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**Case Report**

# PRIMARY BILIARY CHOLANGITIS DIAGNOSIS IN A SERONEGATIVE 19-YEAR-OLD WOMAN

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**ABSTRACT**

Primary biliary cholangitis (PBC) is an autoimmune disease that destroys small bile ducts, culminating in liver failure. It typically affects middle-aged, Caucasian women. Most cases have detectable antimitochondrial antibodies. The authors report a case of a 19-year-old, African, female patient who sought medical help due to scleral icterus, asthenia, and choluria. Abdominal imaging displayed a cirrhotic liver, dilated bile ducts, gallstones, gall bladder wall thickening and a massive splenomegaly. Due to the splenomegaly and epidemiological background, screening for infectious and hematological diseases was preemptory, followed by immune and genetic diseases, which were negative. Hepatic biopsy revealed the unlikely diagnosis of advanced-stage primary biliary cholangitis. Massive splenomegaly as an initial presentation of PBC is rare, as is the absence of serum antibodies. Since prevalence of PBC is rising, high suspicion during diagnosis should be kept, even for young patients, especially when early diagnosis and appropriate treatment, increase liver transplant-free survival. Severity of disease might be higher in African patients.



## 1. Introduction

Primary Biliary Cholangitis (PBC) is a chronic cholestatic disease with a progressive course. The rate of progression varies from years to decades, depending on individual characteristics [1]. It mainly affects women, and most are diagnosed between the ages of 30 and 50 [2]. PBC prevalence appears to be increasing, being higher in northern Europe and North America [1,3], and diseased severity seems to be higher in Black and Hispanic Americans [4]. The diagnosis of PBC is established when two of the following three criteria are met: biochemical evidence of cholestasis with ALP (alkaline phosphatase) elevation; presence of AMA (antimitochondrial antibody), or other PBC-specific autoantibodies, sp100 or gp210, if AMA are negative and/or histologic evidence of nonsuppurative destructive cholangitis with destruction of interlobular bile ducts [1].

AMA is a useful tool to diagnose PBC, making liver biopsy often unnecessary. Nevertheless, liver biopsy not only confirms the diagnosis, but it also provides useful information regarding the disease stage and prognosis [5].

In this case report, we describe the case of a 19-year-old African woman with advanced-stage PBC, accompanied by a massive splenomegaly and negative PBC-specific autoantibodies.

We consider it relevant to report this case, because clinicians should be aware of the rising prevalence of this disease, it's atypical presentation with splenomegaly, undetectable autoantibodies, young age of onset, and heterogenous disease severity.

## 2. Case presentation

A 19-year-old female patient of African origin (Cape Verde), living in Portugal for the past 18 months and a medical history of uncomplicated hepatitis A infection at the age of 15. She was admitted to the emergency department due to a recent onset (one week prior) scleral icterus, asthenia, and choluria. She denied other accompanying symptoms, namely fever, vomiting, and abdominal pain. Upon physical examination, palpable, non-painful hepatosplenomegaly was present. Laboratory findings upon admission are shown in Table 1.

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An abdominal CT scan was ordered, followed by an MRI of the bile ducts, showing an enlarged cirrhotic liver with dilated intra and extra hepatic bile ducts, gallstones present in its lumen, a gall bladder with a parietal wall inflammatory thickening – 9 mm, portal vein of normal gauge, and a splenomegaly with a volume of 1600 $cm^3$, as shown in Figures 1 and 2, without evidence of collateral circulation.

The patient was admitted for further investigation with the diagnosis of cholestatic jaundice with acute liver failure and splenomegaly. Treatment with vitamin K and I.V. fluids was initiated. Endoscopic retrograde cholangiopancreatography was later performed. Sludge and stones were successfully removed, revealing irregular tortuous small bile ducts.

Due to the patient's epidemiological background and massive splenomegaly, infectious diseases were excluded, namely hepatotropic viruses and parasites, shown in Table *2*. Blood, urine, and stool cultures were sterile, and bone marrow aspirate was also performed to exclude Leishmaniosis.

Following the work-up for splenomegaly, hematological disease was suspected. Thus, Sickle cell disease and neoplasia (solid organ and hematological) were excluded with a full body CT scan and blood work.

Autoimmune disease was also suspected, but blood tests were negative, namely AMA antibodies, and others (anti-glycoprotein-210, IgG anti-sp100, double-stranded deoxyribonucleic acid, anti-liver-kidney microsomal, lupus anticoagulant, anti-cardiolipin antibodies, IgA, IgM and IgG anti-tissue transglutaminase, IgM and IgG liver cytosolic antigen type 1, IgM and IgG soluble liver antigen antibody).

As part of the investigation, due to the enlarged spleen, young age, childish features, enlarged tonsils and menarche at the age of 15, although no family history of rare diseases, genetic study was performed for variants of Gaucher disease, which was also negative.

At last, liver biopsy was performed, and anatomopathological report was compatible with Ludwig's Classification Stage III Primary Biliary Cholangitis.

Treatment with ursodeoxycholic acid was started. With a Model for End-Stage Liver Disease (MELD) score of 23 points, the patient was referred to a hepatic transplant center and discharged.

After 24 months, upon follow-up the patient remained clinically stable, with a slight improvement in MELD score – 21 points. Due to pre-transplant work-up, a colonoscopy was performed confirming the diagnosis of Inflammatory bowel disease (IBD).

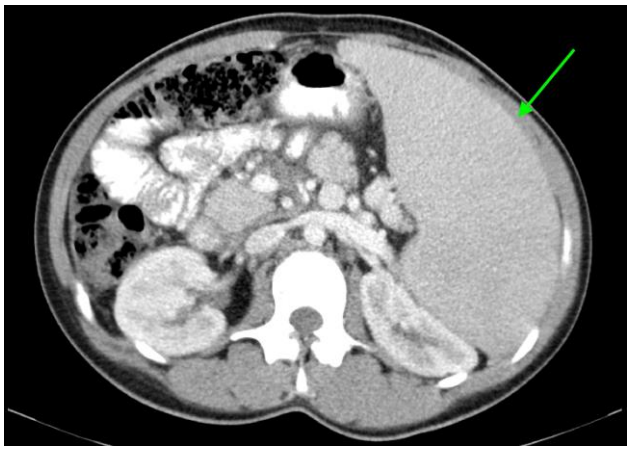

**Figure 1. Axial section of abdominal CT scan. (Legend: Green arrow points to massive splenomegaly)**

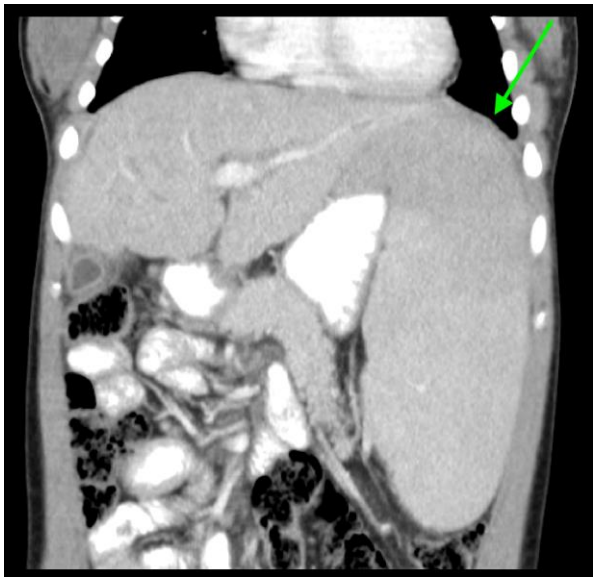

**Figure 2. Coronal section of abdominal CT scan. (Legend: Green arrow points to massive splenomegaly)**

| *Laboratory tests* | Results | Reference values |
|---|---|---|
| *Hemoglobin (g/dL)* | 10.8 | 12–16 |
| *Leukocytes (/µL)* | 4,200 | 4,000–11,000 |
| *Platelets (/µL)* | 100,000 | 150,000–400,000 |
| *Prothrombin time (seconds)* | 22.6 | 9.45–13 |
| *International normalized ratio* | 2.04 | 0.8–1.2 |
| *Total bilirubin (mg/dL)* | 44.0 | <1.2 |
| *Direct bilirubin (mg/dL)* | >15.0 | <0.6 |
| *Aspartate aminotransferase (UI/L)* | 145 | <34 |
| *Alanine aminotransferase (UI/L)* | 107 | <55 |
| *Alkaline phosphatase (UI/L)* | 248 | <150 |
| *Lactate dehydrogenase (UI/L)* | 123 | 120–246 |
| *C-reactive protein (mg/L)* | 12.0 | <0.5 |
| *Sedimentation rate (mm)* | 102 | 2-8 |

**Table 1. Laboratory blood findings upon admission.**

| *Infectious agents* | Results | |
|---|---|---|
| *Hepatitis A* | IgG positive | IgM negative |
| *Hepatitis B* | HbsAg positive | Anti-Hbc Negative |
| *Hepatitis C* | | Negative |
| *Hepatitis D* | | Negative |
| *Hepatitis E* | | Negative |
| *HIV type I/II* | | Negative |
| *Cytomegalovirus* | IgG positive | IgM negative |
| *Epstein-barr virus* | IgG positive | IgM negative |
| *Toxoplasma gondii* | IgG positive | IgM negative |
| *Treponema pallidum* | | Negative |
| *Visceral leishmania* | | Negative |
| *Fasciola hepatica* | | Negative |
| *Malaria blood smear* | | Negative |
| *IGRA* | | Negative |

**Table 2. Infectious agents blood screening results.**

## 3. Discussion

According to Dahlan Y, Smith L, Simmonds D, et al. PBC onset has been reported in patients as young as 15 years of age and diagnosis was confirmed by the presence of AMA antibodies and liver biopsy [2].

In fact, only 5–10% of the cases are seronegative for antimitochondrial antibodies [1]. Liver biopsy is unnecessary in the presence of AMA antibodies and raised serum alkaline phosphatase, after excluding other potential factors (drug reactions, overt bile obstruction, other diseases) [6]. Nevertheless, liver biopsy despite being an invasive technique, can stage and confirm the diagnosis, and rule out overlapping autoimmune hepatitis. As presented in this case, it provided the diagnosis.

Even if African ethnicity might be a risk factor for increased disease severity, the authors were surprised about the insidiousness of the course of the disease in this young patient, as she already presented liver failure at the time of diagnosis, contradicting the pattern observed over the past decades of older age at diagnosis alongside a reduced disease severity [3,7]. Nonetheless, it can have a favorable outcome if diagnosed early-on and treatment with ursodeoxycholic acid is started promptly, improving liver transplant-free survival [8].

Splenomegaly is part of the disease manifestation, being present in the non-cirrhotic histologic stage and persisting thereafter, with a reported weight range of 450 +/- 224g [9]. In this case, the patient's spleen was approximately 1680g, and without evidence of portal hypertension, which we found intriguing. The presence of a massive splenomegaly made the differential diagnosis further challenging, as we felt obliged to excluded infectious (e.g., hepatotropic virus and Fasciola hepatica), hematological (e.g., lymphoma), and genetic diseases (e.g., Gaucher disease) [10-11].

Furthermore, IBD is not usually associated with PBC, but when it is, it is usually diagnosed before or at the time of PBC diagnosis, at a young age and tends to affect more males than females (ratio 2:1). [12]. In this case, we can't exclude if IBD was present at the time of PBC diagnosis, as the patient had no complaints and colonoscopy was performed successively upon follow-up.

It is yet to be known, which other autoantibodies could be responsible for this disease, and whether there is a relationship between a past Epstein–Barr virus, Cytomegalovirus [13], or even Hepatitis A virus infection as the immunological trigger for PBC/IBD.

As stated previously, the prevalence of PBC is rising [1], therefore, clinicians should be aware that it can present at a very young age, with varying degrees of disease severity and different manifestations.

## 4. Conclusions

This case focuses on a 19-year-old African woman presenting a cholestatic pattern with hepatocellular injury and a massive splenomegaly. Since AMA were negative, the diagnosis of advanced stage PBC was made after liver biopsy. Further on, IBD was also diagnosed. Since PBC prevalence is rising, high suspicion should be maintained, even at a very young age. Massive splenomegaly as an initial presentation of PBC is rare, as is the absence of PBC specific antibodies. These, can delay and throw off the etiological investigation, making liver biopsy crucial. Disease severity might be higher in African patients, and other immune triggers are yet to be identified. Early diagnosis and appropriate treatment increase liver transplant-free survival.

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