

# Rare Associations Of Primary Biliary Cirrhosis: A Review Article

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## Abstract

Primary Biliary Cirrhosis (PBC) is the most common chronic cholestatic liver disease in adults in the United States (16). There are several rare conditions associated with PBC. We review all reported associations and present our own case experience. The list of these conditions is extensive but the numbers of cases are limited. Our aim is to make the physicians aware of these rare associations and help in the diagnosis.

A few cases of multiple myeloma in early stages of PBC have been described (3). We report a patient who presented with severe coagulopathy in whom antimitochondrial antibodies were positive. Despite normal liver transaminases and alkaline phosphatase as in previously reported cases (13), liver biopsy showed advanced cirrhosis and histological changes consistent with PBC. A concurrent diagnosis of multiple myeloma IGG type was made by bone marrow biopsy. A possible pathophysiologic mechanism is described.

## INTRODUCTION

The etiology of Primary Biliary Cirrhosis remains unclear. Several lines of evidence support an autoimmune pathogenesis: the presence of activated T cells in areas of bile duct destruction, the occurrence of highly specific auto-antibodies that react with antigens localized on biliary epithelial cells, and the association of PBC with other disorders thought to be autoimmune in nature (15). Genetic and environmental factors have been implicated (15). Primary biliary cirrhosis (PBC) represents the most common chronic cholestatic liver disease in adults in the United States (15). It has been described in association with other entities. We report a case of PBC and multiple myeloma and conduct a review of available literature on rare conditions associated with PBC.

## PRIMARY BILIARY CIRRHOSIS ASSOCIATED WITH MULTIPLE MYELOMA

### CASE HISTORY

A 68-year-old woman was admitted to the Bronx Lebanon Hospital with complaints of dizziness, near syncope and lower back pain. There was no history of fatigue, tiredness, pruritus or any toxic habits. She had a history of hypertension and bronchial asthma.

On admission physical examination revealed multiple ecchymotic skin lesions most prominent on the abdominal wall and thighs. Multiple subcutaneous nodules were noted in the abdominal wall as well. The liver was not palpable and neither shifting dullness nor peripheral edema was found.

## LABORATORY DATA

Laboratory findings on admission included AST: 24 u/l (NV: 9-48 u/l), ALT: 17 u/l (NV: 5-40 u/l), alkaline phosphatase: 129 u/l (NV: 53-128 u/l), total bilirubin: 1.0 (NV: 0.2-1.2 mg/dl), direct bilirubin: 0.4 (NV: 0.0-0.3 mg/dl), platelet count: 208 k/ $\mu$ l (NV: 150-350 k/ $\mu$ l), and albumin: 2.9g/dl (NV: 3.4-4.8 g/dl). Antinuclear antibodies were negative as were tests for hepatitis B and C viruses. Rheumatoid Factor was normal. Serum protein electrophoresis (SPEP) showed a spike in the gamma region with a total protein of 8.6 and gammaglobulins of 39.6%.

Urine protein electrophoresis showed no monoclonal protein.

Quantification of the immunoglobulins in the serum revealed the following values: IGG-4750 mg/dl (N: 844-1912 mg/dl), IGM 100mg/dl (N: 50-196 mg/dl), IGA 191mg/dl (N: 68-423 mg/dl). Alpha-feto-protein and carcino-embryonic

antigen were normal.

The coagulation profile revealed a decrease in factors V, VII, IX consistent with liver disease as shown in table 1.

**Figure 1**

Table 1: Summary of coagulation factors in this patient.

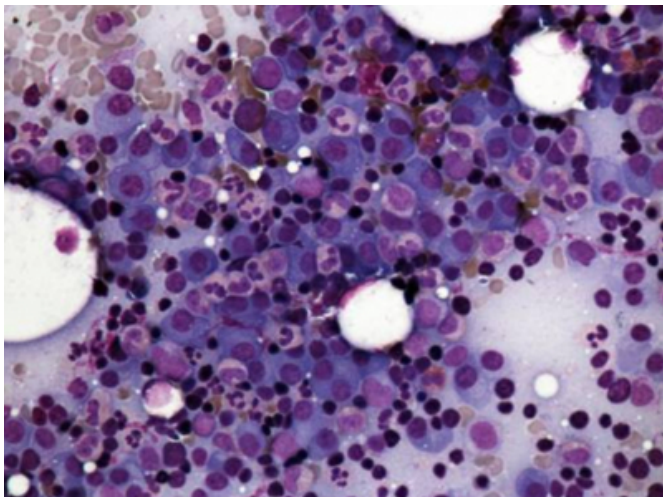
Factor V	5 (N: 50-150%)
Factor VII	22 (N: 50-150%)
Factor IX	75 (N: 50-150%)
Factor X	45 (N: 50-150%)

A computed tomography of the abdomen revealed a dense nodular liver suggestive of cirrhosis. There was no ascites. Multiple heterogeneous masses were seen in the RUQ, peri-pancreatic region and in subcutaneous tissues of the anterior abdominal wall.

Biopsies of the abdominal wall nodules and a right axillary lymph node showed fat necrosis and reactive lymphadenopathy, respectively. Bone marrow biopsy showed plasmocytosis of 28% consistent with the diagnosis of multiple myeloma. (Fig. 1-a).

**Figure 2**

Figure 1a: Bone marrow aspirate with sheets of plasma cells



The patient was started on 40 milligrams of dexamethasone for treatment of multiple myeloma. The patient`s clinical condition and coagulopathy improved. Table 2 summarizes the effects of prednisone treatment on laboratory in this patient.

**Figure 3**

Table 2: Effect of prednisone therapy on laboratory values

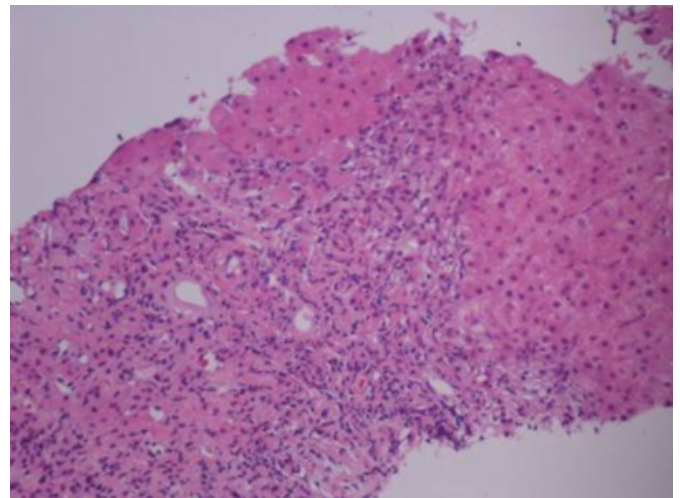
	Pre-treatment	Post-treatment
Hb/ Hct	9.3/ 28*	10.8/31.4
AMA	3 +*	Negative
Prothrombin time/ INR	24.1/ 2.5*	11.7/1.1
B2 microglobulin	4.48 mg/dl*	2.66 mg/dl
Gammaglutamyltranspeptidase (Normal 8-54 I/U)	205 I/U*	138 I/U

\*Abnormal value.

A CT guided liver biopsy showed complete loss of acinar architecture with nodule formation. The portal tracts showed ductopenia, ductular proliferation, chronic inflammatory cell infiltrate and Mallory bodies. No granulomas were seen. The histological features were consistent with PBC (Fig. 1-b). Masson trichrome stain showed increased portal fibrosis with established cirrhosis (Fig. 1-c).

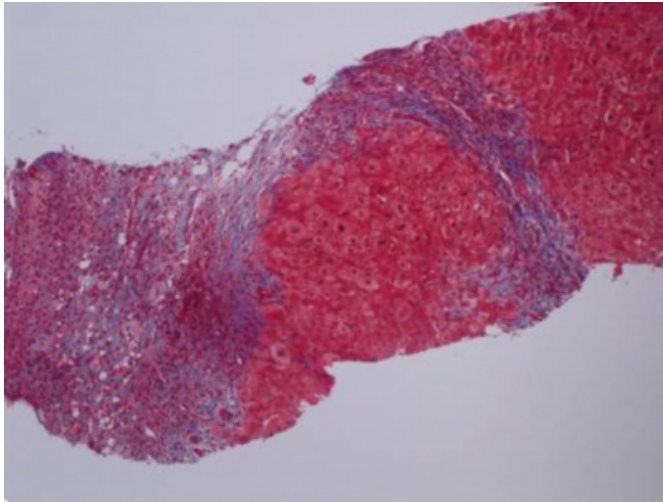
**Figure 4**

Figure 1b: Liver cirrhosis: A widened portal tract with ductopenia and chronic inflammatory cell infiltrate (Hematoxylin and eosin)



**Figure 5**

Figure 1c: Liver cirrhosis: Portal fibrosis with hepatocellular regenerative nodules (Masson Trichrome stain)



Biopsy of the peripancreatic lymph nodes was unsuccessful, revealing only fibrin, blood and minute fragments of fibrous tissue, but no pancreatic or lymphoid tissue obtained.

The patient was discharged home on a tapering dose of dexamethasone. She was readmitted one week after discharge due to bleeding from the lymph node biopsy site in the abdomen. She was observed, but no specific treatment was given. Hospital stay was unremarkable. Upon discharge her INR was 1.7.

Currently she is stable and is followed at the Oncology clinic.

Pathogenesis and Diagnosis: Antimitochondrial antibodies are the serologic hallmark of PBC. Most AMA react against the dihydrolipoamide acetyltransferase component (E2 subunit) of pyruvate dehydrogenase complex (PDC-E2) (7,8,9,10,16). PDC-E2-reacting antibodies are present in 90% to 95% of PBC sera (16).

There are other AMA antibodies present, like the ones directed against the E2 unit of the branched-chain 2-oxo-acid dehydrogenase complex (BCOADC-E2), the E2 subunit of the 2-oxo-glutarate dehydrogenase complex (OGDC-E2), the E1 $\beta$  subunit of PDC and the dihydrolipoamide dehydrogenase-binding protein (E3BP), but these are much less frequent (16)

T lymphocytes, CD4+ and CD8+, are present in high concentration in the portal triads of patients with PBC, often surrounding and infiltrating necrotic bile ducts. Auto-reactive T lymphocytes from PBC patients are specific for

PDC-E2. PDC-E2, normally found in the inner mitochondrial membrane of all cells, is aberrantly expressed in the luminal surface of bile duct epithelial cells only in patients with PBC (5).

PBC is the only disease in which there are B- and T-cells that are auto-reactive against PDC-E2.

The serum aminotransferases may be normal or slightly elevated, but rarely are increased more than fivefold above normal. Serum alkaline phosphatase is almost always elevated, however there are case reports of patients presenting with normal values (13).

The serum bilirubin concentration may be normal but increases in almost every patient with disease progression.

The number of eosinophils may be increased in the blood and liver of PBC patients, which suggests a possible pathogenic role in this disease. Other significant laboratory abnormalities seen in PBC patients are increase cholesterol levels and positive antinuclear antibodies in up to fifty and seventy percent of PBC patients respectively.

## DISCUSSION

There are several entities that have commonly associated with PBC (table 3) and other less common diseases have also been reported, MM is among them. Extrahepatic malignancies typically B cell lymphomas have been described in patients with primary biliary cirrhosis (PBC) (1). Polyclonal hypergammaglobulinemia is common in chronic liver disease (1,2), but only in rare instances has monoclonal gammopathy been found (1,2).

**Figure 6**

Table 3: Commonly accepted associations with primary biliary cirrhosis

Disease	Frequency (%)
Keratoconjunctivitis sicca (Sjögren's syndrome)	72-100
Autonomic dysfunction (23)	81 - 100
Renal tubular acidosis	50-60
Gallstones	33
Scleroderma and its variants (16, 55)	15-19
Autoimmune thyroiditis	15-20
Arthritis/arthropathy	4-42

Hyper-gammaglobulinemia in PBC is thought to be related to polyclonal B cell activators, defects of hepatic clearance of antigens from the gut, or immunologic imbalance between lymphocyte suppressor and helper functions (1,2).

A decreased in suppressor T-cell function in patients with

PBC has been demonstrated (3). B cell hyperactivity with enhanced production of immunoglobulins or autoantibodies appears to be related to this T-cell dysfunction (3).

Monoclonal gammopathy occurring in the course of chronic liver disease is rare and in most cases benign (2). Only a few cases of PBC associated with multiple myeloma and other lymphoproliferative disorders have been reported (1,2,3,4,14). The precise mechanisms of association of PBC and multiple myeloma are not clear, but alterations of both cellular and humoral immune functions have been suggested to play a major role in its pathogenesis (1,4). Transformation of polyclonal to monoclonal gammopathy has also been reported.

There are conflicting data as to whether serum GGT has better sensitivity for hepatobiliary disease than alkaline phosphatase or leucine aminopeptidase (11,12).

The liver biopsy in our case was consistent with advanced cirrhosis, this differs from the early stages of the disease reported in the four cases that had biopsies done previously (2,3,4). The myeloma, as in six out of the eleven previously reported cases had a monoclonal protein of IgG type (1,2,3,4). Our case had a lambda light chain. Of interest our patient had marked eosinophilia 10% (NV: <6) and 1.34 absolute count (NV: 0.05-0.25K/uL).

The reason for the dramatic improvement of the coagulopathy with steroid treatment remains unclear. There are two reports of improvement of serum markers of PBC, specifically alkaline phosphatase and serum Ig M levels after chemotherapy of myeloma (1), another case reports improvement also on coagulation profile of PBC patient after myeloma treatment (13) with melphalan and prednisone. Our case is unique in the dramatic response of coagulopathy and seroconversion of AMA to treatment with prednisone only. It also differs from the majority of previously reported cases of this rare association in the presence of normal alkaline phosphatase, despite an elevated gammaglutamyl transpeptidase. Table 3 summarizes the commonly accepted associations of PBC and table 4 the rare associations found in our review.

**Figure 7**

Table 4: summarizes the rare associations and the number of cases found in the literature.

Condition	Cases reported	Ref. No.
Acute leukemia	2	16
Microscopic polyangitis	2	17,21
Hepatic inflammatory pseudotumor	2	18, 57
SPIDDM	1	19
Takayasu's arteritis	1	20
Evans syndrome	1	22
Pure white cell aplasia	1	24
Syringomyelia	2	26
Bronchitis Obliterans	1	27
Autoimmune hemolysis	1	28
Bullous pemphigoid	4	29
Anterior Uvetis	1	30
Idiopathic myelofibrosis	1	14
Idiopathic retroperitoneal fibrosis	2	31,32
Pernicious anemia	5	33,34,35
Overlap collagen vascular disease	1	36
Turner syndrome, aquired von Willebrand disease, IBD and PBC	1	37
Cutaneous T cell lymphoma	1	38
Minimal change glomerulonephritis	1	39
Ulcerative colitis	19	25, 40, 56
Reynaud's syndrome	1	41
Non-Hodgkin's lymphoma	1	42
Polymyositis	22	43
Cutaneous polyarteritis nodosa	1	44
Hepatic marginal zone B-cell lymphoma, Primary hepatic lymphoma	3	45,46,47
Lichen Planus	25	48
Myasthenia gravis	2	49,56
Type II autoimmune polyglandular syndrome	1	50
Chronic thyroiditis	2	51,52
Autoimmune hypophysitis	1	53
SLE	1	54
Multiple myeloma	11	1,2,58,3,4,59,12,13
Cutaneous amyloidosis	1	60

**CONCLUSION**

Polyclonal gammopathy is common in the course of chronic liver disease but one should be aware of the possibility of an associated monoclonal gammopathy.

Monoclonal gammopathy is rare in chronic liver disease and if present we suggest that malignancy be ruled out and multiple myeloma be considered in the differential diagnosis. Alkaline phosphatase may be normal in the course

of advanced primary biliary cirrhosis, as in this case, and obtaining gammaglutamyltranspeptidase may be of value. Certain laboratory parameters may be expected to improve specifically coagulation profile, transaminases and AMA titer after treatment for multiple myeloma in the setting of its association with primary biliary cirrhosis.

Glossary terms: PBC (Primary biliary cirrhosis), ANA (antinuclear antibodies), AMA (antimitochondrial antibodies), SPIDDM (slowly progressive insulin dependent diabetes mellitus)

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