Japanese Journal of Gastroenterology and Hepatology

Case Report ISSN: 2435-1210 | Volume 8

Rare Association of Crohn's Disease with Small Bile-Duct Primary Sclerosing Cholangitis : A Case Report

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Received: 28 Feb 2022
Accepted: 09 Mar 2022
Published: 14 Mar 2022
J Short Name: JJGH

Keywords:

Crohn's disease; Primary sclerosing cholangitis

Citation:

Semlali R, Rare Association of Crohn's Disease with Small Bile-Duct Primary Sclerosing Cholangitis : A Case Report. J Gstro Hepato.. V8(11): 1-3

1. Abstract

Primary sclerosing cholangitis (PSC) is a chronic and progressive cholestatic liver disorder of unknown etiology characterized by inflammation, fibrosis, and stricturing of intrahepatic and/or extrahepatic biliary ducts. Established subtypes of PSC are:

- Classic*:* Affects small and large bile ducts
- Small-duct*:* Affects only small bile ducts
- Associated with autoimmune hepatitis: Affects small and large bile ducts

Inflammatory bowel disease (IBD) and primary sclerosing cholangitis (PSC) are closely associated disease entities that, when present in combination, create a phenotypically different summative disease referred to as PSC-IBD. It is estimated that about 70% of patients with PSC have underlying IBD, most frequently ulcerative colitis (UC).

We present the case of a patient with a doubly rare association of small duct primary sclerosing cholangitis and Crohn's disease.

2. Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by fibrosing inflammatory destruction of the intrahepatic and/or extrahepatic bile ducts [1], leading to bile stasis, hepatic fibrosis, and ultimately to cirrhosis, end-stage liver disease, and need for liver transplantation. The majority of cases occur in young and middle-aged men, often in association with inflammatory bowel disease [2], most frequently ulcerative colitis (UC). Association with Crohn's disease is rare. Following the advent of endoscopic retrograde cholangiopancreatography (ERCP), it was quickly established that 'classical' primary sclerosing cholangitis (PSC) with multiple structuring of the intra- and extra-hepatic biliary tree was much more common than previously realised [3]. However, it became clear afterwards that there was a minority of patients in whom cholangiography was normal. Wee and Ludwig first described this entity in 1985 and coined the term 'small duct PSC' [4].

Crohn's disease (CD) is a chronic relapsing inflammatory bowel disease (IBD). It is characterized by a transmural granulomatous inflammation which can affect any part of the gastrointestinal tract, most commonly the ileum, colon or both [5]. We report the case of a patient with Crohn's disease associated to small-duct PSC.

3. Case Report

Patient G.A aged 24, presented to our hospital complaining of 1-year history of chronic relapsing diarrhea at a rate of 3-4 per day, with diffuse abdominal pain. Physical examination revealed diffuse abdominal tenderness. No other abnormalities were found. On admission, laboratory tests revealed elevated C-reactive protein levels (37 mg/l) with a normal complete blood count. Liver tests revealed no abnormalities. Anti-Saccharomyces cerevisiae antibodies (ASCAs) were found positive. A colonoscopy was performed, revealing ulcerative and pseudo-nodular mucosal lesions in the ileocecal area. The rest of the colon appeared normal. Biopsies were made and showed non-specific inflammation. Abdominal CT-scan revealed a discrete swelling of the last ileal loop and hyperemia of the mesenteric fat tissue. Based on the aforementioned findings, the diagnosis of Crohn's disease was made and the patient put under immunosuppressive therapy with Azathioprine at a dose of 2mg/kg/ with a marked clinical biological and endoscopic improvement on the 3

and 6 months' marks. However, follow up blood tests at the 6-month mark revealed cytolysis: ALT at 233 (6N) and AST at 92 (2.3N); and cholestasis: GGT at 594 (8N) and ALP at 190 (1.6N). Total bilirubin was slightly elevated at 12.1 mg/l and PT was normal at 92%. After ruling out the main causes of abnormal liver tests (mainly viral hepatitis, drug-induced hepatitis…) and negative auto-antibodies, a cholangiography was performed revealing irregularities of the left intra-hepatic bile ducts, with an alternation of dilation and strictures with no discernible anomaly of the extra-hepatic bile ducts. Liver biopsy was performed and showed periductal concentric fibrosis highly suggestive of PSC. The diagnosis of small-duct PSC was thus made, and ursodesoxycholid acid (UDCA) was started at the dose of 25mg/kg. No adverse events following the introduction of the drug were noted. Follow-up at the 1 year-mark showed a continued positive response to immunosuppressive treatment (The patient was in clinical remission, C- reactive protein was normal at 5mg/l, colonoscopy found no visible lesions) and to UDCA (Normalization of liver tests : ALT at 18, AST at 27, ALP at 81 and GGT at 23. Total bilirubin was slightly elevated at 15.5 mg/l).

4. Discussion

A diagnosis of PSC is made in patients with a cholestatic biochemical profile, when cholangiography (e.g., magnetic resonance cholangiography [MRC], endoscopic retrograde cholangiography [ERC], percutaneous transhepatic cholangiography) shows characteristic bile duct changes with multifocal strictures and segmental dilatations, and secondary causes of sclerosing cholangitis have been excluded [6]. Patient who present with clinical, biochemical and histological features compatible with PSC, but have a normal cholangiogram, are classified as small duct PSC [7] (Figure 1).

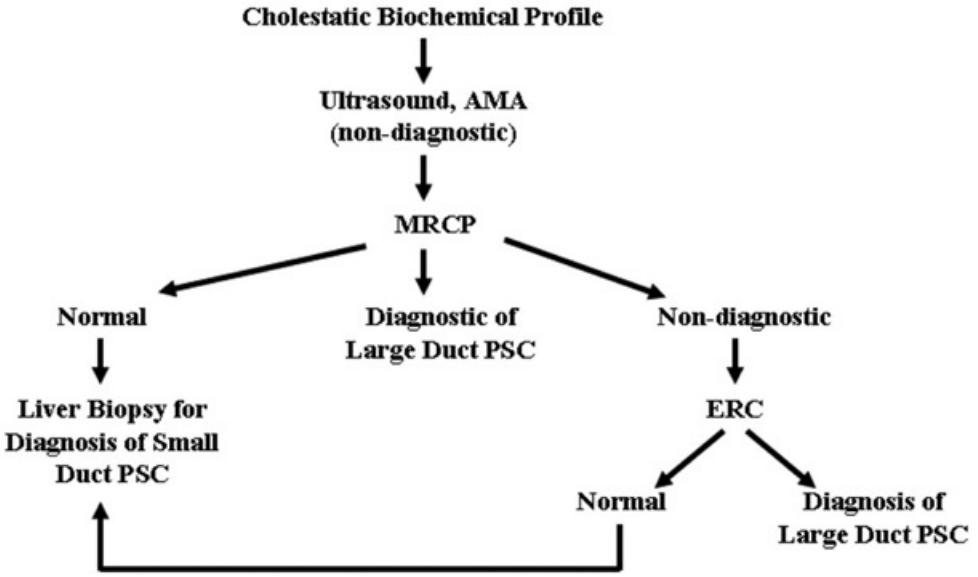

Figure 1: Algorithm for the diagnosis of PSC

Only a few cases of small duct PSC have been reported in the literature. Therefore, information is somewhat lacking on the clinical course and prognosis of patients with this particular disease form [8]. Patients with small duct PSC appear to have a favourable long term prognosis in terms of death or liver transplantation compared to those with large duct PSC. Small duct PSC does not seem to be an early stage of PSC in the majority of cases. Furthermore, patients with small duct PSC rarely progressed to large duct PSC [8]. Comorbid primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) represent a unique disease phenotype with a different risk profile than PSC or IBD alone. The proportion of patients with PSC complicated with IBD is markedly lower in Japan and Singapore than in North America and Europe, with estimates reported as 20-32% [9, 10] and 60-80% [11] of PSC cases, respectively.

Pathogenic mechanisms behind both diseases remain unclear. Patients with PSC-associated IBD typically exhibit pancolitis with a right-to-left intestinal inflammatory gradient associated with a greater incidence of backwash ileitis and rectal sparing. Paradoxically, though there is an increased incidence of pancolitis in this population, bowel symptoms appear to be less significant than in IBD alone. Likewise, the degree of inflammation and symptoms of PSC-associated IBD are usually less clinically significant. Despite the relatively quiescent clinical presentation of PSC-associated IBD, there is an increased risk for colorectal and hepatobiliary malignancy making vigilance for malignancy essential [12].

The treatment of primary sclerosing cholangitis remains challenging. There is no established treatment of PSC yet. Ursodeoxycholic acid (UDCA) has been widely studied as a therapy for PSC patients. Although UDCA is the most commonly used drug for PSC, several meta-analyses of clinical trials indicated that despite the fact that UDCA improves liver biochemicals, it has no effect on progression of disease, health-related quality of life, survival of PSC patients, and finally the requirement for liver transplantation [13]. High doses of PSC (28–30 mg/kg/day) results in an improved liver test, but it does not improve survival [14]. Furthermore, studies show that high doses (28-30 mg/kg/day) of UDCA in long-term are associated with

an increased risk of colorectal neoplasia in PSC patients [15]. On the other hand, a meta-analysis found that use of UDCA at a low dose (8–15 mg/kg/d) significantly decreased the risk of colorectal neoplasia (CRN) in patients with PSC-IBD [16].

Given that the risk of CRN has been widely described in the PSC-IBD population, different gastroenterology societies have commented on recommendations for surveillance in this group. Current recommendations support the use of annual colonoscopy and biopsies in PSC-IBD patients from the time of PSC diagnosis, without taking into account the duration of IBD since it is often not known [17].

5. Conclusion

Small duct PSC is a diagnosis of exclusion, considered in patients with chronic cholestasis and a negative cholangiography. It is associated with a better prognosis than the classical form of PSC.

PSC is often associated with IBD, particularly ulcerative colitis. Association with Crohn's disease is significantly less frequent. UDCA is the standard treatment for PSC. Patients with PSC-IBD have a significantly greater risk of developing colorectal neoplasia, hence the need of regular screening.

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