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Original Article

Are Hepatobiliary Manifestations Related to the Site of Involvement in Inflammatory Bowel Disease?

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Abstract

Objective: This study was carried out to reveal the factors affecting the hepatobiliary manifestations in inflammatory bowel disease.

Methods: Inflammatory bowel disease patients followed in our gastroenterology outpatient clinic between 1999 and 2009 were included in the study retrospectively. The demographic and clinical characteristics of the patients were evaluated. In order to reveal hepatobiliary involvement, all patients were evaluated with clinical, laboratory, imaging examinations, and liver biopsy in some necessary patients.

Results: A total of 504 inflammatory bowel disease patients (48.2% female) (of whom 39.1% had Crohn's disease, 57.5% had ulcerative colitis, and 3.4% had indeterminate colitis) were enrolled in this study. The mean age of patients was 38.7 ± 13 years. The mean duration of disease was 80 ± 59 months, and the mean follow-up period was 32 ± 3 months. The proportion of patients with hepatobiliary involvement was 4.8% (33.3% Crohn's disease, 66.7% ulcerative colitis). In terms of liver findings, the rate of primary sclerosing cholangitis was 50%, and the rate of hepatosteatosis was 50%. In this group, 58.3% of them were male, and the mean duration of disease was 32 ± 3 months (2-96 months). All of the patients with diagnosis of primary sclerosing cholangitis received ursodeoxycholic acid (UDCA) (15 mg/kg), with a median of 84 months. The mean GGT (87 ± 92 IU/L vs. 68 ± 84 IU/L) and ALP (397 ± 507 IU/L vs. 271 ± 255 IU/L) levels were significantly decreased after UDCA treatment ($P < .05$). There was a positive correlation between duration of disease and hepatobiliary manifestation ($r = 0.1$, $P = .025$). Ileocolonic involvement and pancolitis were independent risk factors for the development of hepatobiliary manifestations in Crohn's disease and ulcerative colitis, respectively ($P = .005$). Hepatic failure was not observed in any patient during the follow-up period.

Conclusion: Hepatobiliary involvement is more common in inflammatory bowel disease patients with colonic involvement.

Keywords: Hepatobiliary manifestations, inflammatory bowel disease, primary sclerosing cholangitis

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic idiopathic bowel diseases characterized by remission and relapses. Ulcerative colitis (UC) and Crohn's disease (CD) are the 2 main groups of the IBD. Ulcerative colitis affects the colon, whereas Crohn's disease can involve any part of the gastrointestinal (GI) tract. Inflammatory bowel disease is associated with extraintestinal manifestations (EIMs).[1] Hepatobiliary disorders are one of these EIMs and are more commonly related to UC.[2] Fatty liver and primary sclerosing cholangitis (PSC) are the most common hepatobiliary complications in IBD, especially in UC, but autoimmune hepatitis, IgG4-associated cholangiopathy, primary biliary cholangitis, hepatic amyloidosis, and portal vein thrombosis can also be seen as hepatobiliary manifestations (HBMs) of the IBD.[3] The pathogenesis of liver injury in IBD is still not fully understood. The pathogenesis and correlation between IBD and HBMs are multifactorial, such as genetic and environmental.[4] The aim of this study is to evaluate the predictive factors of HBM in IBD patients.

METHODS

Study Design

This is a single-center, retrospective cohort study. Five hundred four patients with IBD (UC, CD, and indeterminate colitis) who were under follow-up from 1999 to 2009 in our outpatient clinic were included in this study. A combination of clinical, endoscopic, laboratory, histopathological, and radiological examinations was used in the diagnosis of IBD. Those with a definite diagnosis of IBD were included in the study.

Classification and Definitions of the Disease

Demographic characteristics (gender, age of diagnosis), laboratory, clinical, and treatment (medical and/or surgery) data, age of diagnosis, family history, disease location, and type of disease of the patients were recorded. The type of the disease for CD was defined in 3 categories: inflammatory, fistulizing, and obstructive. The involvement of the disease for CD was defined in 3 categories: ileal, ileocolonic, and colonic. The involvement of the disease for UC was defined in 4 categories: distal, left colon, pancolitis, and backwash ileitis+pancolitis.

In this study, we investigated the relationship between the development of hepatobiliary findings (HBM) and gender, age at diagnosis, site of disease involvement, disease type, disease duration, family history, surgical operation, steroid and thiopurine use and we analyzed independent risk factors associated with the development of HBMs.

Hepatobiliary and Other Extraintestinal Manifestations

Hepatobiliary manifestations were defined as follows: PSC and hepatosteatosis. Primary sclerosing cholangitis was diagnosed by biochemical analyses, magnetic resonance cholangiopancreatography/endoscopic retrograde cholangiopancreatography, and liver biopsy in all suspected patients. Hepatosteatosis was diagnosed by ultrasound. Drug-related adverse events or abnormal liver tests were not accepted as HBMs. Other EIMs were defined by organ involved as follows: seronegative arthritis, pyoderma gangrenosum, uveitis, thromboembolism including cerebral thrombosis, and renal calculi after other etiologies were excluded after the evaluation. Complications of IBD such as abscess, perforations, malignancy, and toxic megacolon were not considered EIMs.

Ethics Statement

Consent was obtained from all participants in the study. Approval for this study was obtained from the Ethics Committee of Istanbul University Faculty of Medicine on August 31, 2011. The protocol number is 577. All the applied procedures were complied with the ethical standards of Human Testing Committee of our institution and the Helsinki Declaration.

Statistical Analysis

Statistical Package for the Social Sciences 22.0 (IBM, Armonk, NY, USA) program was used for the statistical evaluation of the study. While evaluating categorical data, frequency and percentage were used, for continuous variables, mean ± standard deviation was used. While investigating the risk factors for HBM, the chi square test was used, and the parameters that were found to be significant were then re-evaluated with logistic regression.

RESULTS

A total of 504 patients (51.8% male) with IBD were included in this study; 57.5% (n=290) of patients had UC, 39.1% (n=197) of patients had CD, and 3.4% (n=17) of patients had indeterminate colitis; 51.8% (n=261) of patients were male. The mean age of patients was 38.7 ± 13 years. The mean duration of disease and follow-up period were 80 ± 59 months and 32 ± 3 months, respectively.

About 24.4% (n=71) of the patients with UC had distal colon involvement, 23.7% (n=69) of them had left side colon involvement, 49.3% (n=143) of them had pancolitis, and others (n=7) had pancolitis+backwash ileitis. About 23.3% (n=46) of the patients with CD had ileal involvement, 6% (n=12) of them had colonic involvement, and others (n=136) had ileocolonic involvement. About 17.6% (n=3) of the patients with indeterminate colitis had left side colon involvement, 41.4% (n=7) of them had ileocolonic involvement, and 41.4% (n=7) of them had pancolitis. The rate of hepatobiliary manifestation was 4.8% (n=24). About 66.7% (n=16) of these patients had UC, and 68.8% (n=11) of them had pancolitis; 33.3% (n=8) of these patients had CD, and 88% (n=7) of them had ileocolonic involvement. None of the patients with indeterminate colitis had HBMs (Table 1).

When patients with and without HBMs were compared, no significant difference was found between IBD types, age of IBD, family histories, durations of azathioprine use, azathioprine withdrawn, follow-up durations, and comorbidities ($P > .05$). Pyoderma gangrenosum, seronegative arthritis, renal calculus, uveitis, and deep venous thrombosis among extraintestinal involvements were found to be significantly higher than those without HBMs ($P < .05$). Primary sclerosing cholangitis and hepatosteatosis were found to be significantly higher in patients with HBMs than those without HBMs ($P < .05$). The patients with HBMs were older than those without HBMs ($P < .05$) (Table 2).

In terms of liver findings, the rate of PSC was 50%, and the rate of hepatosteatosis was 50%. In this group, 58.3% of them were male, and mean duration of disease was 32 ± 3 months (2-96 months). All of the patients with diagnosis of PSC received UDCA (15 mg/kg), with median of 84 months. The mean GGT (87 ± 92 IU/L vs. 68 ± 84 IU/L) and ALP (397 ± 507 IU/L vs. 271 ± 255 IU/L) levels were significantly decreased after UDCA treatment ($P < .05$). There was a positive correlation between duration of disease and HBM ($r=0.1$, $P=.025$). Ileocolonic involvement and pancolitis were independent risk factors for the development of HBMs in CD and UC, respectively ($P=.005$). Hepatic failure was not observed in any of the patients during the follow-up period.

In the 12 patients with PSC, 2 (16.7%) had CD and 10 (83.3%) had UC, and in 12 patients with hepatosteatosis, 6 (50%) had CD and 6 (50%) had UC. Primary sclerosing cholangitis was more frequent in patients with UC rather than CD, and hepatosteatosis was equal between patients with UC and CD. Hepatobiliary manifestations were more frequent in patients with UC rather than CD.

DISCUSSION

Inflammatory bowel disease is a systemic disease characterized by remission and relapses and is not only limited to the gut. Many EIMs can be seen in IBD. The EIMs may affect multiple organs and most frequently affect the musculoskeletal system, the skin, the hepatobiliary tract, and the eye. Peripheral and axial arthropathies, erythema nodosum, pyoderma gangrenosum, Sweet's Syndrome, aphthous stomatitis, PSC, primary biliary cholangitis, episcleritis, and uveitis can be seen frequently, and less frequently, EIMs also affect other organ systems like the lungs, the heart, the pancreas, and the vascular system.[5,6] In our study, most common HBM is PSC (2.35%, n=12).

Careful screening for EIMs in these patients and early diagnosis are important, and to prevent morbidity, a multidisciplinary approach is often needed. Clinicians must recognize those various systemic manifestations because early diagnosing and treatment are important to prevent major morbidity.

Abnormal liver biochemical tests are present in up to 30% of patients with IBD, and chronic liver disease affects approximately 5% of patients with IBD.[7] Abnormal liver tests in IBD can be transient or

MAIN POINTS

- Hepatobiliary manifestations (HBMs) can be seen during the inflammatory bowel disease.
- Primary sclerosing cholangitis and hepatosteatosis are important HBMs that can be seen in inflammatory bowel disease.
- We should examine patients for HBMs in inflammatory bowel diseases with liver enzyme disorders.

Table 1. Comparison of Patients With and Without Hepatobiliary Manifestations

		Hepatobiliary Involvement, No	Hepatobiliary Involvement, Yes	
		N	N	*P**
Gender	**Female**	233	10	*.511*
	Male	247	14	
IBD	**CD**	189	8	*.490*
	UC	274	16	
	Indeterminate	17	0	
Features of IBD	**Distal**	69	2	*.626*
	Left side	69	3	
	Pancolitis	141	11	
	Backwash + pancolitis	7	0	
	Ileal	46	1	
	Ileocolonic	136	7	
	Colonic	12	0	
Family history of IBD	**None**	444	24	*.599*
	CD	8	0	
	UC	11	0	
Medication with AZA	**No**	262	17	*.118*
	Yes	218	7	
Withdrawn of AZA	**No**	332	11	*.789*
	Yes	40	1	
History of bowel operation	**No**	382	21	*.344*
	Yes	98	3	
Extraintestinal involvement	**No**	404	0	***.001***
	Pyoderma gangrenosum	13	0	
	Primary sclerosing cholangitis	0	12	
	Seronegative arthritis	41	0	
	Renal calculi	14	0	
	Hepatosteatosis	0	12	
	Uveitis	4	0	
	DVT	4	0	
Complication of IBD	**No**	403	20	*.756*
	Abscess	29	0	
	Perforation	15	0	
	Malignancy	5	0	
	Toxic megacolon	1	0	
	Others	14	1	
Co-morbidities	**Yes**	88	5	*.758*
	No	392	19	

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; DVT, Deep venous thrombosis; AZA, Azathiopurine.
$p < .005$ is statistically significant

persistent.[8] Transient abnormal liver tests can be related to the activity of IBD, without impact on long-term prognosis. The pathogenesis of hepatobiliary disorders seen in IBD is not fully understood. Immunologic, genetic, and environmental factors can affect the pathogenesis.

Table 2. Comparison of patients with and without hepatobiliary manifestations

	Hepatobiliary involvement No		Hepatobiliary involvement Yes		
	Mean	SD	Mean	SD	*P*
Age (years)	38.45	13.23	44.71	14.15	.025
Follow-up (months)	36.39	45.37	32.04	33.85	.644
Age of IBD	70.00	76.22	80.92	59.02	.490
Duration of AZA medication	31.12	32.71	22.86	15.95	.508

IBD, inflammatory bowel disease; SD, standard deviation.

Hepatobiliary disease in patients with IBD can be symptomatic, such as malaise, jaundice, pruritus, and asymptomatic. The evaluation of patients with IBD and abnormal liver tests is similar to the evaluation of patients without IBD. The initial evaluation includes history of the disease and physical examination.

In a study conducted in Brazil, a significant relationship was found between patient age and HBMs.[9] We also found a positive correlation between duration of disease and HBM ($r=0.1$, $P=.025$).

Drug-induced liver injury, infections, nonalcoholic fatty liver disease, cholestatic liver disease, granulomatous hepatitis, hepatic amyloidosis, and portal vein thrombosis are the HBMs of the IBD.

In our study, we found hepatosteatosis and PSC as HBMs (4.7%, n=24) in IBD patients, but granulomatous hepatitis, hepatic amyloidosis, portal vein thrombosis, infections, and drug-induced liver injury were not found.

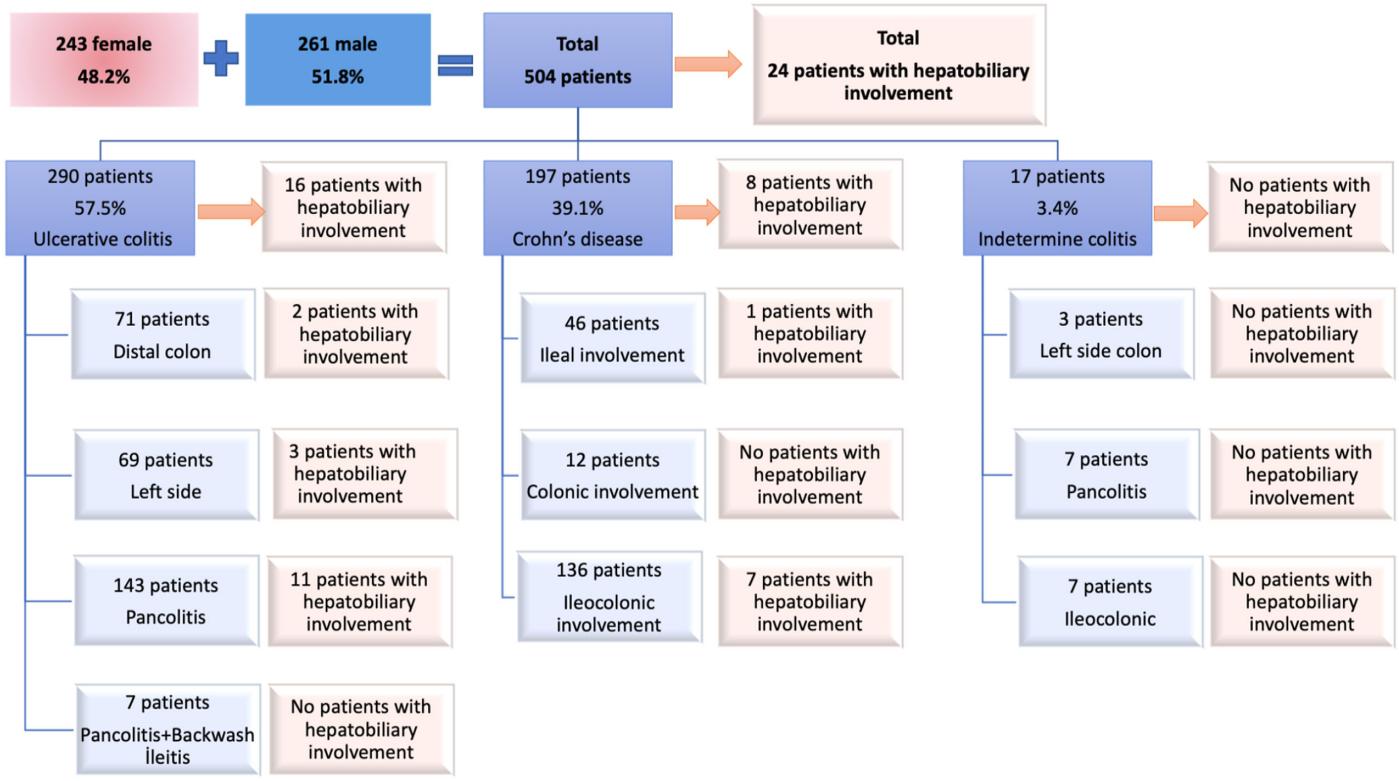

Figure 1. Flowchart of this study is shown in Figure 1.

We found hepatosteatosis in 2.35% (n=12) of our IBD patients. Hepatosteatosis is increasingly being diagnosed in the IBD patients. There were some studies that search hepatosteatosis in IBD patients. Nonalcoholic fatty liver disease (NAFLD) in patients with IBD ranges from 33% to 50%.[10,11] Hepatosteatosis and, as a result of this, non-alcoholic steatohepatitis prevalence is increasing in the world. Because of these conditions, if complications such as cirrhosis, hepatocellular carcinoma, abnormal liver function tests or imaging are identified, IBD patients will need to be evaluated for the possibility of NAFLD.

Primary sclerosing cholangitis is a chronic, cholestatic disease of the liver characterized by inflammation, fibrosis, and stricturing of both intra- and extrahepatic bile ducts. The majority of patients with PSC have underlying IBD (primarily UC).[12] Primary sclerosing cholangitis patients with IBD often have pancolitis. In our study, univariate analysis revealed that ileocolonic involvement and pancolitis were the independent risk factors for the development of HBMs in CD and UC, respectively (P=.005). Colonic involvement in IBD increases the risk of HBMs. In other studies, a significant relationship was found between EIMs and colonic involvement.[13] Patients with PSC and IBD have an increased risk of colorectal cancer compared with patients who have IBD alone.[14] Therefore, it is important to diagnose PSC.

Primary biliary cholangitis (PBC) is a disease characterized by progressive inflammatory destruction of interlobular bile ducts and can be associated with IBD,[15] but in our study, PBC was not found in our patients.

In conclusion, HBMs occur more frequently in UC rather than in CD. It is important to evaluate HBMs in patients with IBD due to the risk of progression to chronic liver disease and other complications. Colonic involvement is a risk factor for HBMs in UC, and ileocolonic involvement is a risk factor for HBMs in CD.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Ethical committee approval was received from the Ethics Committee of Istanbul University Faculty of Medicine. (Date: August 31, 2011, Decision no: 577).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

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REFERENCES

1. Karmiris K, Avgerinos A, Tavernaraki A, et al. Prevalence and characteristics of extra-intestinal manifestations in a large cohort of Greek patients with inflammatory bowel disease. *J Crohns Colitis*. 2016;10(4):429-436. [CrossRef]
2. Gizard E, Ford AC, Bronowicki JP, Peyrin-Biroulet L. Systematic review: the epidemiology of the hepatobiliary manifestations in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2014;40(1):3-15. [CrossRef]
3. Fousekis FS, Theopistos VI, Katsanos KH, Tsianos EV, Christodoulou DK. Hepatobiliary manifestations and complications in inflammatory bowel disease: a review. *Gastroenterology Res*. 2018;11(2):83-94. [CrossRef]

4. Navaneethan U. Hepatobiliary manifestations of ulcerative colitis: an example of gut-liver crosstalk. *Gastroenterol Rep (Oxf)*. 2014;2(3):193-200. [CrossRef]
5. Vavricka SR, Schoepfer A, Scharl M, Lakatos PL, Navarini A, Rogler G. Extraintestinal manifestations of inflammatory bowel disease. *Inflamm Bowel Dis*. 2015;21(8):1982-1992. [CrossRef]
6. Rogler G, Singh A, Kavanaugh A, Rubin DT. Extraintestinal manifestations of inflammatory bowel disease: current concepts, treatment, and implications for disease management. *Gastroenterology*. 2021;161(4):1118-1132. [CrossRef]
7. Cappello M, Randazzo C, Bravatà I, et al. Liver function test abnormalities in patients with inflammatory bowel diseases: a hospital-based survey. *Clin Med Insights Gastroenterol*. 2014;7:25-31. [CrossRef]
8. Uko V, Thangada S, Radhakrishnan K. Liver disorders in inflammatory bowel disease. *Gastroenterol Res Pract*. 2012;2012:642923. [CrossRef].
9. Silva J, Brito BS, Silva INN, et al. Frequency of hepatobiliary manifestations and concomitant liver disease in inflammatory bowel disease patients. *BioMed Res Int*. 2019;2019:7604939. [CrossRef]
10. Saroli Palumbo C, Restellini S, Chao CY, et al. Screening for nonalcoholic fatty liver disease in inflammatory bowel diseases: a cohort study using transient elastography. *Inflamm Bowel Dis*. 2019;25(1):124-133. [CrossRef]
11. Sartini A, Gitto S, Bianchini M, et al. Non-alcoholic fatty liver disease phenotypes in patients with inflammatory bowel disease. *Cell Death Dis*. 2018;9(2):87. [CrossRef]
12. Palmela C, Peerani F, Castaneda D, Torres J, Itzkowitz SH. Inflammatory bowel disease and primary sclerosing cholangitis: a review of the phenotype and associated specific features. *Gut Liver*. 2018;12(1):17-29. [CrossRef]
13. Kayar Y, Dertli R, Konur S, et al. The development of extraintestinal manifestation and related risk factors in Crohn's patients. *J Med Sci*. 2021;190:597-604.
14. Navaneethan U, Rai T, Venkatesh PGK, Kiran RP. Primary sclerosing cholangitis and the risk of colon neoplasia in patients with Crohn's colitis. *Gastroenterol Rep (Oxf)*. 2016;4(3):226-231. [CrossRef]
15. RuiHua S, Hao B, ShunFu X, QiYun T, JianXia J. A patient with primary biliary cirrhosis and ulcerative colitis with progression to primary sclerosing cholangitis and colorectal cancer: a case report. *Int J Case Rep Images*. 2012;3(12):11-15.