Case Report

An unusual case of acute icteric small bile duct disease

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SUMMARY

The present case refers to an acute icteric cholestatic syndrome of unknown aetiology in a 37-year old man. The underlying biliary disease was of mixed type combining features of diffuse pleomorphic cholangitis and focal sclerosing cholangitis affecting interlobular bile ducts. Our case met the inclusion and exclusion criteria of idiopathic adulthood ductopenia (IAD) regarding sex, age, clinical history and laboratory findings (negative drug history, absence of autoantibodies, no evidence of inflammatory bowel disease, no involvement of large bile ducts, no bacterial or viral infection). The diversity of the histological findings was attributed to different progression stages of the disease. Complete clinical and laboratory improvement after corticosteroid therapy suggests a beneficial effect and points towards an immune-mediated process.

Keywords: Small- duct sclerosing cholangitis; Idiopathic adulthood ductopenia; Steroids.

CASE REPORT

A 37-year-old man was admitted to our department due to gradually progressive jaundice and pruritus during the last five days. His medical and family history was non significant and he had not received any medications or herbals. He has been consuming ~ 320g of alcohol twice weekly for the last eight years and he had been an occasional cannabis user and cocaine inhaler for a five month period, until two months before the icteric episode.

At presentation, there was no evidence of splenomegaly or ascites. Laboratory findings showed normal white and red blood cell counts. Liver biochemistry revealed a predominant cholestatic profile (t.bil 9.87mg/dL, d.bil. 7.03 mg/dL, ALP 315 IU/L, γGT 1082 IU/L) and elevated aminotransferase levels (AST 122 IU/L, ALT 245 IU/L). Prothrombin time and serum albumin were within normal limits. Acute phase proteins were elevated. Serological markers of hepatitis A, B, C, anti-HIV1,2 and IgM for CMV were undetectable. Autoantibodies including ANA, anti-ds-DNA, AMA, ASMA, p- ANCA, c-ANCA were negative. IgG, IgA, IgM values and protein electrophoresis were normal.

Ultrasound and MRCP examination demonstrated mild hepatomegaly, no bile duct dilatation or stenosis and no parenchymal abnormalities. ERCP was not done. Esophago-gastroduodenoscopy showed ulcers of gastric body and duodenal bulb. Nevertheless, biopsies of the gastric and duodenal lesions did not support inflammatory bowel disease (IBD). Helicobacter pylori were absent as well. Colonoscopy did not disclose any macroscopic or histological lesions.

A percutaneous liver biopsy specimen (2 cm in length including 15 portal tracts) revealed bile duct injury as the dominant histological finding. The majority of interlobular bile ducts showed changes of pleomorphic cholangitis characterized by neutrophilic and eosinophilic infiltration of the epithelium. The latter exhibited degenerative changes with nuclear polymorphism, cell crowding and flattening, while few ducts showed signs of epithelial destruction. In three bile ducts the lesions acquired features of sclerosing cholangitis combining pericholangitis and concentric periductal fibrosis, while the epithelium appeared focally severely damaged. Bile duct loss was not observed. Por-

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tal infiltrates were of mild to moderate density displaying predominance of neutrophils or lymphocytes, a variable number of eosinophils, and only few plasma cells. The rarity of plasma cells and the absence of IgG4 expression were ascertained immunohistochemically by using the marker CD138 (DakoCytomation, Denmark) and anti-IgG4 (Zymed, Carlsbad, CA, USA), respectively. Portal fibrosis and edema were also present. Mild steatohepatitis and mild cholestasis were observed in the parenchyma (figures 1-4).

The patient's jaundice did not deteriorate further after five days hospitalization and the biochemical liver function tests remained at the same levels. His pruritus was severe and treatment with cholestyramine and hydroxyzine was ineffective. He was initiated corticosteroid therapy with 32 mg methyl-prednisone and ursodeoxycholic acid (UDCA) 15 mg/Kg daily. One week after the beginning of treatment clinical and laboratory improvement was observed. Jaundice was improved and he did not suffer from pruritus any more. Laboratory tests were as follows; t.bil 3.42mg/dL, d.bil 2.34, AST 50 IU/L, ALT 101 IU/L, γGT 543 IU/L, ALP 261 IU/L. Tapering of steroids started two weeks later. The patient remains asymptomatic, without any rise of aminotransferases or markers of cholestasis, 6 months after completion of therapy.

DISCUSSION

Interlobular bile ducts often referred to as small bile ducts are frequently the target of inflammatory and toxic attacks in immunological, infectious and drug-induced disorders.[1] Immune mediated biliary diseases include primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). They are both associated with progressive bile duct involvement and show a chronic deteriorating cholestatic profile. Diffuse small bile duct damage is related to alloimmune reactions, drugs and toxins and rarely to infectious agents and usually appears as an acute cholestatic syndrome. However, rare biliary disease variants which do not fulfill the conventional diagnostic criteria also exist. They lack uniformity, established definition and confident treatment proposals. Overlap syndromes and idiopathic adulthood ductopenia (IAD) belong to this category. IAD most probably represents a heterogeneous entity. To date, no distinct diagnostic features have been

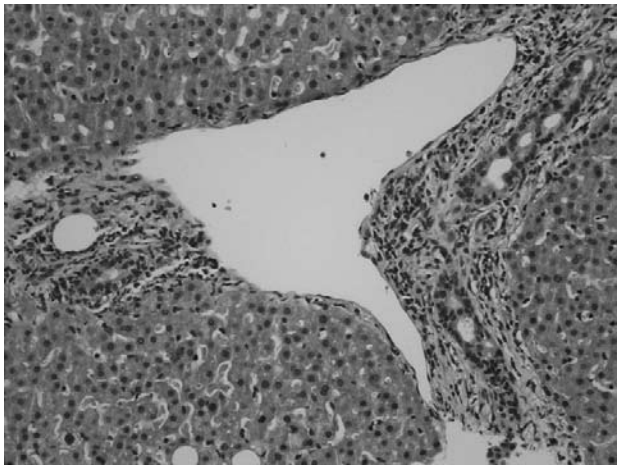

Figure 2. Interlobular bile ducts showing acute cholangitis and prominent degenerative changes . (H-E x 200)

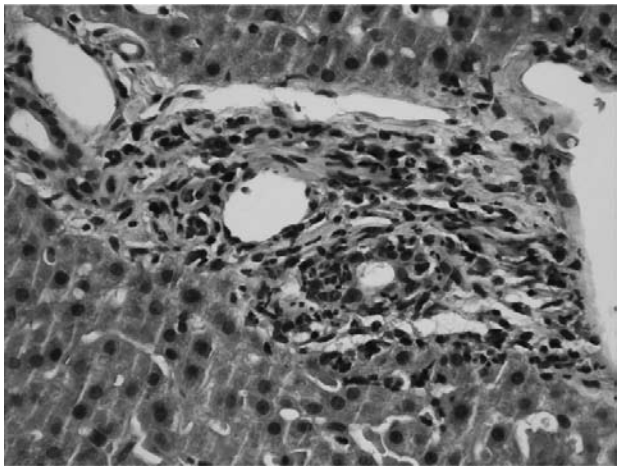

Figure 1. Small interlobular bile duct infiltrated by neutrophils and showing nuclear crowding and polymorphism of the epithelium. (H-E x 400)

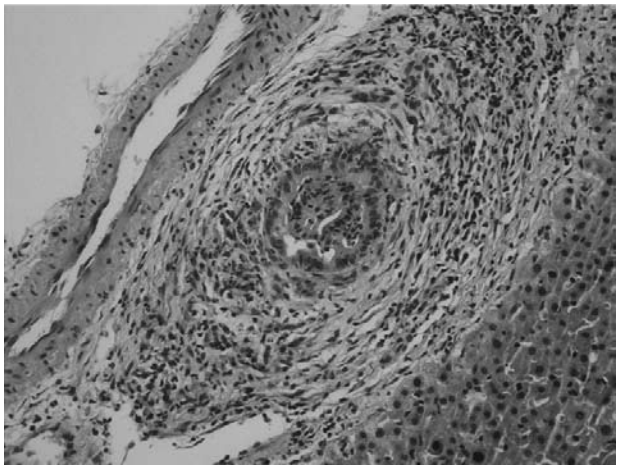

Figure 3. Interlobular bile ducts showing pericholangitis with concentric fibrosis as well as prominent degenerative changes and damage of the epithelium. (H-E x 400)

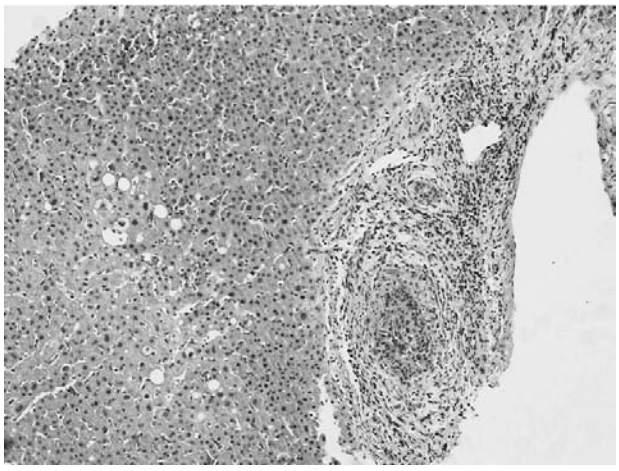

Figure 4. Interlobular bile ducts showing pericholangitis with concentric fibrosis as well as prominent degenerative changes and damage of the epithelium. (H-E x 200)

defined, the pathogenesis is obscure and the diagnosis is one of exclusion.[1,2]

The reported case presents an acute cholestatic syndrome which does not fulfill the clinicopathological criteria of any of the established biliary diseases. The main characteristics were absence of autoantibodies, negative drug history, no evidence of IBD and no involvement of large bile ducts. Histologically, it combined two distinct small bile duct lesions, namely diffuse pleomorphic cholangitis and focal sclerosing cholangitis.

Small interlobular bile ducts are targets of alloimmune and autoimmune reactions, of drug toxicity and rarely of bacterial and viral infections,[6] while a congenital ductopenic cholestatic liver disease has been associated with a mutation in ABCB4.[7] Progressive small duct involvement leading to ductopenia occurs in PBC and small duct PSC. The latter represents the less frequent variant of PSC and is diagnosed only on liver biopsy in patients without any signs of large bile duct participation, having inflammatory bowel disease (IBD) and showing histological features of fibrous obliterative cholangitis usually accompanied by chronic cholestasis and bile duct loss.[6] Our case is incompatible with the referred biliary diseases due to its acute clinical presentation, to the lack of any indications of immunological disorders, including IBD, and due to its response to steroids. What additionally differentiates our case is the histological component of diffuse pleomorphic cholangitis. Inconsistent clinical, imaging, serological and histological criteria including absence of plasma cells and IgG4 expression in liver tissue,[3-5] ruled out the steroid responsive IgG4 autoimmune cholangitis. Diffuse involvement of small bile ducts may result from the impact of drugs and rarely of infectious pathogens and manifests clinically with jaundice. Drug induced bile duct injury may be destructive accompanied by neutrophils and eosinophils.[2,6] In most cases the damage is reversible but duct loss and ductopenia may also occur. However, none of the reported cases in the literature was associated with features of sclerosing cholangitis. Furthermore, in our case there was no history of drug use or exposure to toxic agents,while cocaine inhalation had been stopped two months ago. Additionally neither cocaine nor alcohol have been implicated for bile duct injury.[2,8]

Suppurative cholangitis within the context of ascending cholangitis and rarely of septicemia may cause diffuse and severe bile duct injury,[6,9,-12] while recurrent or longstanding episodes may complicate or lead to secondary sclerosing cholangitis.[6,13,14] It has to be mentioned that opportunistic infections (CMV and cryptosporidium) may be the cause of secondary sclerosing cholangitis in immunocompromised patients,[6,13,14] while hepatitis C virus has been implicated for diffuse destructive cholangitis with duct loss in transplant recipients[15] and occasionally for ductopenia in immunocompetent patients. Our patient lacked the background of immunodeficiency and did not exhibit either clinical or laboratory findings of viral or bacterial infection. Moreover, histological features were inconsistent with suppurative cholangitis.

Our diagnostic approach did not succeed in ending in a certain diagnostic entity and raised the possibility of adulthood ductopenia as a diagnosis of one of exclusion. Idiopathic adulthood ductopenia (IAD) affects young or middle- aged adults and occurs with a distinct male predominance.[16,17,19,20] IAD most probably does not constitute a homogeneous entity and the cause is by definition unknown. It has been described as a chronic cholestatic liver disease with progressive deterioration, especially in younger age groups.[16,17] However, approximately one third of the patients presented with episodic jaundice and pruritus.[2,18] Common criteria constitute negative AMA, no large bile duct involvement, no history of drug use and no evidence of IBD. Four possible etiologies are under discussion: 1. late onset of non-syndromic paucity of intrahepatic bile ducts, 2. viral cholangitis, 3. autoimmune cholangitis with negative autoantibodies, 4.small duct PSC.[2,14,17] The variability in clinical presentation is reflected on the diversity of histology. Some patients showed only ductopenia,[16,21] while in others cholangitis was encountered in coexistence and occasionally independently from bile duct loss. Cholangitis was defined as lymphocytic[19] and more often as pleomorphic destructive cholangitis.[16,22,23] In two cases, severe epithelial damage was accompanied by inflammatory infiltra-

tions composed mainly by neutrophils as in our case.[22,23] Another histological picture that has been reported is similar to small duct PSC.[16,17] The possibility of different disease stages has been proposed as an explanation for the variable histological lesions.[22]

Our case meets the exclusion and inclusion criteria of IAD regarding age, sex, clinical history, clinical presentation, and laboratory findings. There are also some histological similarities on the one hand with diffuse pleomorphic cholangitis and on the other with small duct PSC. Such a mixed pattern probably reflects progressive stages of a rapid evolving disease with vigorous onset which starts as pleomorphic cholangitis and progresses to small duct PSC, eventually leading to ductopenia. The fact that the simultaneous appearance of these two different bile duct lesions is missing in the reviewed literature with the exception of one case reported by Ludwig,[16] could be attributed to longstanding and less severe disease variants diagnosed in more advanced stages with burn out bile duct lesions.

There is not enough information available in order to make a meaningful recommendation for the treatment of IAD. UDCA appears to improve liver biochemistry in some patients. However, its impact on the progression of the disease is unknown.[2,20] Additionally, there are no sufficient data suggesting corticosteroids to be effective. One of the two reported patients who received corticosteroid treatment showed improvement of the disease.[2] In our patient the improvement of the disease after corticosteroid administration points towards its beneficial effect.

Six months after having stopped his medical treatment the patient remains asymptomatic, with normal liver function tests.

In conclusion, we report an unusual case of acute icteric biliary disease with a mixed pattern of bile duct lesions, which was classified into the heterogeneous entity of IAD. The response to corticosteroid therapy probably prevented the development of small duct PSC and speaks in favour of an immune-mediated entity.

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