Difficult to Diagnose Case of Primary Sclerosing Cholangitis in Young Woman

Shalikiani Nino*, Bakulin Igor and Kharlamenkov Evgeny
Department of Hepatology, Moscow Clinical Scientific Center, Russia

Abstract
Primary sclerosing cholangitis (PSC) is a chronic liver disease leading to strictures and dilations of the intra- and extrahepatic bile ducts. PSC can eventually progress to liver cirrhosis and cholangiocarcinoma. Liver function tests reveal cholestasis, predominantly on behalf of alkaline phosphatase (ALP) elevation. ERC and MRC are diagnostic modalities of choice. Liver biopsy is not necessary to confirm the large bile ducts PSC if a cholangiogram is normal. In case of small bile ducts PSC, liver biopsy allows to exclude the overlap syndromes.

This article represents a case of a patient who presented with fatigue, right upper quadrant discomfort, mildly elevated ALP and high level of aminotransferases. Characteristic pattern of radiological changes of PSC was not identified, and the patient was treated with corticosteroids. Later the cholestatic pattern of the biochemical profile and dilated bile ducts in the absence of biliary obstruction raised the suspicion of PSC again. We repeatedly used all diagnostic tools including the liver biopsy. In 4 years the radiological and morphological picture had significantly changed, and PSC was established.

INTRODUCTION
PSC is a chronic cholestatic liver disease characterized by inflammation and fibrosis of both the intra- and extrahepatic bile ducts, developing into their multifocal strictures and dilations. Its prevalence is up to 16 cases per 100,000 persons, and incidence has increased over the last decade with more than 35% [1]. The exact etiological factor of the disease remains unclear. Infectious, immunologic and especially genetic factors are being lately investigated as potential contributors to the pathogenesis and etiology [2]. PSC is strongly associated with IBD, mostly ulcerative colitis (about 80% of cases) [3]. The serious, life threatening complications include liver cirrhosis and cholangiocarcinoma.

Liver function tests indicate cholestasis; elevated alkaline phosphatase (3-5 times reference range) is a dominant feature of the profile, although normal values do not exclude the diagnosis of PSC. Serum aminotransferase (2-3 upper times upper limits of normal) and bilirubin levels (mainly the conjugated component) might rise, but not markedly so. IgG levels might be slightly elevated in more than half of patients [4]. A number of serum autoantibodies (perinuclear antineutrophil cytoplasmic antibodies (p-ANCA); antinuclear antibodies) reveal an altered immune state, but their prevalence rates and titers are low. The endoscopic retrograde cholangiopancreatography (ERCP) is regarded as the criterion standard for establishing a diagnosis of PSC; if it is unsuccessful, transhepatic cholangiography may be considered. Magnetic resonance cholangiopancreatography (MRCP-sensitivity 86%, specificity 94%) is a preferred diagnostic modality [5], as it is non-invasive and potential complications of ERCP such as bacterial cholangitis and pancreatitis can be avoided.

The most common histopathologic liver change is a periductal concentric fibrosis known as onion skin fibrosis, but the finding is quite infrequent and is not an obligatory diagnostic modality in case of abnormal cholangiogram [6].

No pharmacologic treatment has proven effectiveness in PSC. Ursodeoxycholic acid (UDCA) might improve the biochemical test profile in some cases and in complex with endoscopic dilation, might increase the survival rate.

CASE PRESENTATION
A 31 old female (Mrs. S.) was referred to our clinical center in June 2015. She reported fatigue, chills and right upper quadrant discomfort. The patient denied abdominal pain, change in bowel patterns, weight loss, fever or jaundice.

Mrs. S. worked as a teacher in the primary school, married with two children. She did not smoke, denied alcohol use, and consumed two or more caffeinated beverages every day. Her past medical history consisted of vitiligo and erosive gastritis. There was no family history of cancer or other significant
gastrointestinal diseases. She did not have known allergies. She had not left the country for the past year and had not got antibiotics or any other medications other than UDCA.

Her clinical problems started in 2011. She presented to the outpatient clinic with a slight pruritus and right upper quadrant discomfort. Clinical examination revealed ALP elevation and ALT AST 10 times normal. All auto antibodies, including IgG4, were negative. No pathology was found on ultrasound. She did not visit the clinic during the next year. A year later (2013) an endoscopic ultrasound revealed signs of the biliary hypertension and bile duct strictures. ALP was elevated and aminotransferases were up to 5 times normal again. Firstly MRCP and then ERCP were performed. The visualization of bile ducts was less than optimal. Liver biopsy was performed. Based on morphology, biliary papilomatosis was diagnosed (Figure 1).

Corticosteroids were weaned off. The patient was recommended to go on treatment with UDCA. On examination in our clinic Mrs. S. was well oriented and not distressed. Vital signs were as follows: temperature of 36.5°C, respirations of 17, heart rate of 80. The chest was clear. Cardiac rhythm was regular, no murmurs. The abdomen was soft, non-tender, no masses, hepatomegaly or splenomegaly was palpated. Rectal exam: stool heme negative, no anal or perianal lesions. Skin exam was benign: no rash, jaundice or edema.

Full blood count and biochemical profile was normal except the elevation of ALP - 268, aspartate aminotransferase (AST) - 86, alanine aminotransferase (ALT) - 144. Anti-neutrophil cytoplasmic, antinuclear, anti-smooth muscle, anti-endothelial, anti-cardiolipin antibodies were negative.

Large bile duct wall thickening was identified on abdominal ultrasound. The liver and spleen size was normal, no ascetic fluid found. Recent MRCP, in contrast to the previous study, was consistent with the diagnosis of PSC. Colonoscopy was normal. Carbohydrate antigen 19-9 was not elevated. Transcutaneous liver biopsy was performed. Periductal fibroses and peribiliary gland hyperplasia were identified (Figure 2). So, PSC was diagnosed.

The patient was recommended UDCA 750 mg/day. A month later the liver function tests were normal. The patient is being followed up.

**DISCUSSION**

There were several unusual points in our case. The first one was the epidemiological point, as in contrast to our patient, typically PSC is diagnosed in middle-aged male patients with IBD presenting with abnormalities in biochemical profile [3,6].

Cholestatic liver diseases of unknown origin are frequently seen in clinical practice of gastroenterologists and there are number of entities, which have to be ruled out, including skeletal diseases. PSC is always important to consider as the potential cause. The initial presentation was quite unspecific in our case. The patient was treated as having an autoimmune hepatitis. Later the cholestatic pattern of the biochemical profile and dilated bile ducts in the absence of biliary obstruction raised the suspicion of PSC. ERC and MRC are diagnostic imaging modalities with a similar accuracy [6]. Although ERC is a gold standard, MRC is preferred as it lacks radiologic exposure and potential complications. In our case the characteristic pattern of radiological changes - annular strictures and bile duct dilations were not identified during the first referral. Based on results of the liver biopsy, biliary papilomatosis was suspected.

Later we repeatedly used all diagnostic tools again, as the case was still confounding. So, we faced the cholestatic liver function profile, mildly elevated transaminases, autoantibodies negative and nonspecific radiological and morphological changes on previous examination. Liver biopsy is not usually compulsory; it is used when the bile ducts are not finely visualized, or if an overlap syndrome with autoimmune hepatitis or primary biliary cirrhosis is suspected. In our case the morphological study had to be done twice because of unreliable imaging study results. We found that during 4 years the radiological and morphological picture had significantly changed, and PSC was established.

Treatment options for PSC are controversial. The benefits of using hydrophilic UDCA have been debated for years. Although American Association for the Study of Liver Diseases (AASLD) does not recommend UDCA in PSC patients, due the European guidelines UDCA (15-20 mg/kg BW) can be used. In our case preliminary results of using UDCA turned to be positive [7].

**FOLLOW-UP**

PSC patients with high levels of carbohydrate antigen 19-
9, even in the absence of cholangiocarcinoma, more rapidly progress to advanced liver disease and have worse survival rates without transplantation compared to those with a normal CA 19-9 value. Although our patient has not have elevated CA 19-9, she still needs to be closely followed up, as the cumulative incidence of cholangiocarcinoma among PSC patients is obviously higher, being more than 10% [8,9]. And besides, CA 19-9 is not sensitive in early stages of cholangiocarcinoma.

The meantime from the diagnosis of PSC to fatal complications if not having the liver transplant is 12-18 years. So, in future as the disease progresses, the only curative option for the patient will be the liver transplantation.

REFERENCES