RESEARCH PAPER | Medical Science | Volume : 3 | Issue : 9 | Sept 2013 | ISSN - 2249-555X

Primary Biliary Cirrhosis Presenting as Immune Hemolytic Anemia: A Case Report

KEYWORDS: primary biliary cirrhosis, autoimmune hemolytic anemia, anti-mitochondrial antibody.

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ABSTRACT *The association between primary biliary cirrhosis (PBC) and autoimmune hemolytic anemia (AIHA) has rarely been reported in the literature. To this date, less than twenty five cases have been described. We came across a case of immune hemolytic anemia manifesting in a 21 year old female presenting with jaundice and lethargy. On examination besides pallor and icterus, no significant findings were elicited on clinical examination. The peripheral smear showed features consistent with hemolysis. The patient was placed on corticosteroids but the 6 week follow up did not show a rise in hemoglobin level. The bone marrow examination showed erythroid hyperplasia with few "Tart" cells. We advised a work-up for autoantibodies, which revealed positivity for anti-mitochondrial antibody (AMA). The patient was placed on immunemodulators and supportive therapy and has showed clinical and hematologic recovery.*

Introduction:
Primary biliary cirrhosis is a chronic, progressive, and often fatal cholestatic liver disease, characterized by the destruction of intrahepatic bile ducts along with portal inflammation and scarring, and the eventual development of cirrhosis and liver failure. Because cirrhosis develops only after many years, the patients are seldom diagnosed early in their course.[1, 2] Immune hemolytic anemia is characterized by increased unconjugated bilirubin levels and a positive direct Coomb's test. The secondary causes of hemolysis have been conventionally associated with hematological malignancies, drugs and autoimmune disorders. But an association of primary biliary cirrhosis and immune hemolytic anemia has seldom been reported in literature. This feature may potentially be an early feature of the underlying disorder. We report a case which we encountered recently and was a diagnostic challenge.

Case report:
A 21 year old female patient presented to the medicine department with a presenting feature of fatigue and weakness. The symptoms had gradually increased since 4 months. There was no history of fever or bleeding. She also complained of jaundice. The menstrual history was unremarkable. On admission, the physical examination revealed mild icterus and conjunctival pallor. No organomegaly or lymphadenopathy was noted. Laboratory data revealed severe anemia: hemoglobin (Hb) 7.4 g/dl; whereas the white blood cell count (WBC): 4300/mm^3 and blood platelet count : 134x10^3 mm^3 were mildly reduced. Reticulocyte count was increased at 6.3% (range 0.2–2.0%).

The peripheral smear examination showed sparsely distributed RBCs with normocytic normochromic anemia. The smear also showed spherocytes and polychromasia (figure 1). The leucocyte and platelet counts were consistent with the machine dataBased on the available parameters, we advised a hemolytic work up consisting of Coomb's test and liver function tests.

The biochemical parameters showed an increase in total serum bilirubin 9.2mg/L. The indirect fraction of bilirubin was measured at 6.8mg/L. The transaminases; ALT and AST were mildly deranged. The albumin and globulin levels were mildly reversed. The enzymes were as follows: alkaline phosphatase 156 IU/L (range 40–160 IU/L) and a raised γ-glutamyl transpeptidase (γ-GT) level: 82 IU/L(range 0–50 IU/L).
The direct coomb's test was negative but the indirect coomb's was weakly positive (anti-IgG); suggesting the presence of antibodies in the serum. Hepatitis B surface antigen and antibody to hepatitis C virus were both negative. Antibodies to both HIV1 and HIV2 were negative. Ultrasonography showed mild hepatomegaly with dilated intrahepatic ducts. Gall bladder was normal.

A final clinical diagnosis of immune hemolytic anemia was made and the patient was placed on low dose corticosteroids. The six week follow up did not show a rise in hemoglobin levels. The reticulocyte count continued to be on the higher side (5.2%). The liver function tests were also deranged. The refractory anemia necessitated a bone marrow examination. The liver biopsy was not conducted.

The bone marrow aspirates showed hypercellular particles with erythroid hyperplasia with an increase in basophilic and orthochromic normoblasts. The myeloid elements were relatively suppressed. Megakaryopoiesis was normal in number and morphology. The lymphoid and plasma cells were unremarkable. The histiocytes were increased with erythrophagocytosis. Few "tart" cells were noted. Activated macrophages with hemophagocytosis were also noted (figure 2). However, no LE cells were seen. Based on the marrow findings, we advised a work-up for systemic lupus erythematosus.

The autoantibody screening panel revealed positivity for both ANA and AMA at a titer of 1:1000. Remaining antibodies were negative. Based on all the tests combined with the clinical profile, a diagnosis of primary biliary cirrhosis associated with an immune hemolytic anemia was rendered.

The patient was placed on high dose corticosteroids and intravenous immunoglobulin therapy. At the time of submitting this article, a two month follow up has shown that her Hb level had recovered to 8.8 g/dl, reticulocyte count had normalized (2.36%), and her liver function had improved.

Discussion:
PBC is a slowly progressive autoimmune disease; characterized by the destruction of intrahepatic bile ducts along with portal inflammation and scarring. The end result is usually liver failure. The diagnosis of PBC is conventionally based on three criteria: elevation of liver enzymes (most commonly ALP and γ-GT), presence of detectable AMA in the serum and liver histologic findings that are compatible with the presence of the disease.[3] The evidence for autoimmune etiology for primary biliary cirrhosis include the aberrant expression of MHC class II molecules on bile duct epithelial cells and accumulation of autoreactive T cells around bile ducts.[4] In addition to antimitochondrial antibodies (AMA), antibod-

Volume : 3 | Issue : 9 | Sept 2013 | ISSN - 2249-555X

ies against other cellular components (nuclear pore proteins, centromeric proteins, among others) are also produced, demonstrating the autoimmune nature of the disease.[5]

AIHA is also an immune disease; punctuated by antibodies directed against autologous red cells. The diagnosis is based on the presence of anemia, signs of hemolysis with reticulocytosis, increased lactate dehydrogenase, elevated indirect bilirubin, and a positive Coombs' test.[6] The association between PBC and other autoimmune diseases has been reported, mostly rheumatoid arthritis, Sjögren syndrome, scleroderma, thyroiditis, membranous glomerulonephritis and celiac disease.[7] But the relationship between AIHA and PBC has seldom been explored despite the autoimmunity being the common denominator. Till date less than two dozen cases have been reported in literature.[8]

The antimitochrondrial antibodies (AMA); considered as specific for PBC are directed against the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2), dihydrolipoamide acetyltransferase. This enzyme complex is located on the inner face of the inner mitochondrial membrane and hence is well shielded from circulating antibodies in undamaged hepatocytes.[9] In patients with AIHA, the immune attack focuses on red blood cells, where mitochondrial autoantigens are not found. So, is this association causal or a mere coincidence? The ever increasing case reports in literature seem to defy the coincidence theory.

In a recently published review article by Yu Tian and colleagues, the authors noted that AIHA occurred after PBC development in most of the patients; although few cases pointed a simultaneous prevalence of both diseases.[8] They also speculated that PBC patients are likely to have some underlying mechanisms which can induce the generation of anti-erythrocyte antibodies.[8,10] The indirect coomb's test was positive in the present case indicating the presence of antibodies directed against the red blood cells. With corticosteroids, hemolysis control was noticed in the previous reported cases of PBC with AIHA .[11-15] The patient was placed on low dose corticosteroids but failed to respond adequately. Thus a bone marrow examination was done. The erythroid hyperplasia was accompanied by activated histiocytes showing phagocytosed leucocytes, called Tart cells. Though not specific for PBC, it led us to a clue as to the possibility of an autoimmune disease.
Antimitochondrial antibodies (AMA) (titers > 1: 40), the serologic hallmark of PBC, are rarely associated with any other clinical condition; hence termed specific. Several AMA subtypes (M1, M3, M5, M6) are seen in patients with syphilis, collagenoses, and drug-induced liver disease.[2, 16] But the specificity increases when AMA is combined with other features such as elevation of serum gamma glutamyl transpeptidase and elevated immunoglobulin M.[16] The elevated liver enzymes and presence of AMA clinched the diagnosis in this case.

Serum bilirubin levels have prognostic value in assessing the prognosis of PBC, but a concomitant hemolysis may lead to erroneous conclusions about the severity of PBC. Since PBC is asymptomatic in about 60% of cases, patients with PBC whose serum unconjugated bilirubin levels rise suddenly should the hematopathologist and clinician about the likelihood of a simultaneous AIHA.

After initiating high dose steroid and intravenous immunoglobulin therapy, the hemoglobin picked up and a two month follow up has shown a favourable response.

Conclusion:
The association between primary biliary cirrhosis (PBC) and autoimmune hemolytic anemia (AIHA) has rarely been reported in the literature. This case could be a rare addition to the ever-increasing revelations on this causal association. Additionally, the early presentation of PBC as immune mediated hemolysis may be a step in the early detection of this autoimmune disease. Futher studies may help to shed light on this phenomenon.

figures:

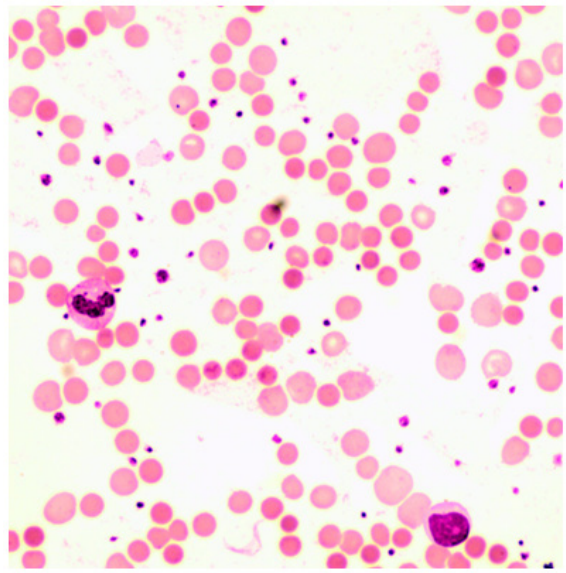

Figure 1: The peripheral smear examination showing features of hemolysis. Note the spherocytes and polychromasia. (Leishman; 200x)

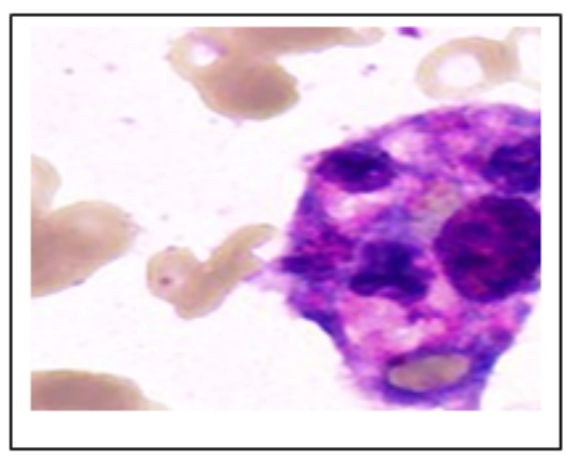

Figure 2: The bone marrow aspirate smears showing an activated macrophage with hemophagocytosis (Leishman; x400)

Volume : 3 | Issue : 9 | Sept 2013 | ISSN - 2249-555X

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