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(CASE REPORT)

A rare autoimmune association: Primary biliary cirrhosis and autoimmune haemolytic anaemia

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Abstract

There are many autoimmune diseases associated with primary biliary cholangitis (PBC), known as primary biliary cirrhosis. The association between PBC and autoimmune hemolytic anemia (AIHA) has rarely been reported. Among the 23 concomitant cases reported since 1970, PBC was diagnosed first in 10 cases and both diseases were almost simultaneously diagnosed in the remaining 13 cases. This suggests that there were few concomitant cases in which AIHA developed first before PBC.

We report in this paper a 74 years old woman with concomitant autoimmune haemolytic anaemia and primary biliary cholangitis. This case suggests an association between AIHA and PBC.

Keywords: Anaemia; Autoimmune; Haemolytic; Haemolytic anaemia; Primary biliary cirrhosis

1. Introduction

Primary biliary cholangitis (PBC), known as primary biliary cirrhosis, is an autoimmune liver disease principally affecting middle-aged women [1], characterized by progressive destruction of intrahepatic bile ducts, resulting in chronic cholestasis, portal inflammation and fibrosis that can further lead to cirrhosis[**2**]. This disease is associated with various autoimmune diseases. It has been estimated that up to 84% of patients with PBC have at least one associated auto- immune disease and 41% of the patients have two or more [**1**]· On the other hand, autoimmune hemolytic anemia (AIHA) involves a hemolysis induced by the interaction of autoantibodies with red blood cells (RBCs) [3]. However, It has not been well described in association with PBC [2]. To date, there have been few systematic literature reviews of concomitant PBC and AIHA as well as sporadic cases reported in the literature.

In this paper we report a patient with significant autoimmune haemolytic anaemia and end-stage liver failure PBC simultaneously.

2. Case presentation

Our patient, is a 74 year old North African woman from Morocco, who was diagnosed, based on clinical and immunological features, with autoimmune hemolytic anemia one month before her admission to our department. It was revealed by episodes of hematuria and abdominal pain and a strongly positive direct Coombs test. She was then put under corticosteroids. This patient got admitted to the department of hematology following the discovery of a splenomegaly with cirrhotic liver. There was no history of skin rash, photosensitivity, symptoms of dry eyes or mouth, or other ophthalmological or neurological complaints.

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Physical examination revealed an afebrile woman with scleral icterus. Examination of the abdomen revealed a liver span measured at 10cm at the right mid clavicular line with a firm edge and mild splenomegaly. The abdomen skin examination showed collateral veinous circulation . Head and neck examination was within normal limits as were the cardiopulmonary, musculoskeletal, dermatological and neurological systems examinations.

Laboratory investigations revealed the following abnormalities : hemoglobin (HB) level was at 7.5g/dl(normal level :12-16g/dL), platelet count at 133 000, white blood cell count at 3800/mm″ (normal range : 4000- 10000), lymphocytes at 844 (normal count : 1000-4500 /mm^3). Reticulocyte count was 775 X 109L (normal count :40-120 x 1 09/L) and haptoglobin, <41 mg/dl (normal range : 100–300 mg/dl).

The liver enzymes levels of both Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were within the normal range :AST at 19 UL (normal range : < 35 UL), ALAT at 20 UL (normal range : 7-33UiL). We found a Hyperbilirubinemia with direct predominance with a total bilirubin of 21.9 mg/L (normal < 12 mg/L), direct bilirubin 11.8 mg/L (normal < 2mg/L). Also, the alkaline phosphatase was normal 75 U/L , but γ- glutamyltranspeptidase (γ-GTP) was slightly elevated 127U/L (6-42 U/L) and lactic dehydrogenase (LDH) 427 U/L (normal range 207–414U/L). Serum albumin was within the normal range 36.7 g/L (normal 32-45g/L) and the International Normalized Ratio (INR) was 1.18 (normal 1.0-1.25).The direct antiglobulin test (direct Coombs test) was strongly positive for anti-IgG . Antinuclear antibodies (ANA) and anti-tissue antibodies (anti-smooth muscle antibodies, anti-LKM-1antibodies, anti-LC-1antibodies, anti-SL Aantibodies) were both negative. Viral markers for hepatitis A, B and C were negative as well. Peripheral blood morphology revealed the presence of spherocytes and polychromasia. Gathering previous information, the patient was diagnosed with AIHA and was given prednisolone 60 mg/day with subsequent improvement in the following days. After five days of treatment, the patient was discharged. At that time she had a Hb level of 10 g/L and improvement of general condition. She was readmitted toour department one month after due to fortuitous discovering of portal hypertension and liver cirrhosis on an abdominal ultrasound. An upper gastrointestinal endoscopy was performed, reporting a grade III esophageal varices and congestive hypertrophic gastric mucosa. In addition, a fibroscan revealed a F4 stage of fibrosis. The antimitochondrial antibody (AMA) was positive. The liver biospsy wasn't performed because of the end stage liver of CBP. Consequently, the patient was diagnosed with coexistent primary biliary cholangitis and hemolytic anemia.

The prednisone dose slowly tapered over the next three months to a maintenance dose of 10 mg/day. Ursodeoxycholic acid was given too. Four months after the initial presentation , the follow up laboratory data revealed a haemoglobin level of 13.5 g/d and a levels normalization of all the liver enzymes.

3. Discussion

AIHA is a rare autoimmune disorder affecting approximately three in 100 000 annually, in which auto antibodies directed against erythrocytes antigens lead to their increased destruction [2]. The classification of AIHA according to the antibody-type mediating the haemolysis: warm antibody or cold antibody [4]. This classification is based on the optimal RBC - autoantibody reactivity temperatures [2]. AIHA could be idiopathic (50%) or secondary to lymphoproliferative disorders (20%), autoimmune diseases (20%), infections and tumors (10%).

To our knowledge, there have been no diagnostic criteria for AIHA, but it is suspected with the following laboratory findings: normocytic or macrocytic anemia, increased reticulocyte level, low serum haptoglobin levels, increased serum LDH and IB levels and a positive direct Coombs test against immunoglobulin and/or its complement. When erythrocytes are covered with IgG or IgG plus C3d, the antibody is usually a warm antibody (wAIHA). When RBC are coated with C3d only, the antibody is usually but not always a cold antibody (cAIHA) .Our patient had immune haemolyticanaemia with a warm auto-antibody.

Typical diagnostic clues in PBC are the detection of chronic non-suppurative destructive cholangitis or AMA [1]. Other characteristic features include PBC-specific ANA (Sp100 and gp210), elevated serum immunoglobulin (Ig) M, hypercholesterolemia or xanthomas, Sicca syndrome, pruritus and fatigue [2].Most autoimmune disorders are more frequent in women, and this is particularly the case in PBC, where women outnumber men with ratios reported to be as high as 10/1 [2]. Our patient had AMA positive. The etiology of PBC remains unknown. Several observations suggest that an immune response disorderis responsible for PBC. PBC is frequently associated with a variety of disorders presumed to be autoimmune nature [1]. Collagen diseases, particularly rheumatoid arthritis (RA),mixed connective tissue disease, and systemic lupus erythematosus (SLE) are frequently associated with PBC [2]. The association between various immunologic disorders and PBC has gradually been gaining recognition, only 23 cases of PBC associated with AIHA have been reported since 1970 [4]. It has been unclear whether the cases of concomitant PBC and AIHA occur by chance or have a common immunological or genetic basis [3].

One of the possible mechanisms is that immune dysregulation caused by cholestasis accompanied with PBC may allow the emergence of an auto-reactive B-cell clone or the development of RBC autoantibodies [3]. Moreover, the increased plasma levels of the endogenous bile salts in cholestasis have been shown in vitro to damage the RBC membrane, particularly in acidic environments [3].

Among the 23 cases, 17 (73.9%) were females and six (26.1%) were males. PBC was diagnosed first in 10 cases, and both diseases were almost simultaneously diagnosed in the remaining 13 cases. Cases in which AIHA was diagnosed prior to the diagnosis of PBC were not identified [4]. The time interval between the diagnosis of the primary and the concomitant disease had a range of 2–22 years.

The recommended treatment for PBC-related AIHA includes prednisone (1mg/kg per day) to manage the hemolysis at the acute setting, and UDCA (13–15mg/kg per day). Although a successful outcome has been reported with only UDCA therapy in a patient having PBC associated with mild AIHA.[2]

In our case, the patient had a positive response to corticosteroid therapy with a normal haemoglobin four months after initial presentation, although the direct antiglobulin (Coombs) test remained positive. The biliary enzymes, as indicated by total bilirubin, also returned to within normal limits after four months of corticosteroids, despite non-introduction of ursodeoxycholic acid [4].

4. Conclusion

Autoimmune haemolytic anaemia associated with PBC alone is rarely reported. However, these two diseases maybe caused by heterogenous and complicated autoimmune reaction. The simultaneous appearance of two rare immunologically-mediated diseases in a previously healthy patient suggests a true association rather than a chance occurrence

Compliance with ethical standards

Acknowledgments

Pr. TAZI, Dr. BENHALIMA, Dr. JIDDI and Pr. KARATI participated in design and development of the case report, managing and treating the patient, writing of the case report and final approval of the submitted version after critical review.

Disclosure of conflict of interest

All the authors: Yasmina BENHALIMA, Soukaina JIDDI, Illias TAZI, Fatimaezzahra LAHLIMI and Khadija KARATI report no conflict of interest in relation to the subject matter.

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans subjects by any of the authors

Statement of informed consent

Statement of informant consent: Informed consent was obtained. The patient understands that her name and initials will not be published and has given her consent for clinical information to be reported in a case report.

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