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Primary Biliary Cholangitis in Men: A Rare and Particular Presentation (About 2 Cases and Review of the Literature)

Chama El Manjra[1*], Abderrahmane Jallouli[1], Ibtissam Bounouar[1], Oussama Nacir[1], Fatima Ezzahra Lairani[1], Adil Ait Errami[1], Sofia Oubaha[2], Zouhour Samlani[1], Khadija Krati[1]

[1]Hepato-Gastroenterology Department, University Hospital of Mohammed VI, Marrakesh, Morocco
[2]Physiology Laboratory, Faculty of Medicine and Pharmacy, Cadi Ayyad University, Marrakesh, Morocco

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***Corresponding author:** Chama El Manjra
Hepato-Gastroenterology Department, University Hospital of Mohammed VI, Marrakesh, Morocco

Abstract **Case Series**

Primary biliary cholangitis (PBC) is a rare etiology of cholestatic jaundice in men. We report two rare cases of PBC in men revealed by chronic cholestasis (jaundice, pruritus, dark urine, discolored stools, ALP greater than 1.5 times the upper limit and GGT greater than 3 times the upper limit). The first case had positive anti-mitochondria type 2 antibodies, while in the second case they were negative with positive anti gp-210 antibodies. The histological study of liver biopsies in the first case confirmed PBC. The second case was diagnosed at the stage of cirrhosis.

Keywords: Primary biliary cholangitis – Men - Jaundice - Cholestasis - Anti-mitochondrial antibodies type 2.

INTRODUCTION

Primary biliary cholangitis (PBC) is an autoimmune cholestatic disease, characterized by inflammatory destruction of peri-lobular bile ducts, which may progress to fibrosis or even liver cirrhosis. It predominantly affects middle-aged women (generally between 30 and 60 years old) [1-2]. The occurrence of this disease in men is very rare, with an estimated incidence 0.7 per 100,000 person-years and a median age of diagnosis at 62 years [3].

We report two cases of PBC in men revealed by chronic cholestatic jaundice.

CASE REPORTS

First Case

A 67-year-old male patient with a medical history including a COVID-19 infection treated three months ago, cervical herniated disc surgery in 2013, and meningioma surgery in 2014, treated with anticonvulsant (Lamotrigine) in the postoperative period due to persistent intermittent convulsions. The patient had also a history of chronic smoking for 20 years weaned 14 years ago and no history of alcoholism.

He presented with a persistent mucocutaneous jaundice, dark urine, and discolored stools as well as generalized pruritus for the past 2 months. There were no reports of vomiting, externalized digestive hemorrhage or abdominal pain. The symptoms have been evolving in the absence of fever, with a decline in the general state of health including a weight loss of 11 kg over 2 months, marked asthenia and anorexia. Clinical examination revealed mucocutaneous jaundice and diffuse scratching lesions, with no other discernible abnormalities.

The laboratory investigations revealed a biochemical cholestatic syndrome, with alkaline phosphatase (ALP) at 274 U/L (2.1 times the upper limit), gamma-glutamyl transferase (GGT) at 79 U/L (1.1 times the upper limit), and total bilirubin at 150 mg/L with predominance of the conjugated form (140 mg/L). There were also minimal cytolysis, with aspartate aminotransferase (AST) at 112 U/L (2.2 times the upper limit) and alanine aminotransferase (ALT) at 72 U/L (1.7 times the upper limit). Prothrombin and serum albumin levels were within normal ranges. Abdominal ultrasound was normal, including no dilation of the bile ducts. Additional testing with magnetic resonance cholangiopancreatography (MRCP) showed no specific abnormalities. Markers for viral hepatitis (A, B, C), Epstein-Barr virus (EBV) and cytomegalovirus (CMV) were negative. Ferritin level was elevated to 841 umol/g (normal range: 15-150 umol/g) with a normal transferrin saturation coefficient (32%). Immunological assessments showed positive anti-mitochondrial antibodies type 2 (13 AU/ml), while the rest of immunological panel (antinuclear antibodies, anti-

smooth muscle antibodies, anti-cytosol 1 antibodies (LC1), anti-liver and kidney microsome 1 antibody (LKM1), anti-soluble liver antigens (SLA), total IgG levels) were within normal limits. A liver biopsy was performed, revealing moderate portal fibrosis destroying the bile duct structures, estimated ductopenia at 25%, Peace-meal necrosis lesions, and an inflammatory infiltrate with lymphocytic predominance in the periportal and lobular regions. Additionally, there were degenerative hepatocellular lesions, characterized by ballooning and clarification.

The diagnosis of primary biliary cholangitis (PBC) was established, and the patient was initiated on ursodeoxycholic acid (UDCA) at a dose of 13 mg/kg/day. Further investigations for associated autoimmune diseases, including celiac disease, autoimmune thyroid disorder, Sjogren's syndrome, scleroderma, and rheumatoid arthritis, were negative.

Over a follow-up period of 2 years, the patient's condition showed marked improvement, characterized by the resolution of jaundice and normalization of the biochemical profile according to the Paris criteria (ALP <1.5 times the upper limit, AST < 1.5 times the upper limit and normal bilirubin level).

Second Case

A 47-year-old patient, under follow-up for 23 years due to type 1 diabetes managed with insulin therapy, was admitted to our facility for persistent mucocutaneous jaundice. The jaundice presented with cholestatic features, including dark urine, discolored stools, and generalized pruritus, without additional associated signs. The symptoms had been evolving over the past three months in the context of marked asthenia. Clinical examination revealed no abnormalities except for mucocutaneous jaundice and scratching lesions.

The laboratory investigations revealed a biochemical cholestatic syndrome, with alkaline phosphatase (ALP) at 479 U/L (3.7 times the upper limit), gamma-glutamyl transferase (GGT) at 246 U/L (3.4 times the upper limit), and a total bilirubin at 49 mg/L with predominance of the conjugated form (44 mg/L). There was minimal cytolysis, with aspartate aminotransferase (AST) at 56 U/L (1.3 times the upper limit) and alanine aminotransferase (ALT) at 50 U/L (1.1 times the upper limit). Prothrombin and serum albumin levels were within normal ranges.

Abdominal ultrasound showed a dysmorphic liver with heterogenous parenchyma, hypertrophy of the left lobe and hypotrophy of the right lobe, but no detectable nodular lesions, and no dilation of the bile ducts. MRCP also revealed a dysmorphic liver with signs of portal hypertension without dilation or stenosis of the bile ducts. Virological markers for hepatitis B and C were negative. Alpha-fetoprotein (AFP) level was normal. Immunological assessment, including anti-mitochondrial antibodies type 2, antinuclear antibodies, anti-smooth muscle antibodies, anti-cytosol 1 antibodies (LC1), anti-liver and kidney microsome 1 antibody (LKM1), anti-soluble liver antigens (SLA), and total IgG levels were normal. Anti sp100 antibodies were also within normal limits. However, anti-GP210 antibodies were strongly positive. Esophagogastroduodenoscopy (EGD) revealed the presence of grade 1 esophageal varices without red signs, which indicated a portal hypertension.

The diagnosis of primary biliary cholangitis complicated by hepatic cirrhosis with portal hypertension was established, and the patient was initiated on ursodeoxycholic acid (UDCA) at a dose of 13 mg/kg/day. Further investigations for associated autoimmune diseases were also negative, except for type 1 diabetes.

After an 18-month follow-up, the patient showed favorable evolution marked by the resolution of clinical and biochemical cholestasis according to the Paris criteria. The routine semi-annual follow-up for his cirrhosis is being continued.

DISCUSSION

Primary Biliary Cholangitis (PBC), the new nomenclature for Primary Biliary Cirrhosis, is an autoimmune cholestatic disease, characterized by immune-mediated inflammatory destruction of the small intrahepatic bile ducts, which can progress to fibrosis and eventually lead to hepatic cirrhosis. This condition predominantly affects individuals of the female gender, with a female-to-male sex ratio ranging from 9/1 to 22/1, and is typically diagnosed in individuals between the ages of 30 and 60 [1-2]. The occurrence in male patients is rare.

Various factors, including genetic, environmental, and infectious factors, are considered essential in the development or progression of PBC [3-6]. The pathophysiological mechanism of PBC appears to involve T lymphocyte dysregulation [7-10], as well as molecular mimicry and cross-reactivity involving microbial or self-antigens, leading to an inflammatory and destructive reaction in the epithelial cells of the small intrahepatic bile ducts [8]. The disease can manifest in various ways, with patients either being asymptomatic at the time of diagnosis, or presenting with nonspecific symptoms, often including fatigue, mucocutaneous jaundice, generalized pruritus, among others. The disease may also be revealed at later stages, particularly during compensated or decompensated hepatic cirrhosis [7-10].

From a biological standpoint, PBC is characterized by chronic cholestasis, evident through elevated levels of alkaline phosphatase (ALP) greater than 1.5 times the upper limit of normal and gamma-

glutamyl transferase (GGT) greater than 3 times the upper limit of normal. An increase in bilirubin levels is not always present nor necessary for diagnosis, and minimal cytolysis is often associated.

In 10% of cases, PBC is associated with autoimmune hepatitis, leading to an overlap syndrome. In this particular form, there is a significant elevation in aspartate and alanine aminotransferase (more than 5 times the normal level), along with an increase in IgG levels and the presence of specific antibodies [11].

Anti-mitochondrial antibodies type 2 are the gold standard for diagnosing PBC, with a sensitivity and specificity of 90% and 97% respectively [2]. If this marker is negative, further investigation for specific anti-nuclear antibodies related to PBC, such as anti-gp210 or anti sp-100 antibodies is recommended [12].

Histological confirmation through liver biopsies can provide information about the stage of the disease, which has been classified by Scheuer into 4 stages: non-suppurative nor destructive cholangitis at stage 1, periportal ductular proliferation at stage 2, extensive septal fibrosis at stage 3, and cirrhosis at stage 4 [13].

The development of PBC in males is rare. Its incidence has been estimated at 0.7 per 100,000 person-years with a median age of diagnosis at 62 years [3]. Several studies failed to demonstrate significant differences between genders regarding the biochemical, immunological and histological characteristics of PBC. However, it has been reported that intense pruritus and systemic manifestations are less common in men than women. On the other hand, jaundice, signs of portal hypertension, including digestive hemorrhage, and the development of hepatocellular carcinoma are more frequently described in men [8-15].

The first-line treatment for PBC is ursodeoxycholic acid (UDCA) at a dosage of 13-15mg/kg/day. The efficacy of UDCA treatment is assessed by the biological response one year from the initiation of treatment. The most widely used definition of biological response is based on the Paris II criteria: alkaline phosphatase (ALP) < 1.5 times the upper limit of normal, aspartate aminotransferase (AST) < 1.5 times the upper limit of normal, and normal bilirubin levels at one year from the start of treatment [16]. In cases of non-response to UDCA treatment, it is essential to investigate poor adherence, associated autoimmune hepatitis (overlap syndrome), or another autoimmune disease (such as autoimmune thyroiditis of celiac disease).

Obeticholic acid is the second-line treatment, either as a replacement for UDCA in case of poor tolerance or in combination of UDCA if there is no biological response to UDCA. Other molecules, such as fibrates and budesonide, also constitute second-line treatments [12].

CONCLUSION

Primary Biliary Cholangitis (PBC) represents a rare etiology of cholestatic jaundice in men. It's clinical, biological, immunological, and histological profile is similar in men and women. However, the development of signs of hepatocellular insufficiency, particularly hemorrhagic complications, and hepatocellular carcinoma is more frequent in men. This may be attributed to delayed diagnosis. Hence, it is crucial to consider this entity to prevent progression to cirrhosis and its complications.

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Authors' Contributions

All authors participated in the conception, drafting the work, critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

Consent to Publication

The patients have declared their consent freely and in an informed manner, in order to allow the production and publication of this manuscript.

Ethical Approval: Ethical approval is not required at our institution to publish an anonymous case report.

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