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Primary Biliary Cholangitis in Men: A Case Report

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Abstract **Case Report**

Primary biliary cholangitis (PBC) is a rare chronic autoimmune liver disease, especially in men, that causes progressive inflammation and destruction of the intrahepatic bile ducts. This leads to hepatic fibrosis that can progress to cirrhosis. PBC diagnosis is suggested by cholestatic jaundice in the absence of abnormalities in intrahepatic and extrahepatic bile ducts, with alkaline phosphatases (ALP) > 1.5 times the upper limit of normal and gamma-glutamyl transferase (GGT) > 3 times the upper limit of normal, with or without elevated bilirubin levels. Confirmation is made through immunological tests, and liver biopsy (PBH) is necessary if tests are negative. The disease is often diagnosed at an advanced stage. Poor prognostic factors include early diagnosis, male gender, severe symptoms, and biological abnormalities such as elevated bilirubin levels. Specific autoantibodies, such as anti-gp210 and anti-sp100, also predict unfavorable disease progression. The first-line treatment is ursodeoxycholic acid (UDCA), which helps slow disease progression and improve symptoms. If UDCA is ineffective, other options include obeticholic acid (OCA) or fibrates like bezafibrate, often used in combination with UDCA. Liver transplantation is the only curative treatment for severe cases. Research is ongoing for new treatments, including PPAR agonists and bile acid transporter inhibitors.

Keywords: Primary biliary cholangitis, men, ursodeoxycholic acid.

INTRODUCTION

Primary biliary cholangitis (PBC) is a cholestatic liver disease with an immune-mediated origin, mainly diagnosed in middle-aged women, with a sex ratio (M/F) of 0.086 [1]. It is characterized by destructive lymphocytic cholangitis affecting the intrahepatic bile ducts, leading to cholestasis, fibrosis development, and eventually cirrhosis [2]. The diagnosis is often made during an etiological evaluation for pruritus sometimes associated with cholestatic jaundice and supported by biological tests, immunological markers, and especially histological findings from liver biopsy (PBH) [3]. PBC is often associated with other autoimmune conditions such as autoimmune hepatitis, overlap syndrome, Sjögren's syndrome, thyroid disorders, and sometimes celiac disease [3]. First-line treatment involves ursodeoxycholic acid (UDCA) to manage symptoms and achieve a biochemical response, slowing disease progression [4]. New pharmacological advancements are in development [4].

CASE PRESENTATION

Patient Information: The patient is a 26-year-old male with no significant medical history apart from informal dental care, hospitalized for cholestatic skin and mucous jaundice evolving over the past 6 months with no history of toxic substance use.

Clinical Results: Clinical examination showed no particular findings except for scratching lesions of different ages.

Diagnostic Approach: Paraclinical investigations revealed total hyperbilirubinemia at 347.4 mg/L with predominant conjugated bilirubin (BC at 302.9 mg/L), and alkaline phosphatases at 3.5 times the normal level. GGT and transaminases were normal. Initial prothrombin time was 54%, corrected to 100% with the Kohler test. Abdominal ultrasound showed a liver of normal size and regular contours, with normal portal and hepatic veins and a normal-sized spleen, without bile duct abnormalities. Immunological tests were negative for anti-mitochondrial M2, anti-gp210, and anti-sp100 antibodies, and viral serologies for B and C. Magnetic resonance cholangiography (MRI) showed no obstruction in intrahepatic and extrahepatic bile ducts and no bile duct anomalies. The patient underwent liver biopsy (PBH) with histological study, which revealed lymphocytic cholangitis, ductopenia, and moderate

hepatocellular degenerative lesions. A diagnosis of seronegative PBC was confirmed based on these histological findings. The patient did not have associated autoimmune diseases, including thyroid disorders, celiac disease, autoimmune hepatitis, or Sjögren's syndrome.

Therapeutic Intervention and Evolution: The patient was treated with UDCA at a dosage of 15 mg/kg/day, showing good progress with normal liver function tests after 12 months of treatment.

DISCUSSION

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease characterized by destructive lymphocytic cholangitis of the small intrahepatic bile ducts, responsible for progressive hepatic fibrosis and potential evolution to cirrhosis [2]. It is rare in men, with a sex ratio (M/F) of 0.086 [5, 6]. Diagnosis is suspected with cholestatic jaundice associated with pruritus and fatigue in the absence of bile duct abnormalities. Biologically, PBC manifests as chronic cholestasis (elevated alkaline phosphatases (ALP) > 1.5 times the upper limit of normal and gamma-glutamyl transferase (GGT) > 3 times the upper limit of normal) with or without elevated bilirubin levels [4]. Moderate elevation of transaminase activity is often noted [4]. Other biological signs may relate to complications of chronic cholestasis such as deficiencies in fat-soluble vitamins and hypercholesterolemia [4]. Confirmation is made through immunological tests: positivity of anti-M2 antibodies, recently anti-kelch-like 12 and anti-hexokinase 1, and occasionally anti-gp210 and anti-sp100 antibodies. In cases of negative autoimmune tests [7], PBH is essential to identify destructive cholangitis affecting mainly the interlobular bile ducts and to evaluate the degree of fibrosis and severity of the disease [4, 8].

PBC is a chronic disease with clinical manifestations appearing months or years after onset, leading to many patients being diagnosed at an advanced stage [2]. Although the clinicobiological and immunological profiles are similar in both sexes, disease progression is often more unfavorable in men [9]. In fact, it is common to observe the coexistence of other autoimmune diseases in women compared to men [9]. The presence of other autoimmune diseases is associated with reduced quality of life and health [5].

PBC is a severe disease progressing to cirrhosis and its complications. Poor prognostic factors include young age at diagnosis, male gender, presence of symptoms (pruritus and fatigue), clinical signs of cirrhosis, initial histological stage or fibroscan results [4]. Biological poor prognostic factors include elevated bilirubin levels (>17 µmol/L), low albumin levels (<35 g/L), thrombocytopenia, very high ALP (>5 times normal), ASAT/platelet ratio (APRI score) >0.54 associated with a higher risk of death and liver transplantation, and the calculation of UK-PBC risk score and Globe score combining albumin and platelet levels for long-term mortality risk prediction and need for liver transplantation [4].

Additionally, the presence of specific autoantibodies (anti-gp210 and anti-sp100) is a predictive factor for PBC severity and unfavorable disease progression regardless of bilirubin levels. Complications are more frequent with portal hypertension syndrome and lack of response to treatment [3].

PBC treatment aims to suppress the underlying pathogenic process (and thus slow disease progression) and manage both symptoms and complications of chronic cholestasis [10]. The treatment of choice is UDCA, due to its choleretics, cytoprotective, anti-inflammatory, and immunomodulatory properties, improving cholestasis, slowing histological progression, and prolonging survival [10]. It should be combined with symptomatic treatment of pruritus and management of associated conditions and/or complications. Treatment response is defined by normalization of bilirubin and alkaline phosphatase (ALP) and aspartate aminotransferases (ASAT) <1.5 times the normal level, according to Paris II criteria [11]. The exact definition of a biological response is controversial, and several criteria are described in the literature, with Paris II criteria being among the most used [11].

Bilirubin	**< 17 µmol/l**
ASAT	**< 1,5 normale**
ALP	**< 1,5 normale**

Paris II criteria

Optimal daily UDCA dosage is 13 to 15 mg/kg, preferably in a single dose, with a maximum of two doses. UDCA should be introduced gradually to increase tolerance, especially digestive (diarrhea) [10]. It does not significantly affect pruritus or fatigue, which may require multidisciplinary management to improve patient quality of life. A retrospective cohort including over 1,047 patients over 15 years, conducted by Corpechot et al and published in January 2024, found that good UDCA response was associated with a 7.6-month survival gain without complications at 10 years, with a more significant gain in patients with elasticity ≥10 kPa and/or age ≤62 years, estimated at 52.8 months at 10 years without complications [11].

For non-responders or UDCA-resistant cases, after excluding curable causes (insufficient dosage, poor compliance, added hepatic insults (obesity, alcohol), overlap syndrome, thyroid disorders, celiac disease), second-line therapy involves obeticholic acid (OCA), a derivative of chenodeoxycholic acid, a potent farnesoid X receptor (FXR) agonist regulating bile acid synthesis and transport with anti-inflammatory and antifibrotic effects. However, its main side effect is dose-dependent pruritus [12]. It is contraindicated in decompensated

cirrhosis Child-Pugh B and C and should be used cautiously in compensated cirrhosis without portal hypertension with maximum doses not exceeding 5 mg/day [12]. The European Association for the Study of the Liver (EASL) recommends using obeticholic acid (OCA) in combination with UDCA for patients with insufficient response to UDCA or as monotherapy for those intolerant to UDCA, starting at 5 mg/day and increasing up to 10 mg/day based on tolerance and biological response [5].

Fibrates, particularly bezafibrate, are mainly indicated for treating hypertriglyceridemia but also have anti-cholestatic effects involving anti-inflammatory action and consequently reduced hepatic bile acid synthesis and increased phospholipid excretion [13]. Corpechot et al.'s research shows a complete biochemical response in 31% of patients treated with bezafibrate and UDCA, compared to 0% of patients treated with UDCA alone. For non-responders, combining it with UDCA is recommended, but it has not yet received market authorization for use in PBC [13]. Possible side effects of fibrates include hepatotoxicity, renal insufficiency, and the occurrence of myalgia. It is contraindicated in cases of decompensated cirrhosis. The optimal daily dose is 400 mg with monitoring of liver function and creatinine levels, with discontinuation required if cytolysis exceeds five times the normal level or creatinine increases by more than 25% with an eGFR < 60 ml/min [4]. In cases of resistance to second-line treatments, the combination of OAC+fibrates+UDCA (triple therapy) may improve biochemical response and symptoms, although no third-line treatment has formally demonstrated its efficacy [4].

New therapies are being studied at various stages of clinical development, targeting several pharmacological pathways. These include: new PPAR agonists (such as Seladelpar), inhibitors of NOX isoforms 1 and 4 (such as Setanaxib), and ileal bile acid transporter inhibitors (such as Maralixibat) [14].

Liver transplantation is the only curative treatment for primary biliary cholangitis (PBC) and remains the standard treatment for severe and late-stage cases [15]. It is indicated in cases of decompensated cirrhosis, hepatocellular carcinoma, jaundice with bilirubin levels exceeding 50 µmol/L, or exceptionally in cases of refractory pruritus [4]. The risk of PBC recurrence in the transplanted liver is 30% to 50% at 10 years, highlighting the importance of prevention through the administration of ursodeoxycholic acid (UDCA). This has been demonstrated by a retrospective cohort study by Corpechot *et al*., which included 780 transplanted patients, 190 of whom received preventive treatment with UDCA (10-15 mg/kg/day) between 1983 and 2017 across 16 centers (on 5 continents) and followed for a median of 11 years [16].

CONCLUSIONS

Primary biliary cholangitis (PBC) is rarely observed in men but presents a similar clinical, biological, immunological, and histological profile, except for a generally more unfavorable progression in males [5]. In addition to male sex, factors such as the presence of specific autoantibodies, symptoms, and potential development of cirrhosis are associated with a poor prognosis, highlighting the importance of early diagnosis [4]. First-line treatment is ursodeoxycholic acid (UDCA), which has demonstrated its ability to improve survival without the need for liver transplantation [3]. The prognosis of the disease depends on the assessment of hepatic fibrosis using fibroscan and the biological response to UDCA treatment [3]. In cases of intolerance or lack of biological response to UDCA, obeticholic acid now has regulatory approval as a second-line treatment [12].

Human Ethics: Consent was obtained by all participants in this study

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