antibody against lysyl oxidase-like 2 (Loxl2), an enzyme that acts as a profibrotic protein in PSC. Furthermore, 24-nor-ursodeoxycholic acid, a synthetic bile acid known to produce bicarbonate-rich cholereses dependent on bile acids, may have beneficial effects in patients with hepatic fibrosis and is currently under investigation.

The disease can progress to cirrhosis and eventually liver failure. Liver transplantation may be considered at that point. For patients with end-stage PSC, liver transplantation remains the only effective treatment. One report described a patient with CD and PSC who had an active terminal ileal ulcer that improved after liver transplantation. However, other reports show increased rates of colorectal cancer following liver transplantation. It remains to be determined whether this is due to prolonged use of immunosuppressants or confounding variables such as the long duration of the disease. The prognosis of CD associated with PSC is poor. The median survival rate, after diagnosis and without liver transplantation, is about 12 years, with a lower survival rate for those who were symptomatic at presentation. Two major risks are associated with the progression and prognosis of PSC: the development of secondary biliary cirrhosis and degeneration into cholangiocarcinoma, and the occurrence of colorectal cancer, which represents the main cause of mortality. Recent studies have found an increased prevalence of colonic dysplasia and cancer in patients with PSC and IBD compared to those with IBD alone. Immunosuppressive therapy may have contributed to this risk.

In combined studies, the development of dysplasia or colorectal cancer is observed in about 24% of patients with PSC and IBD. In contrast, in IBD control groups, dysplasia or colorectal cancer is observed in 9% of patients, with a cumulative risk estimated at 10 years of 2%. Additionally, a recent large French prospective study on neoplasia in IBD found an even lower rate of patients developing colonic neoplasia. In this study, 0.3% of 19,486 patients developed high-grade dysplasia or colorectal cancer. Some practical recommendations suggest that patients with PSC and CD should undergo periodic CA 19-9 tests, abdominal ultrasound examinations, and annual surveillance colonoscopies with multiple random biopsies for dysplasia detection.

CONCLUSION

The diagnosis of PSC should be considered in patients with CD presenting with abnormal serum liver tests of unknown etiology, after excluding common causes of liver damage such as viral and drug-induced hepatitis. Systematic screening with serum liver tests should be performed in all patients with CD, as PSC often presents asymptomatically. Given the unfavorable long-term prognosis, vigilance is crucial. Once diagnosed, periodic colonoscopic surveillance and CA 19-9 measurements should be conducted, and potential inclusion in a transplantation program should be considered.

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