ANTI-MITOCHONDRIAL ANTIBODY NEGATIVE PRIMARY BILIARY CIRRHOSIS: A CASE REPORT

Aliena Badshah¹, Mohammad Humayun²

¹,² Department of Medicine, Khyber Teaching Hospital, Peshawar - Pakistan.

Address for correspondence: Dr. Aliena Badshah
Trainee Medical Officer, Department of Medicine, Khyber Teaching Hospital, Peshawar - Pakistan.

Email: alienabadshah@yahoo.com

Date Received: June 11, 2016
Date Revised: September 18, 2016
Date Accepted: September 28, 2016


ABSTRACT

Primary Biliary Cirrhosis (PBC) is an idiopathic, cholestatic destruction of intra-hepatic microscopic bile ducts. Up to 80% of the patients presenting with PBC are females. Patients usually present with fatigue, pruritis and jaundice. Suspicion of PBC arises when cholestasis and cirrhosis are present in middle-aged women. Anti-mitochondrial antibodies (AMA) are present in 95% of the patients. AMA is considered the serological hallmark of PBC, but may be absent in a proportion of these patients. We hereby present a case of AMA-negative PBC.

Key Words: Primary biliary cirrhosis, Splenomegaly, Anti-mitochondrial antibodies, Alkaline phosphatase

INTRODUCTION

Primary biliary cirrhosis (PBC) is an idiopathic chronic inflammatory, cholestatic, primarily T cell-mediated destruction of intra-hepatic microscopic bile ducts¹. The clinical observation of a broad array of immune-mediated symptoms and phenomena suggests the disease to be of autoimmune etiology, in the course of which progressive and irreversible destruction of small interlobular and septal bile ducts progressively and irreversibly ensues¹.

Up to 80% of the patients presenting with PBC are females. Patients usually present with fatigue, pruritis and jaundice. Female patients may develop amenorrhea and this may be the presenting complaint in some patients². Suspicion of PBC arises when cholestasis and cirrhosis (which occurs over a course of years or decades) are present in middle-aged women. Elevated alkaline phosphatase and gamma glutamyl transferase are most commonly seen. Anti-mitochondrial antibodies (AMA) directed against the E2 subunit of pyruvate dehydrogenase (PDH-E2) which is a member of the inner mitochondrial membrane-expressed oxoacid dehydrogenase complex, and ketoglutarate dehydrogenase are present in 95% of the patients³. Some patients are AMA-negative but diagnosed on liver biopsy. We hereby present a case of AMA-negative PBC.

CASE REPORT

A 12 year old female patient presented from Khost, Afghanistan with a 1 year history of slowly progressive abdominal pain. The pain was episodic, stabbing, and localized to left and right hypochondrium. It was aggravated post-prandially and relieved with pain killers but only temporarily. She had suffered from high grade fever associated with sweating for 3 days back in Khost for which she had taken 2 cycles of oral anti-malarials. She had experienced one episode of epistaxis, but no bleeding from the gums or oral mucosa, eyes, ears, hematuria or hematocochezia. She had never experienced enlarged lymph nodes. She attained menarche at the age of 10 (now 12 years of age), but had developed secondary amenorrhea for the last 1 year. She had 3 other siblings, one of whom expired from some hematological disorder and had splenomegaly. The patient had also recovered from a short-lived episode of jaundice in the recent past. Rest of the family and past medical / surgical history were unremarkable.

On examination, her BP=110/60mmHg, pulse=90/min, temperature =98°F. She was pale, but had no jaundice, scratch marks, petechial haemorrhages or palpable lymphadenopathy. Abdominal examination revealed hepatomegaly with liver span of 23cm, smooth contour, regular margins, no thrill or bruit; and splenomegaly, 4 finger breadth below left hypochondrium, with no thrill or bruit. There was no evidence of ascites, and her bow-
el sounds were audible. Cardiovascular, respiratory and central nervous system examinations were unremarkable.

Investigations revealed a hemoglobin =9.2g/dl, White cell count =5000/cmm (neutrophils=20%, lymphocytes=70%, monocytes=08%, eosinophils=02%), platelet count = 206,000/cmm, hematocrit =30.2, mean corpuscular volume =87.3fl, anisocytosis, polychromasia and a reticulocyte count =2%. Serial tests for malarial parasite were negative. Alkaline phosphatase =5515 IU/liter, bilirubin =1.60 mg/dl, alanine aminotransferase =35 U/L, random blood sugar=97 mg/dl, creatinine=0.82 mg/dl, blood urea=55mg/dl, lactate dehydrogenase =579mg/dl (>35mg/dl), coombs test (direct/indirect) =negative. Urine routine examination was negative for sugar, showing traces of albumin, pus cells =6-8/hpf, RBCs =4-6/hpf.

A bone marrow biopsy was planned which revealed hyper-cellularity with active erythropoiesis, myelopoiesis, lymphopoiesis and thrombopoiesis. Reticulocyte count =1%. Serum ferritin =166ng/ml (upto 140ng/ml). Hemoglobin electrophoresis was normal. HBsAg =reactive. Anti HCV =non-reactive. Serum albumin =3.1g/dl (3.2-5.0), prothrombin time =13/14sec, activated partial thromboplastin time =28/28sec, bleeding time =3 min, 25 sec; clotting time =4 min, 50 sec.

Ultrasound abdomen and pelvis showed massive enlarged liver, measuring 23.4cm, and having no focal mass. Parenchymal echogenicity was increased, echo-pattern was homogenous, no duct dilatation was seen, and the contour was smooth. Common bile duct measured normal (03mm). Spleen was also grossly enlarged, measuring 16cm with normal echo-pattern, and no focal lesion. There was no ultrasonic evidence of para-aortic lymph node enlargement or free fluid in the peritoneal cavity.

X-rays of the pelvis and long bones were normal. Gamma glutamyl transferase =303U/L (11-50); this confirmed liver as the source of raised alkaline phosphatase. Anti-nuclear antibodies were positive in a nucleus granular pattern. Anti-smooth muscle antibodies, Anti-mitochondrial antibodies and Anti-liver kidney muscle (LKM) antibodies were negative by Western immunoblot. Magnetic resonance cholangio-pancreatography (MRCP) was inconclusive owing to compressed intra-hepatic biliary channels (figure 1).

Ultimately, a liver biopsy was planned. Liver biopsy section showed liver cores showing 14 portal tracts. The portal tracts were expanded by dense lymphocytic infiltrate and diminished bile ducts (ductopenia) were seen. Four of the portal tracts showed non-caseating granulomas. Few portal tracts showed mild to moderate peri-portal inflammation. The hepatic lobules showed foci of lytic necrosis (3/10 hpf). No confluent or peri-cel-ular fibrosis was identified. Immuno-histochemical staining was positive for CK 19 which suggests loss of bile ducts. Histo-chemical staining was negative for acid fast bacilli and fungi. Serology was correlated (ANA positive, anti-smooth, anti-mitochondrial, anti-LKM1 antibodies negative). The histology was reported as highly suggestive of primary biliary cirrhosis despite non-supportive serology. The patient was therefore diagnosed as a case of Anti-mitochondrial antibody (AMA) negative primary biliary cirrhosis (PBC).

The patient was prescribed prednisolone (1mg/kg body weight), and ursodeoxycholic acid and advised follow up after 6 weeks.

**DISCUSSION**

AMA is considered the serological hallmark of PBC, but may be absent in a proportion of these patients. AMA-negative PBC is also called auto-immune cholangitis.

A study was carried out to assess sensitivity and specificity of the currently available techniques for AMA detection in a large series of PBC patients and controls. It analyzed clinical and immunological features of patients according to the AMA status. In PBC patients, Western immunoblot detects AMA significantly more...
often than indirect immunofluorescence on HEp-2 cells (85% versus 72%, \(P=0.02\)) or rodent tissue sections (71%, \(P=0.01\))^5.

Western immunoblot or ELISA should be regarded as first-line assay for the detection of AMA. Up to 15% of PBC patients are consistently AMA-negative, yet they share the same clinical, biochemical and histological features of AMA-positive PBC^4,6. AMA is commonly detected with assays such as indirect immunofluorescence (IFL) on frozen sections of rat liver kidney and stomach sections and Hep2 cell lines, and only seldom by Western Immunoblot (W-IB) using sub-mitochondrial particles of bovine or porcine heart as antigen source, and ELISA with the recombinant mitochondrial target proteins^7.

In AMA-negative PBC, a biopsy is indicated to contribute to the establishment of diagnosis; in the presence of AMA, histology is used primarily for staging of cirrhosis and is not necessary^4. Given the high specificity and sensitivity of AMA as immunoserological hallmark of PBC, the determination of the best methodological approach for AMA detection is crucial.

**REFERENCES**