ANNALS OF GASTROENTEROLOGY 2006, 19(2):146-151

Lecture

Inflammatory Bowel Disease (IBD) and the Liver

A. B. Adamopoulos

SUMMARY

Hepatobiliary Diseases (HBDs) accompanies in a 5-10% of patients with Inflammatory Bowel Diseases (IBD). They are either extra-intestinal manifestations or drug side effects.

The main extra-intestinal manifestation is Primary Sclerosing Cholangitis (PSC), which as an entity, includes the former "pericholangitis", now called small duct Primary Sclerosing Cholangitis. It mainly affects young males with ulcerative colitis. It is a chronic cholestatic disease with a broad spectrum of clinical manifestations. The asymptomatic disease has a better prognosis than the symptomatic one. It eventually leads to cirrhosis and is the 4th cause of orthotopic liver transplantation. Cholangiocarcinoma is the most ominous complication and its presence is also accompanied by increased frequency of colon dysplasia or cancer. A less frequent complication is the ascending cholangitis with or without (pigmented) biliary stones.

Auto-immune Hepatitis (type-1) is another extra-intestinal manifestation of IBD, but its frequency seems to be very low under the new diagnostic criteria, compared to the frequency reported in previous publications. An overlap syndrome may also occur.

Fatty liver is the commonest occurring liver disease, specially in patients with ulcerative colitis and is usually indolent.

Uncommon manifestations include granulomas and granulomatous hepatitis, amyloidosis and hepatic abscesses.

Biliary stones are often related to Crohn's Disease, probably due to altered bile component balance.

Drugs used for the treatment of IBD may cause liver damage, either acute or chronic. Azathioprine and cyclosporine are newly recognized as such dings. Alertness, proper use and serial tests for monitoring the liver function and morphology can minimize their side effects. More sophisticated tests are not yet routine clinical practice.

Gastroenterology Unit, Third Department of Internal Medicine, University of Athens, Sotiria General Hospital, Athens

Author for correspondence:

Adam Adamopoulos, P.O. Box 607, 19009 Pikermi, Greece, Tel.: +210-6044251, e-mail: adamadam@hol.gr

I) INTRODUCTION AND CRITICAL OVERVIEW

Liver Diseases (LDs), or more precisely HepatoBiliary diseases (HBDs), have been estimated to accompany IBD in 5-10% of cases[1] (Table 1).

The underlying pathogenetic mechanism may be common, although not clarified yet for the majority of the extra-inestinal manifestations of IBD, including HBDs.

Iatrogenic complications, during therapeutic intervention for IBD, may lead to LDs or HBDs. Finally, the altered gut physiology, mainly through the altered bile salt composition, may lead to HBD. Sometimes a vicious circle occurs as the former may worsen the latter, ultimately changing the patients' stage of disease and/or his or her performance status.

The above mentioned disease paths may coexist in the same patient. It is of importance to detect or recognize them early, in order to make the appropriate treatment decisions. It should be noted that Primary Sclerosing Cholangitits (PSC) is the 4th cause of Orthotopic Liver Transplantation (OLT).

Sometimes, doctors confront several difficulties in IBD patients with HBDs, which can confuse them. The difficulties and confusion are mainly due to two reasons. One is the difference in terminology between old and new studies, due to the different technology, with which these patients were investigated. The second is

that there are only a few prospective studies, using the new terminology or scoring criteria (for autoimmune hepatitis).

II) THE IBD ASSOCIATED DISEASES

1. Primary Sclerosing Cholangitis (PSC)

A. Epidemiology and Overview

PSC, a chronic cholestatic disease is strongly associated with IBD, mainly with Ulcerative Colitis (UC). Fortunately PSC is present only in 2-7% of patients with UC and in 0.7-3.4% [2] of patients with Crohn's Disease (CD). Conversely, it has been estimated that the prevalence of IBD is 50-80% in patients with PSC, with a wide geographic variation.[3] Eighty seven to ninety eight percent of them have IBD colitis, whilst small bowel disease is extremely rare. It is more frequent in young males (60-70%), two thirds of which are 45 years old or younger, at the time of diagnosis. Females tend to be 10 years older.[4]

As the cholangiocarcinoma is 7-14% in PSC, the latter should be regarded as a pre-malignant disease. Additionally, patients with PSC carry a higher risk for presence of colonic dysplasia or cancer compared to those with UC alone or to the general population.[5,6] The natural history of these cancers does not change either by colectomy for cholangiocarcinoma prevention or OLT for colon cancer prevention.[7]

B. Clinical features- Diagnostic criteria

Fifteen to seventy percent of patients are asymptomatic. IBD, in the majority of the population, is present before the development of PSC. Abnormal liver tests, mainly alkaline phosphatase, should alert for further investigation and differential diagnosis. One should keep in mind, that PSC is much rarer in distal than in pancolitis (0.05% versus 5%)[8] and no correlation exists between severity of UC or PSC. Some patients with PSC have actual IBD, which becomes overt 1-7 years after the PSC diagnosis. Colonoscopy and colon biopsies are mandatory in this instance.

If clinical features are present, there are: malaise, diminished appetite (70%), pruritus (70%), jaundice (30-69%), weight loss(10-34%),ascending cholangitis(5-28%) and features of cirrhosis (2-62%).Symptoms may have been present two years previously (fatigue, malaise, diminished appetite), but as these are common, patients do not ask for additional medical attention. This fact has also confused many studies as they could characterize "asymptomatic" patients who actually were not.

Alkaline phosphatase may be normal in 8.5-10% of patients, even in advanced histologic stages. Bilirubin may be normal initially but raises thereafter.[8,9] Aminotransferases may be normal or slightly elevated. Hypergammaglobulinaemia may be present in 30%of patients due to either IgG (44%) or IgM (20-45%) elevated levels. Autoantibodies (ANA, ASMA) may be present in 22-55% of patients. p-ANCAs can be detected but are present in UC alone or Auto-Immune Hepatitis type 1 (AIH-1), which is another rare extra-intestinal manifestation of IBD. It seems that the p-ANCAs are different in PSC than those in AIH-1. The former antibodies have been proposed to be termed as p-ANNAs (peripheral antineutrophil antinuclear antibodies). In general, all these auto-antibodies are not considered as either specific or sensitive markers for PSC, they do not seem to play any role in its pathogenesis and, finally, do not correlate with the disease's severity.[10]

Cholangiography [by ERC(P) and recently by MRCP[11]] is a sine qua non examination for PSC diagnosis. Inclusion and exclusion criteria are shown in **Table 2**.

C. Cholangiography-Histopathology[12,13]

The common denominator of PSC is the fibrosing inflammation of the bile ducts, resulting in stenosis, reduction of the luminal diameter and thickening of their walls without dilatation. The appearance in diagnostic ERCP can be considered pathognomonic, with areas of irregular structuring and dilatation (beading) of the intra and extra- hepatic tree. The strictures are short (0.5-2cm) and angular with intervening segments of normal ducts. The lesions may occur either in intra-, or extra-, or both, bile ducts or even in one hepatic duct. In addition, ductopenia occurs but is prominent in liver biopsies.

D. Natural History

PSC develops over time and a mean time from diagnosis to OLT, is approximately 12 years (up to twenty). Four stages of the disease have been described:[14] first, the asymptomatic stage without laboratory abnormalities, second, the asymptomatic stage with laboratory abnormalities, third, the symptomatic stage (in which 50% have cirrhosis) and the fourth stage where decompensated cirrhosis or cholangiocarcinoma are present. This schematic classification does not exclude the possibility of a patient with a second stage disease to have cirrhosis or cholangiocarcinoma (proven in a small study the same applies for the first stage, but is extremely difficult and expensive to detect). It obvious after all, that a prognostic score is needed. Actually four prognostic scores have been suggested, but the domi-

nant seems to be the Mayo Clinic Revised Prognostic Score.[15]

E. The PSC of the Small Ducts (Formerly: Pericholangitis)[13]

The term is applied to those patients with no evidence of PSC in cholangiography, but with laboratory profiles similar to PSC. Autoantibodies are more commonly detected than in the classic PSC. Histologic features in liver biopsy, including ductopenia, are characteristic of this entity. It sometimes co-exists with AIH-1 and the disease is termed "overlap syndrome".

F. Pathogenesis[10, 16, 17]

Despite the fact, that pathogenesis is still unclear, good evidence, from recent laboratory studies, leads to a more comprehensive understanding of the process. Enteric flora seems to play a crucial role in activating the immune system. Sharing colonic antigens, associated with genetic susceptibility (HLA-B8, DR-3 phenotype in UC), could finally attack both colon and biliary tract. Indeed, in a group of patients with UC and PSC, anticolonic mucosal auto-antibodies that cross react with bleary epithelium have been identified. Recently, a colonic epithelial protein (CEP) and the human tropomyosin isoform 5 (hTM5), which are expressed both in colon and the biliary tree (as well as in other sites of the body, in which extra-intestinal manifestations of IBD can occur) have been considered to be the major common targets of auto-immune attack in IgG1 specific molecules in UC. So, in an immune induction site, most probably the colon, T cells are primed. Immune cells infiltrate the effector sites (biliary tree) and proliferate with the help of adhesion molecules (A4b7 integrin, vascular adhesion protein 1). Cytokine over-expression along with overexpression of adhesion molecules (MadCAM, CCL25) and lymphocyte recruitment lead eventually to damage. As patients with colectomy may express PSC later on, memory lymphocytes primed in the bowel may play a central role for the induction of the above mentioned cascade of events, when a noxious and proper hepatic stimulus is able to activate them.

G. Complications

The complications of PSC are shown in **Table 3.** *Cholangiocarcinoma's* prevalence is seven to fourteen percent.[18] Its detection is extremely difficult as the laboratory tests are not sensitive. Liver tests are not helpful at all.[19] Colonic dysplasia or cancer may co-exist with cholangiocarcinoma.[20] The most sensitive test to date ERCP (sensitivity´60%) and some points are added by the cytological examination of aspirated bile and brushings from the biliary tree during the ERCP.[21,22] Suggestive features are: a short dominant stricture, excessive bile duct dilatation and progression of dilatation or structuring on serial cholangiographies. Positron Emission Tomography (PET) scan with fluoro-2-deoxy-D-glucose is promising, in one series.[23] The prognosis is dismal and palliation is often recommended. For many transplant centers cholangiocarcinoma is considered as an absolute contraindication for OLT as it relapses very soon in the transplanted liver.

2. Auto-immune hepatitis (AIH)

It is associated mainly with UC. Its frequency seems to be low,[24] as old series are contaminated by PSC with auto-antibodies. Only type I (AIH-1) has been described in association with UC. Its activity and progression do not correlate with the extent or severity of the IBD. ERCP (or MRCP) is mandatory, in order to exclude PSC. Other auto-immune diseases, such as thyroiditis, glomerulonephritis or polyarthritis may coexist. AIH-1may precede or accompany IBD. PSC of the small bile ducts may be confused, but liver biopsy and the newly revised autoimmune hepatitis score can differentiate them, unless an overlap syndrome exists.[25]

3. Fibrosis and Cirrhosis[13]

Their frequency varies in different series but 1-5% seems closer to reality. They commonly occur in patients with extensive UC or CD colitis. Clinical features of fibrosis alone are actually absent. Cirrhosis may be the end stage of PSC (either the classic or the small duct disease), or AIH-1 or of the overlap syndrome. The presence of IBD does not influence the course of cirrhosis. Although both macronodular in the majority of patients, cirrhosis of PSC has different histopathologic findings from these of AIH-1. The former has a portal-portal Z destruction and fibrosis pattern (bridging portal hepatofibrosis) while the latter has a portal-central destruction pattern with flourishing inflammation and bridging necrosis.[26, 27]

4. Fatty liver

It occurs in both UC and CD patients and is of the macrovesicular fat type. Reported frequencies show wide distribution (mean´35%), but, actually, steatosis is the commonest HBD. It seems to be a multifactorial process caused by protein-calorie malnutrition, malnutrition per se, corticosteroid treatment[28] and some speculate a role for its induction, of a bacterial metabolite or toxin[13]. Non-alcoholic steatohepatitis may occur. Therapy is directed towards IBD. In the past colectomies have been

reported, but as the frequency was the same before and after colectomy 3 to 7 years after,[29] this method has been abandoned.

5. Amyloidosis[28]

It is rare and has been described more often in patients with CD (0.9% versus 0.07% in UC patients). It is reactive (secondary) AA amyloidosis. There seems to be no relationship to suppurative complications, duration or extent of IBD. The amyloid can affect any organ, so if liver is involved, hepatomegaly is the result. Optimal therapy aims to control the underlying IBD, thereby decreasing the release of the acute phase reactant serum amyloid A. In a few cases, with systemic amyloidosis, colchicine has been tried with good results but in the presence of CD, colchicine may be hazardous.

6. Granulomas and Granulomatous Hepatitis

Hepatic granulomas have been associated more often with CD.[30,31] Their mean frequency is about eight percent. They do not cause symptoms, but can be found in liver biopsy performed for elevated alkaline phosphtase levels. Their presence does not predispose to granulomatous hepatitis.[13,28] Of course, other causes may be responsible for their presence in the liver of a patient with IBD. Microgranulomas may be found in liver biopsy done for several reasons. Factors other than IBD are mainly responsible i.e drugs or fatty liver.[32] Granulomatous hepatitis is an uncommon, but well recognized complication of CD.[28] It usually has a benign course. The laboratory tests mainly show elevations of cholestatic enzymes. If necessary, corticosteroids or immunosuppressive drugs can be tried.

7. Hepatic abscesses [33]

They occur in patients with CD but also, rarely, they precede CD, being the feature for its diagnosis. The clinical presentation does not differ from hepatic abscesses of any other cause. Although their pathogenesis is unclear, portal pyemia or direct extension of intra-abdominal abscesses have been suggested. Percutaneous drainage under radiologic guidance and therapy for CD are effective measures.

III) LIVER DISEASE (LD) CAUSED BY DRUGS

It seems, fortunately, that the overall incidence of adverse drug effects, affecting the liver is low:

a) ***The aminosalisylates (mesalazines)***: It extremely rare to cause liver damage. They are is of the hypersensitivity type and can cause both hepatocellular and cholestatic disease.

b) ***The thiopurines***[34]

b1) Azathioprine: can cause liver injury through hypersensitivity, idiopathic reaction and endothelial toxicity. The clinical spectrum is wide. Asymptomatic aminotransferase elevations of 5%, overt cholestasis, veno-occlussive disease and peliosis hepatis have been described. Endothelial toxicity is the culprit for the last two. Intravenous thiopurines may cause CMV hepatitis.[13]

b2) Mercaptorurine: as it an azathioprine metabolite, has the same profile. Measurement of TPMT (ThioPurineMethylTransferase) activity prior to its use, my be partly useful, but is not a routine test.[35]

c) ***Cyclosporine***: may cause hepatotoxicity of mixed type. It has been described in patients with either abnormal pre-existing liver tests or in those in intravenous feeding.[36]

d) ***Methotrexate*** : it has been implicated for mild histologic abnormalities up to hepatic fibrosis and cirrhosis. Routine liver biopsy whenever the cumulative dose reaches 1.5-2.0g has been challenged as those managed with methotrexate, according to the guidelines of the American College of Rheumatology, show a very low incidence of LD. Alcohol consumption must be strictly avoided.

IV) HBDS CAUSED BY ALTERED GUT PHYSIOLOGY, RELATING TO BILE SALTS

Cholelithiasis

It ranges between 13-34%.[38] 20% of PSC patients have cholelithiasis.[39] The malabsorption of the bile acids, interfering with their enterohepatic circulation, leads to depletion of bile salts and the formation of lithogenic bile. In the absence of PSC, no additional risk factors have been recognized, except that of ileoanastomosis. **Ascending cholangitis** is a well established complication of PSC, and in 80% of bile aspirates, bacteria are found,[40] whilst the stones in this condition are of pigmented type.

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