World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(CASE REPORT)

Beyond serology: Leveraging radiological and pathological tools in seronegative primary biliary cholangitis

Nathalie Marina Pérez Fontalvo [1,*], Lorena Rocío Orozco Álvarez [1], Abel Enrique Manjarres Guevara [2], Michael Mario Vélez Lora [1] and Iván Alfredo De Ávila Consuegra [1]

[1] *Department of Internal Medicine, Faculty of Health Sciences, Universidad Libre, Barranquilla, Colombia.*
[2] *Department of Medicine and Health Sciences, Universidad del Norte, Barranquilla, Colombia.*

World Journal of Advanced Research and Reviews, 2024, 22(03), 1105–1108

Publication history: Received on 07 May 2024; revised on 16 June 2024; accepted on 18 June 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.22.3.1833

Abstract

Primary biliary cholangitis is a chronic autoimmune inflammatory disease that affects the bile ducts, presenting a broad clinical spectrum characterized by cholestasis and the presence of antimitochondrial antibodies. This report describes the case of a young adult presenting with fever, musculoskeletal pain, and altered bowel habits, alongside markers of hepatocellular damage with a cholestatic pattern, but with negative antimitochondrial and antinuclear antibodies. A liver biopsy revealed findings consistent with cholangitis. This case underscores the importance of considering cholangitis in the differential diagnosis of patients with abnormal liver biochemistry tests showing a cholestatic pattern, even in the absence of specific immune serological markers.

Keywords: Primary Biliary Cholangitis; Autoimmune liver disease; Cholestasis; Liver Biopsy; PET.

1. Introduction

Primary biliary cholangitis (PBC) is a chronic autoimmune condition that causes cholestasis [1]. It results from the immune system's loss of tolerance to mitochondrial antigens, influenced by a combination of environmental factors and genetic predisposition [2]. Fatigue is the most common and debilitating symptom, affecting up to 80% of patients over the course of the disease [2],[3]. PBC is defined by cholestasis and the presence of antimitochondrial antibodies (AMA), which target the mitochondrial membranes of biliary epithelial cells [4]. The diagnosis, according to the American Association for the Study of Liver Diseases, requires two out of three criteria: elevated alkaline phosphatase, positive AMA with a titer of at least 1:40, or PBC-specific antinuclear antibodies (ANA), and/or liver histopathology consistent with PBC [5],[6]. Typically, a liver biopsy is not necessary for diagnosis, except in AMA-negative individuals or those suspected of having concurrent autoimmune hepatitis [3].

We present the case of a young adult with fever and nonspecific symptoms, who exhibits markers of hepatocellular damage with a cholestatic pattern, negative AMA and ANA, and a liver biopsy indicating cholangitis.

2. Case Report

In this report, we describe a 23-year-old male patient who presented with a one-month history of intermittent fever, reaching up to 40°C, accompanied by myalgias, arthralgias, unintentional weight loss, and intermittent episodes of non-bloody, mucus-free diarrhea and hyporexia; without other reported symptoms. He had no significant personal or family medical history. During the course of his illness, he had previously visited the emergency department where infectious processes were ruled out through radiological studies, cultures, and an echocardiogram to investigate vegetations.

* Corresponding author: Nathalie Marina Pérez Fontalvo

Elevated alkaline phosphatase levels were documented, but bilirubin levels were normal. With stable evolution and afebrile status for 72 hours, he was discharged. However, fever recurred, prompting the patient to seek medical attention again.

A complete blood count and blood chemistry revealed mild elevation of aminotransferases less than twice the upper limit of normal, along with elevated alkaline phosphatase and GGT consistent with a cholestatic pattern. The diagnosis of fever of unknown origin was considered, and repeat cultures were negative for microbiological growth. Serologies for major hepatotropic microorganisms, including cytomegalovirus and toxoplasma, were negative. Further imaging studies, including chest and sinus CT scans, were negative, while abdominal CT revealed incidental homogeneous splenomegaly and retroperitoneal lymphadenopathy. Physical examination did not reveal palpable masses or other lymphadenopathies.

Given the persistent elevation of alkaline phosphatase and GGT, primary biliary cholangitis vs. primary sclerosing cholangitis were considered as differential diagnoses. Magnetic resonance cholangiography showed no intrahepatic or extrahepatic biliary tract abnormalities. PET-CT imaging revealed hypermetabolic lymph node conglomerates in the right internal mammary chain, celiac trunk, hepatic hilum, portocaval region, peripancreatic area, as well as para-aortic and lateral caval regions of undetermined etiology, alongside non-hypermetabolic splenomegaly. Tumor markers were negative, and immunological studies showed negative antimitochondrial antibodies (AMA), ANA, and p-ANCA (Table 1).

Laparoscopy was performed to obtain liver biopsy and biopsy of lymph nodes identified on PET-CT. Macroscopic findings indicated congestive liver and hepatosplenomegaly with isolated retroperitoneal lymph nodes measuring less than 15 mm. Histological examination of the lymph node suggested reactive changes due to chronic inflammation, while liver pathology reported chronic hepatitis with moderate necroinflammatory activity and ductal proliferation suggestive of subacute cholangitis.

Considering these findings, the possibility of seronegative primary biliary cholangitis is considered, based on the Paris criteria, with no indicative cirrhosis findings. The patient was referred to hepatology for further management and follow-up.

Table 1 Liver and Immunological Tests

Laboratories	**Result**
ALT (U/L)	16.8
AST (U/L)	13.9
GGT (U/L)	375
Alkaline Phosphatase (U/L)	286
Total Bilirubin (mg/dL)	0.48
Direct Bilirubin (mg/dL)	0.27
Indirect Bilirubin (mg/dL)	0.21
Albumin (g/dL)	3.98
IgG (mg/dL)	1458
ANA	Negative
P-ANCA and C-ANCA	Negative
AMA	Negative
ANTI SM	Negative
ANTI RNP	Negative
ANTI SSA	Negative

3. Discussion

Primary biliary cholangitis (PBC) is a chronic liver disease characterized by immune-mediated inflammation that damages intrahepatic bile ducts, leading to cholestasis, progressive fibrosis, cirrhosis, and ultimately liver failure. It is considered the most prevalent form of autoimmune liver disease [7], with a global prevalence estimated between 40 and 400 cases per million individuals [5]. While its incidence and prevalence appear to be increasing, possibly due to improved understanding of its pathogenesis, earlier diagnosis, and improved patient survival rates, the exact reasons for the female predominance, with a ratio of 4 to 5:1, remain unclear [8]. The precise etiology of PBC remains poorly understood, but it is thought to involve a combination of genetic predisposition, environmental triggers, and alterations in immune tolerance mechanisms. Loss of immune tolerance to nuclear and mitochondrial antigens leads to bile duct damage through inappropriate T and B cell activation [5]. Enhanced understanding of the disease's clinical and histopathological evolution, characterized by dense inflammatory infiltrates around damaged intrahepatic bile ducts, prompted the shift from the previously used term "primary biliary cirrhosis" to "primary biliary cholangitis" [1].

PBC typically takes 10 to 15 years to progress from asymptomatic stages to symptomatic disease [9]. Many patients are asymptomatic at diagnosis, with fatigue being the most prevalent symptom, affecting 50-80% of patients. Pruritus, exacerbated at night, is another common symptom. Approximately 40% of patients experience musculoskeletal discomfort due to inflammatory arthropathy, suggesting potential coexistence with other autoimmune conditions [3]. Gastrointestinal bleeding, more frequent in males, and a higher prevalence of type 2 diabetes mellitus in men are also notable [7]. Alkaline phosphatase elevation is a hallmark of PBC, while aminotransferases may be normal or mildly elevated. Higher bilirubin levels often indicate disease severity and correlate with adverse outcomes and biliary necrosis [3]. Diagnosis is suspected in cases of chronic cholestasis and positive AMA, with liver biopsy generally unnecessary if alkaline phosphatase has been elevated for over 6 months and serum AMA titers exceed 1:40 [7].

AMA, an immunoglobulin A targeting the E2 subunit of the pyruvate dehydrogenase complex on biliary epithelial cell mitochondrial membranes, causes ductular damage [4], [5]. AMA positivity is seen in approximately 95% of PBC cases [7], even in asymptomatic patients with normal liver function tests [9]. However, it can also be detected in 0.1-0.5% of apparently healthy individuals or those with other autoimmune liver diseases [10]. Highly specific antibodies such as ANA against glycoprotein 210 and sp100 can predict treatment response and adverse outcomes [7]. Up to 5% of PBC patients lack AMA but present clinically, biochemically, and histopathologically similar [4], with a significant proportion having positive ANA, indicating early disease stages [9].

Juliusson et al. described AMA-negative PBC patient characteristics, with 96% being female and a mean age of 55 years. ANA positivity was observed in 58%, with AMA seroconversion occurring in 6% during follow-up [11]. In another study, Cançado et al. compared AMA-positive and -negative PBC patients in Brazil, with 95.4% females and a mean age of 56. AMA positivity was 83%, and 17.2% were AMA-negative. AMA-negative patients were younger at symptom onset compared to AMA-positive counterparts [10].

Structural abnormalities are not typically observed in early PBC stages, though abdominal ultrasound is recommended to exclude extrahepatic biliary obstruction. Abdominal and periportal lymphadenopathy, seen in up to 88% of all histological stages, is generally reactive and not malignant [12]. The patient presented with multiple lymph node conglomerates.

Occasionally, biopsy is necessary for staging or to diagnose overlap syndrome [7]. Histologically, PBC is characterized by interlobular and septal bile duct inflammation, focal lesion formation, and epithelioid granulomas. A four-stage histological model for PBC ranges from portal triad inflammation to hepatic cirrhosis and regenerative nodules [3].

Current PBC treatment aims to alleviate symptoms, improve cholestasis parameters, and slow disease progression, though many patients do not respond adequately [6],[8]. Pruritus management includes reducing bile acid levels through nasobiliary drainage, cholestyramine therapy, or UVB light therapy [3]. Some studies report poorer ursodeoxycholic acid (UDCA) response, increased cirrhosis progression, higher mortality/transplant rates, and increased hepatocellular carcinoma risk in men compared to women [2]. Treatment efficacy is similar between AMA-positive and -negative patients [4], with no significant mortality differences noted [7]. However, studies like that of Juliusson et al. suggest poorer outcomes in AMA-negative PBC patients [11].

This case is noteworthy for its occurrence in a male patient, contrary to PBC's predominant female demographic. Additionally, the patient's age at presentation differs significantly from the literature's average onset. Furthermore, fever, the primary reason for the patient's consultation, is atypical for initial PBC symptoms. While liver biopsy is

generally unnecessary for diagnosing PBC with elevated alkaline phosphatase and AMA positivity, it proved crucial in this case due to the patient's unusual clinical features and lack of both AMA and ANA.

4. Conclusion

Primary biliary cholangitis is a chronic autoimmune condition. This case illustrates the diagnostic complexity of autoimmune diseases such as PBC, particularly in patients with atypical presentations and negative serologic markers of immunity. Detailed evaluation of clinical data and laboratory findings forms the basis for diagnostic approach; however, liver biopsy assumes significance in achieving an accurate diagnosis. Furthermore, this case underscores the importance of maintaining a high index of suspicion for immune disorders in young patients with liver abnormalities, even in the absence of typical serologic markers. Further studies are needed to better understand the underlying mechanisms in seronegative patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Younossi ZM, Bernstein D, Shiffman ML, et al. Diagnosis and Management of Primary Biliary Cholangitis. Am J Gastroenterol. 2019;114(1):48-63.

[2] Trivella J, John BV, Levy C. Primary biliary cholangitis: Epidemiology, prognosis, and treatment. Hepatol Commun. 2023 Jun 2;7(6).

[3] Faisal MS, Gonzalez HC, Gordon SC. Primary biliary cholangitis. Clin Liver Dis. 2024;28(1):63–77.

[4] Matli VVK, Dies DF, Pandit S, Wellman G, Morris JD. Distinction between mitochondrial antibody-positive and -negative primary biliary cholangitis. Case Rep Gastroenterol. 2023;17(1):14–20.

[5] Xu Q, Zhu W, Yin Y. Diagnostic value of anti-mitochondrial antibody in patients with primary biliary cholangitis: A systemic review and meta-analysis. Medicine (Baltimore). 2023;102(45).

[6] Leung KK, Hirschfield GM. Autoantibodies in primary biliary cholangitis. Clin Liver Dis. 2022;26(4):613–27.

[7] Shaker M, Mansour N, John BV. Primary biliary cholangitis in males. Clin Liver Dis. 2022;26(4):643–55.

[8] Colapietro F, Bertazzoni A, Lleo A. Contemporary epidemiology of primary biliary cholangitis. Clin Liver Dis. 2022;26(4):555–70.

[9] Zhu Y-J, Li J, Liu Y-G, Jiang Y, Cheng X-J, Han X, et al. Role of biochemical markers and autoantibodies in diagnosis of early-stage primary biliary cholangitis. World J Gastroenterol. 2023;29(34):5075–81.

[10] Cançado GGL, Braga MH, Ferraz MLG, Villela-Nogueira CA, Terrabuio DRB, Cançado ELR, et al. Anti-mitochondrial antibody-negative primary biliary cholangitis is part of the same spectrum of classical primary biliary cholangitis. Dig Dis Sci. 2022;67(7):3305–12.

[11] Juliusson G, Imam M, Björnsson ES, Talwalkar JA, Lindor KD. Long-term outcomes in antimitochondrial antibody negative primary biliary cirrhosis. Scand J Gastroenterol. 2016;51(6):745–52.

[12] Onofrio FQ, Hirschfield GM, Gulamhusein AF. A practical review of primary biliary cholangitis for the gastroenterologist. Gastroenterol Hepatol (N Y). 2019;15(3):145–54.