

Concomitant Cases of Primary Biliary Cirrhosis and Autoimmune Hemolytic Anemia: Literature Review

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Abstract

Although autoimmune diseases are often concomitant, the coexistence of primary biliary cirrhosis (PBC) and autoimmune hemolytic anemia (AIHA) is not common. This is a review of the English and Japanese literature, regarding concomitant cases of PBC and AIHA. Among the 23 concomitant cases, PBC was diagnosed first in 10 cases and both diseases were almost simultaneously diagnosed in the remaining 13 cases. This suggests that there have been few concomitant cases in which AIHA developed first before the development of PBC. Moreover, there may be no correlation between the occurrence of AIHA and the staging or progression of PBC.

Keywords: Primary biliary cirrhosis; Auto-immune hemolytic anemia; Evans syndrome; Immune (Idiopathic) thrombocytopenic purpura

Introduction

Primary biliary cirrhosis (PBC) is an autoimmune liver disease of unknown etiology, and is characterized by chronic progressive cholestasis with destruction of the small intrahepatic bile ducts [1-3]. On the other hand, autoimmune hemolytic anemia (AIHA) involves an autoimmune process and is caused by a hemolysis induced by the reaction of autoantibodies with red blood cells (RBCs) [4-8].

Although it has been well-known that patients with one autoimmune disease often have other autoimmune diseases [9] the coexistence of PBC and AIHA is uncommon. Moreover, it is unclear whether the cases of concomitant PBC and AIHA occur by chance or have a common immunological or genetic basis.

To date, there have been few systematic literature reviews of concomitant cases of PBC and AIHA, and there have been sporadic case reports in the literature. Here we performed literature search and reviewed cases with concomitant PBC and AIHA including cases of Evans syndrome, which is the coexistence of AIHA and immune (idiopathic) thrombocytopenic purpura (ITP).

Methods

We reviewed the English- and Japanese-literature for cases of concomitant PBC and AIHA including Evans syndrome since 1980 and summarized the findings of all relevant published reports. A literature search was performed using the following keyword combinations: (1) primary biliary cirrhosis and hemolytic anemia, (2) primary biliary cirrhosis and autoimmune hemolytic anemia, and (3) primary biliary cirrhosis and Evans syndrome. The English and Japanese literature searches were performed using PubMed and Japana Centra Revuo Medicina (Igaku Chou Zasshi) respectively.

In addition, we excluded the drug-induced AIHA cases from the concomitant cases of PBC and AIHA for this article.

PBC

PBC is considered an autoimmune disease characterized by chronic progressive cholestasis with the destruction of the small intrahepatic bile ducts, particularly the interlobular bile ducts [1-3]. PBC affects middle-aged women more frequently than men (with a ratio of 9-10:1) [10].

The clinical features and clinical course of PBC among the individual patients vary significantly from an asymptomatic condition to a progressive disease (cirrhosis or liver failure) [11]. Although jaundice and pruritus from cholestasis are typical symptoms in PBC patients, up to 60% of patients may have no clinical symptoms. Useful laboratory characteristics of PBC are the elevated serum biliary enzymes such as alkaline phosphatase and the presence of antimitochondrial antibodies (AMA), which are useful for the serological diagnosis of PBC (90%-95% of patients with PBC are AMA-positive) [2]. Florid bile duct lesions such as chronic, nonsuppurative destructive cholangitis and epithelioid granuloma formation are some of the histopathological findings of PBC [11].

Administration of Ursodeoxycholic Acid (UDCA) is the standard pharmacotherapy for PBC; however, up to 40% of PBC patients do not achieve a complete response to UDCA. Patients with end-stage liver failure require an organ transplant [12].

Silveria et al. [13] reported that among 67 patients with PBC, 32 (48%) had at least one extra-hepatic autoimmune disease. Floreani et al. [14] also reported that among 361 patients with PBC who were followed for 8 ± 6.9 years, 221 (61.2%) had at least one extrahepatic autoimmune disease. Although PBC has been reported in association with a variety of autoimmune diseases, the common complications in PBC that have been reported are Sjögren's syndrome (SjS), autoimmune thyroiditis (Hashimoto's thyroiditis), and rheumatoid arthritis (RA) [12]. Other complications include type I diabetes mellitus, scleroderma, and pernicious anemia [12].

AIHA

AIHA is caused by hemolysis induced by a reaction of autoantibodies with RBCs [4-8]. Events that can lead to AIHA include extravascular hemolysis caused by the phagocytosis of erythrocyte-bound IgG in the spleen (hemolytic mechanism), activation of polyclonal B cells, reactions induced by molecular mimicry of exogenous antigens, breakdown of immune tolerance, and abnormal cytokine expression (autoimmune mechanism) [4-7].

AIHA is a rare condition with a reported incidence in the range of 1 per 75,000 to 2 per 100,000 people [15]. The peak incidence of AIHA occurs during the age range of 60–70 years with a male to female ratio of 40:60 [8].

Based on the optimum temperature for autoantibody reactivity, AIHA has been categorized as warm type [4,6-9,16], mixed type, and cold type [cold agglutinin disease (CAD) or paroxysmal cold hemoglobinuria (PCH)]. The former is the most common and is frequently direct antiglobulin test (DAT) (or Coombs test)-positive; DAT-negative AIHA has been reported in 2%–4% of the cases [8].

AIHA can be also classified as primary (idiopathic) or secondary [17]; approximately half of the AIHA cases are considered primary or idiopathic. Secondary AIHA is induced by drugs (e.g., methyl dopa and penicillin); carcinomas such as malignant lymphoma; rheumatological or autoimmune diseases such as RA or systemic lupus erythematosus (SLE); and infectious diseases [4,6,7,9,17,18].

Moreover, Evans syndrome is diagnosed by the simultaneous presence or sequential occurrence of AIHA, which is detected using DAT and ITP in the absence of an underlying etiology [19,20]. This syndrome is characterized by hemolytic anemia, thrombocytopenia, and the production of either antibodies or complement, or both that attack RBCs and platelets [20,21]. Evans syndrome has been associated with SLE, thyroid diseases, and scleroderma and so on [20].

Suspected mechanisms of coexistence of PBC and AIHA or Evans syndrome

It has been unclear whether the cases of concomitant PBC and AIHA occur by chance or have a common immunological or genetic

basis and obvious mechanisms of occurrence of AIHA in PBC patients.

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 [22]. 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 [22].

Moreover, antibodies to platelets have been frequently detected in PBC patients, suggesting that the occurrence of the immune phenomena may also involve immunomediated platelet destruction [20,23]. This destruction may be associated with the development of Evans syndrome or ITP in PBC patients.

Previous reports as regard to AIHA complicated with PBC

Omata et al. [15] previously summarized 13 patients with reported cases of concomitant PBC and AIHA in the English and Japanese literature from 1970 to 2008; 12 of the patients were women (one case had no gender description), and were predominantly middle-aged. In 10 of the 12 cases, AIHA was either of the warm or mixed type. In the patients who underwent liver biopsy, the pathological findings varied from stage I to IV according to the Scheuer classification. In almost all cases except the cold type AIHA, the therapy for AIHA comprised immunosuppressive treatment such as the administration of steroids, whereas in most cases, UDCA was administered to treat PBC except in one case in which the patient received a liver transplantation. Tian et al. [24] also identified 15 patients with reported cases of concomitant PBC and AIHA in the English and Spanish literature from 1970 to 2007; 12 of the 15 patients were female. In 12 of the 15 cases, the type of AIHA was either warm or mixed type. In most cases except those cases with the simultaneous onset of both diseases, PBC was the first diagnosed disease.

Characteristics of cases of concomitant PBC and AIHA

The characteristics of the reported cases of concomitant PBC and AIHA (20 from the English [9,15-17,20,22,24-32] and 3 from the Japanese literature [18,33,34]) are summarized in Table 1.

Case (year)	Sex	Age at diagnosis of PBC (years)	Age at diagnosis of AIHA (years)	PBC prior to AIHA	Scheuer's classification	Type of AIHA	Complications	Remarks	References
1(1980)	F	57	57	sim		WARM			[30]
2(1984)	F	32	32	sim		WARM			[28]
3(1996)	M	66	66	sim		WARM			[17]
4(1997)	F	49	49	sim		mixed	Sjögren's syndrome		[29]
5(1997)	F	49or50	49/50	sim		WARM			[34]
6(2000)	F	68	68	+		WARM	Hashimoto's thyroiditis		[9]
7(2000)	F	41?	49	+		COLD	Hypothyroidism		[27]
8(2000)	F	64?	66?	+		WARM			[27]
9(2001)	M	45	51			WARM			[18]

10(2003)	F	62	62	Sim		WARM			[22]
11(2007)	F	81	83			WARM	ITP(Evans syndrome)		[26]
12(2007)	F	44?	66			WARM			[25]
13(2007)	M	51?	59			WARM			[25]
14(2007)	M	44?	59			WARM	ITP(Evans syndrome), RA, Hypothyroidism	Sepsis, ARDS → death	[25]
15(2007)	F	52	52	Sim		Cold			[16]
16(2008)	F	66?	71?			Warm	Myelofibrosis	Sepsis, AML → death	[32]
17(2008)	F	77	77	Sim		Warm			[15]
18(2009)	F	74	74	Sim		Warm			[24]
19(2009)	M	60	60	Sim		Warm			[24]
20(2009)	M	55	55	Sim		Warm	ITP(Evans syndrome), Sjögren's syndrome		[24]
21(2009)	F	37	50			Warm	AIH, Hashimoto's thyroiditis		[31]
22(2012)	F	51	60			Warm	Sarcoidosis	Familial PBC	[33]
23(2013)	F	53	53	Sim		Warm	ITP(Evans syndrome), AIH		[20]

Table 1: Characteristics of 23 Patients with Comorbid Primary Biliary Cirrhosis and Autoimmune Hemolytic Anemia.

Among the 23 cases, 17 (73.9%) were female and 6 cases (26.1%) were male. Among the 23 cases, 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. Therefore, there may be a clear tendency for PBC to precede AIHA.

The concomitant disease was diagnosed between the ages of 32 and 83 years; however, the patients were predominantly middle-aged. The interval between the diagnosis of the primary and the concomitant disease had a range of 2–22 years. Among the 23 cases, one had familial GD; her father had developed PBC and Graves' disease [33]. The most prevalent complicated disease was ITP (Evans syndrome), which occurred in 4 of the 23 cases of concomitant PBC and AIHA. Moreover, SJS, Hashimoto's thyroiditis, and hypothyroidism (causes were not mentioned) were found in 2 of the 23 cases, respectively.

In patients who underwent liver biopsy, the pathological findings varied from stage I to IV according to the Scheuer classification. In AIHA, 22 of the 23 cases were DAT-positive, 19 cases were of the warm type, 1 case was of the mixed type [29], and 3 cases were of the cold type [16,27,30].

Therapies for PBC were the administration of UCDA or liver transplantation in concomitant cases; liver transplantation was

performed in four cases [16,25]. Moreover, according to Retana et al. [25], the manifestation of AIHA occurred after liver transplantation for PBC in three cases. In most cases except the cold type AIHA, the therapy for AIHA was immunosuppressive treatment such as the administration of steroids, azathioprine, or immunoglobulin, or splenectomy in concomitant cases.

Conclusion

In this literature review, 23 cases of concomitant PBC and AIHA including Evans syndrome were reviewed. It is notable that there were no cases in which AIHA was diagnosed prior to the occurrence of PBC.

At present, it remains uncertain whether these concomitant diseases occur by chance or if they reflect a common immunological basis.

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