

# Coexistence of Primary Biliary Cirrhosis and Inflammatory Bowel Disease

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## Abstract

The coexistence of Primary Biliary Cirrhosis (PBC) and Inflammatory Bowel Disease (IBD) is uncommon, although hepatobiliary complications in IBD patients are not rare. This report reviews the English and Japanese literature and covers reported cases of concomitant PBC and IBD. We identified 2 cases of concomitant PBC and Crohn's Disease (CD) and 18 cases of concomitant PBC and Ulcerative Colitis (UC). In most instances (15/18), IBD (CD or UC) developed before PBC, with the exception of 2 cases that were almost simultaneously diagnosed with both conditions. There is no evidence that UC cases with concomitant PBC are more severe than those without; however, the clinical features of concomitant PBC and CD are unclear due to few reports.

**Keywords:** Primary biliary cirrhosis; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

## Introduction

Inflammatory Bowel Diseases (IBD), including Crohn's Disease (CD) and Ulcerative Colitis (UC), are chronic recurrent, and characterized by intestinal inflammation that appears to result from a complex of environmental and immune factors [1,2]. Approximately 25% of IBD patients exhibit symptoms below the age of 18; however, its diagnosis is frequently delayed until later in life [1,2].

On the other hand, Primary Biliary Cirrhosis (PBC) is an autoimmune liver disease that presents with chronic cholestasis characteristic histological findings of non-suppurative destructive cholangitis; it progresses to liver fibrosis and cirrhosis [3,4]. PBC occurs more commonly in women than in men (female-to-male ratio of 9-10:1) and often in middle-age [3,4].

Although the development of extra intestinal manifestations during the course of IBD is well known, a controlled study indicated that 6.6% of UC patients and 1.9% of CD patients had at least 1 autoimmune disorder [5]. Cases of concomitant PBC and IBD are uncommon [6-22]. In addition, cases of concomitant PBC and CD appear to be extremely rare [21,22]; however, cases of concomitant PBC and UC have been sporadically reported [6-20]. Currently, it is uncertain whether concomitant PBC and IBD occurs by chance or has a common immunological basis [21]. As a result, there are few systematic literature reviews of concomitant PBC and IBD.

For this report, we conducted a literature search and review of cases of concomitant PBC and IBD (CD plus UC).

## Methods

We aimed to review the English and Japanese literature describing these conditions and to summarize the findings in this report. A literature search was performed using the following keywords: (1) primary biliary cirrhosis and inflammatory bowel disease; (2) primary biliary cirrhosis and Crohn's disease; (3) primary biliary cirrhosis and ulcerative colitis. English and Japanese literature searches were performed using PubMed and Japana Centra Revuo Medicina (Igaku Chou Zasshi), respectively.

## Hepatobiliary manifestations in IBD patients

Hepatobiliary manifestations in IBD have been described as Primary Sclerosing Cholangitis (PSC), cholangiocarcinoma, pericholangitis, fatty liver, gallstones, and autoimmune liver disease

such as autoimmune hepatitis or PBC [15,19,21,23]. The incidence of hepatobiliary diseases with UC has been reported to be 3%-15% and up to 90% with abnormal liver histology at surgery or autopsy [16,24]. PSC is best known for hepatobiliary manifestation with UC, and the frequency of incidence of patients with concomitant PSC and IBD has been reported to be in the range of 2.4%-7.5% [10,16,23,25,26]. Moreover, the severity of colitis has been reported to bear no relation to the coexistence of PSC [23].

On the other hand, Sjögren's syndrome, systemic sclerosis, and chronic thyroiditis also commonly occur concomitantly with PBC [10,15,27,28]. The precise frequency of IBD occurring concomitantly with PBC has been unclear.

## Concomitant PBC and IBD

We identified 20 reported cases of concomitant PBC and IBD in 18 English and 2 Japanese reports. To the best of our knowledge, the first reported English case of concomitant PBC and UC was in 1985 by Kato et al. [7], (and the first reported Japanese case was in 1984 by Morimoto et al. [19]). The first reported English case of concomitant PBC and CD was in 2005 by Jang et al. [21]. The characteristics of these 20 cases are summarized in Table 1. Of these, there were only 2 cases of concomitant PBC and CD and 18 cases of concomitant PBC and UC [7-22].

One characteristic of cases of concomitant PBC and UC has been the reported lower female-to-male ratio compared with that for PBC cases without UC [13,21]. In fact, out of the 20 cases of concomitant PBC and IBD cases, 8 cases (40%) were male, and out of the 18 cases of concomitant PBC and UC, 7(39%) were male (Table 1), thus indicating a higher than general frequency of occurrence in males. It has been suggested by some reports mentioned above that PBC is more common in women than in men, with a female-to-male ratio of 9-10:1 [3,4]. In

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Case	Sex	IBD	Age at diagnosis of IBD (years)	Age at diagnosis of PBC (years)	IBD prior to PBC	UC type	Complications	References
1	F	UC	65	69?	+	Pancolitis	Chronic pancreatitis	[7]
2	F	UC	47	48?	+	Proctitis		[8]
3	M	UC	26	32	+	Proctitis		[8]
4	M	UC	44	52?	+	Proctitis		[8]
5	F	UC	28	40?	+	Left-sided colitis		[8]
6	F	UC	49	49	Sim	Left-sided colitis	Chronic myelocytic leukemia	[9]
7	M	UC	40	45	+	Left-sided colitis		[10]
8	F	UC	43?	45	+	Proctitis	Chronic pancreatitis	[11]
9	F	UC	48	48?	+	Pancolitis	Renel cell carcinoma	[12]
10	M	UC	50	58	+	Pancolitis		[13]
11	F	UC	36	68	+	Pancolitis		[13]
12	F	UC	43	45	+	Pancolitis		[14]
13	M	UC	61	60	-	Proctitis		[15]
14	F	UC	50	50	Sim	Proctitis		[16]
15	M	UC	77	78?	+	?	Myasthenia gravis	[17]
16	F	UC	43	31	-	Left-sided colitis		[18]
17	F	UC	63?	65	+	Left-sided colitis	Chronic pancreatitis	[19]
18	M	UC	64	62 or 63	-	Proctitis		[20]
19	M	CD	19	19 or 20	+			[21]
20	F	CD	30	44	+			[22]

UC: Ulcerative Colitis; CD: Crohn's Disease; F: Female; M: Male; Sim: Simultaneous

**Table 1:** Characteristics of 20 Patients with Concomitant Primary Biliary Cirrhosis and Inflammatory Bowel Disease.

contrast, UC has not been estimated to be a sex-specific disease; the female-to-male ratio for UC differs between 0.51 and 1.58 [2,29].

The ratio of CD versus UC cases was 2:18 in the cases of concomitant PBC and IBD (Table 1) although a recent systematic review indicated that the prevalence of CD and UC in Western and European countries has been 90 and 505 per 100,000 and 319-322 per 100,000, respectively [1,2,29].

In most instances, (15/18) IBD developed before PBC; except in 2 cases, which were almost simultaneously diagnosed [9,16]. The concomitant diagnoses were made between the ages of 19 and 78 years. In the aforementioned 20 reported cases, the time interval between the development of PBC and IBD was 0-32 years (Table 1).

Antimitochondrial Antibodies (AMA or M2) are useful for the serological diagnosis of PBC, and 90%-95% of PBC patients are AMA positive [30]. In a total of 20 cases of concomitant PBC and IBD, 2 cases (10%) were AMA-negative although titers of M2 antibodies were not mentioned [16,21].

#### IBD subgroup: cases of concomitant PBC and CD

Case reports of concomitant PBC and CD are extremely rare, even more so than those of PBC and UC. We identified 2 cases of concomitant PBC and CD in the English literature (Table 1) [6,21,22].

The 2 reported cases of concomitant PBC and CD were as follows:

Jang et al. [21] reported the case of a 19-year-old man who developed AMA-negative PBC after diagnosis of CD. His serological findings normalized a month after administration of ursodeoxycholic acid. Sisman et al. [22] reported the case of a 44-year-old female who developed AMA-positive PBC 14 years after CD diagnosis. She developed PBC during infliximab treatment for CD, and liver enzymes and AMA levels normalized after cessation of infliximab. She had undergone a right hemicolectomy for ileocolonic CD.

#### Possible mechanism of developing PBC following UC

One of the accepted hypotheses for the pathogenesis of IBD is that the mucosal immune system exhibits an aberrant response towards luminal antigens such as commensal bacteria [18]. A chronic low-grade portal infection caused by UC leading to chronic biliary tract inflammation and fibrosis has been suggested as a pathogenic mechanism [9,15]. Some researchers have reported that lipoteichoic acid, a component of bacteria, may be involved in the pathogenesis of PBC and UC [18,31].

#### IBD subgroup: cases of concomitant PBC and UC

A retrospective population-based study of UC in Stockholm County in Sweden noted 2 cases of concomitant PBC out of 1274 UC patients [24]. Although some reports have suggested the possibility that the prevalence of PBC in UC patients is greater than that in general populations, it is currently unclear [6,13].

In reports of concomitant PBC and UC, histological findings according to Scheuer's classification were mentioned. Staging of PBC was as follows: 6 cases at stage I, 1 at stage II, 2 at stage III, 1 at stage III~IV. No cases of liver failure or death due to PBC were found although 1 case of suspected liver cirrhosis with ascites was noted [15]. Moreover, no cases received liver transplantation.

Eighteen cases of concomitant PBC and UC were reported as follows: 5 cases of pancolitis, 5 of left-sided colitis, 7 of proctitis, and 1 unclear (Table 1). In contrast, PSC patients tended to have pancolitis [10]. There were no cases with flare-up of UC after the onset of PBC. Moreover, colitis with concomitant PBC and UC has been reported to be less severe than that typically seen in isolated UC [10,15]. Most cases of concomitant PBC and UC that went into remission were treated with amino salicylates, corticosteroids or both [20]. Only 1 case resulted in surgery because of persistent inflammation of UC before the onset of PBC. Moreover, severe complications, such as toxic megacolon or death due to colitis, have not been reported in cases of concomitant PBC and UC [14-20].

On the other hand, it is noteworthy that 3 of the 18 cases of concomitant PBC and UC were also diagnosed with chronic pancreatitis [7,11,19]. One of the reasons may be that an endoscopic retrograde cholangiopancreatography examination was carried out for differentiation of PSC in these cases.

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