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Liver biopsy in inflammatory bowel disease patients with sustained abnormal liver function tests: a retrospective single-center study

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Abstract

Background Inflammatory bowel disease (IBD) may be associated with a wide range of hepatobiliary manifestations. This study aimed to characterize the spectrum of hepatobiliary disorders in patients with IBD who underwent liver biopsy for sustained abnormal liver function tests (LFT).

Method A retrospective study was performed of all patients with IBD who underwent liver biopsy between January 2010 and December 2020 for sustained abnormal LFT (at least 6-month duration).

Results A total of 101 patients were included, mostly male (62.4%), with a mean age of 44.4±13.3 years. The most common IBD type was Crohn's disease (61.4%). Median time interval between abnormal LFT and biopsy was 14 (7-36) months. Abnormal LFT was predominantly hepatocellular in 40 patients (39.6%), cholestatic in 26 (25.7%) and mixed in 35 (34.7%). The most frequent diseases were nonalcoholic fatty liver disease (NAFLD) in 33 patients (32.7%), drug-induced liver disease (DILI) in 30 (29.7%), autoimmune hepatitis (AIH) in 13 (12.9%) and primary sclerosing cholangitis (PSC) in 13 (12.9%). Three patients had primary biliary cholangitis. Remarkably, 70 patients (69.3%) already had fibrosis by the time of liver biopsy and in 6 (5.9%) liver disease was already detected in the stage of cirrhosis.

Conclusions Abnormal LFT in IBD patients had a wide range of etiologies and histology was often essential for reaching a correct diagnosis. NAFLD, DILI, AIH and PSC were the most common diagnoses and patients often presented in cirrhotic stage. Therefore, liver biopsy must be considered early in IBD patients with unexplained sustained abnormal LFT.

Keywords Inflammatory bowel disease, hepatobiliary disorders, liver biopsy

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Introduction

Inflammatory bowel disease (IBD) is a chronic idiopathic gastrointestinal condition, with the main subtypes being Crohn's disease (CD) and ulcerative colitis (UC). Several extraintestinal manifestations may be associated with both CD and UC and the disease may have a profound impact on patients' quality of life [1].

Hepatobiliary disorders are common extraintestinal manifestations in IBD and may appear at any time during the natural course of the disease or in association with treatment. It is estimated that approximately 50% of patients may present abnormal liver function tests (LFT) during their disease course. Although these are most commonly transient liver enzyme elevations associated with an IBD flare, the spectrum of clinical manifestations is wide, ranging from an incidental finding in asymptomatic patients to more severe manifestations, including liver failure, liver cirrhosis, portal hypertension and death [2,3].

These manifestations may be linked to IBD in several ways: 1) disorders that have a proven association with IBD and possibly a common pathophysiology, including primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH); 2) diseases directly and structurally related to intestinal inflammation, including portal vein thrombosis, liver abscesses and granulomatous hepatitis; 3) adverse events of IBD treatment; and 4) disorders linked to the metabolic consequences of IBD, including cholelithiasis, nonalcoholic fatty liver disease (NAFLD), and amyloidosis [4]. Considering this extensive differential diagnosis and wide spectrum of clinical manifestations, the diagnostic workup of patients with IBD and hepatobiliary abnormalities is often challenging. The aims of this study were to characterize the spectrum of hepatobiliary disorders in patients with IBD and to define the role of liver biopsy in the diagnostic workup of IBD patients with sustained abnormal LFT.

Patients and methods

All adult patients with follow up in specialized IBD consultation at Centro Hospitalar Universitário de São João (Porto, Portugal) who underwent liver biopsy for sustained abnormal LFT between January 2010 and December 2020 were eligible for this retrospective study. Patients were excluded if a diagnosis of CD or UC was not firmly established or if they were followed for other forms of IBD, such as microscopic colitis or eosinophilic colitis. Sustained abnormal LFT was defined as an elevation, for at least 6 months, of aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, alkaline phosphatase, or total bilirubin. Subsequently, the hospital's electronic medical records were searched in order to retrieve demographic, clinical, laboratory, imaging and histological data. This study was approved by the local ethics committee.

Liver biopsies were performed using a Menghini needle after adequate liver evaluation and marking with abdominal ultrasound. The procedures were performed under conscious sedation after administration of intravenous midazolam. All patients signed written informed consent before procedure and remained under surveillance for 4 h after the procedure. All routine hematoxylin and eosin stains and immunohistochemical stained slides and other ancillary testing results were reviewed by 2 expert liver pathologists. Liver fibrosis was scored according to the Metavir score on a 5-point scale (F0-F4) [5].

Statistical analysis

Categorical variables were expressed as frequencies and percentages and compared using the chi-square or Fisher's exact test. Continuous variables were expressed as mean and standard deviation for variables with normal distribution, or median and interquartile range for variables with skewed distribution, and compared using Student's *t*-test or nonparametric test. A 2-tailed P<0.05 was considered statistically significant. Statistical analysis was performed using the SPSS 27.0 software package.

Results

A total of 101 patients were included (Table 1), 63 (62.4%) male, with a mean age of 44.4±13.3 years. There were 62 (61.4%) with CD and 39 (38.6%) with UC (Table 2). Median disease duration was 42 (interquartile range [IQR] 8-112) months. The most common therapy was 5-aminosalicylic acid (5-ASA) derivatives in 68 (67.3%), followed by azathioprine in 58 (57.4%). Forty-six patients were under biological agents, most commonly infliximab in 29 (28.7%), adalimumab in 11 (10.9%), vedolizumab in 3 (3.0%), and ustekinumab in 3 (3.0%). The pattern of abnormal LFT was most commonly hepatocellular in 40 (39.6%) patients, whereas a cholestatic pattern was found in 26 (25.7%) and a mixed pattern in 35 (34.7%). The median time between detection of abnormal LFT and liver biopsy was 14 (IQR 7-36) months.

The prevalence of abnormal histological findings is described in Table 3. Some degree of inflammation was noted in 97 (96.0%) patients. The presence of steatosis was observed in 65 (64.4%) patients, siderosis in 24 (23.8%), and overt cholestasis in 4 (4.0%). Remarkably, 70 (69.3%) patients

Table 1 Patients' characteristics

Characteristics	Value	
Number of patients	101	
Age (mean ± standard deviation), years	44.4±13.2	
Sex		
Male	63	(62.4)
Female	38	(37.6)
IBD type *		
Crohn's disease	62	(61.4)
Ulcerative colitis	39	(38.6)
Disease duration (median, IQR), months	42 (8-112)	
IBD treatment		
5-ASA	68	(67.3)
Azathioprine	49	(48.5)
Azathioprine + infliximab	9	(8.9)
Infliximab	20	(19.8)
Adalimumab	11	(10.9)
Vedolizumab	3	(3.0)
Ustekinumab	3	(3.0)
Methotrexate	2	(2.0)
Abnormal LFT pattern		
Hepatocellular	40	(39.6)
Cholestatic	26	(25.7)
Mixed	35	(34.7)
Time interval between abnormal LFT and liver biopsy (median, IQR), months	14 (7-36)	

*For details regarding patients' distribution according to the Montreal classification, please see Table 2

IBD, inflammatory bowel disease; IQR, interquartile range; LFT, liver function tests

already had fibrosis by the time of liver biopsy and in 6 (5.9%) liver disease was already detected in the stage of cirrhosis (Metavir F4). Other findings providing important diagnostic clues occasionally reported included interface hepatitis in 13 (12.9%), Mallory hyaline bodies in 5 (5.0%), periductal concentric fibrosis in 5 (5.0%), multifocal sinusoidal dilatation in 2 (2.0%), signs of hepatitis B virus (HBV) infection in 1 (1.0%), amyloid deposition in 1 (1.0%), and nodular regenerative hyperplasia (NRH) in 1 (1.0%).

Table 2 Patients' distribution according to the Montreal classification

	Age at diagnosis (A)	No. of patients	%
Crohn's disease (n=62)	A1: <17	5	8.2
	A2: 17-40	34	55.7
	A3: >40	22	36.1
	Location (L)		
	L1: ileal	27	43.6
	L2: colonic	12	19.4
	L3: ileocolonic	23	37.1
	L4: isolated upper disease	0	0
	Behavior (B)		
	B1: non-stricturing, non-penetrating	25	40.3
	B2: stricturing	14	22.6
	B3: penetrating	23	37.1
	Perianal disease (p)	18	29.0
Ulcerative colitis (n=39) Extension	E1: ulcerative proctitis	10	25.6
	E2: left-sided ulcerative colitis	12	30.8
	E3: extensive colitis	17	43.6

Table 3 Prevalence of abnormal histological findings

Histological changes	n=101,	%
Inflammation	97	96.0
Steatosis	65	64.4
Siderosis	24	23.8
Cholestasis	4	4.0
Fibrosis	70	70.3
F1	41	40.6
F2	12	11.9
F3	11	10.9
F4	6	5.9
Others		
Interface hepatitis	13	12.9
Mallory hyaline bodies	5	5.0
Periductal concentric fibrosis	5	5.0
Multifocal sinusoidal dilatation	2	2.0
Signs of HBV infection	1	1.0
Amyloid deposition	1	1.0
Nodular regenerative hyperplasia	1	1.0

HBV, hepatitis B virus

After integration of clinical, histological and other important data, the overall prevalence of each hepatobiliary disorder is depicted in Fig. 1. The most common diagnosis was NAFLD in 33 (32.7%) patients, followed by drug-induced liver disease (DILI) in 30 (29.7%), PSC and AIH in 13 (12.9%) each, alcoholic liver disease in 4 (4.0%), PBC in 3 (3.0%) and AIH/PSC overlap syndrome, hemochromatosis, α1 antitrypsin deficiency, amyloidosis, and NRH in 1 (1.0%) patient each. When grouped by abnormal biochemical pattern (Fig. 2), one can see that NAFLD and DILI were the most common IBD-associated hepatobiliary manifestations, regardless of the predominant pattern of abnormal LFT. Nevertheless, it is evident that the main differential diagnosis varied according to the predominant pattern of abnormal LFT, with a trend for AIH, hemochromatosis and α1 antitrypsin deficiency to present with hepatocellular pattern, as opposed to PSC, amyloidosis or nodular regenerative hyperplasia, which more commonly present with a cholestatic pattern, for example.

NAFLD was the most common diagnosis, found in 33 patients; 24 (72.7%) were male and 23 (69.7%) had CD. Sixteen (48.4%) had excess body weight, defined by body mass index (BMI) 25-29.9 kg/m^2, and 7 (21.2%) were obese (BMI >30 kg/m^2). Other metabolic risk factors included dyslipidemia (66.7%), hypertension (21.2%), and type 2 diabetes mellitus (6.1%). Importantly, in 21 patients under immunosuppressive therapy with potentially hepatotoxic drugs (azathioprine and/or biological agents), liver biopsy was important to establish the differential diagnosis with DILI. Lifestyle changes, control of metabolic risk factors and optimization of IBD treatment resulted in improvements in LFT in 27 (81.8%).

DILI was the second most commonly detected hepatic manifestation and was found in 30 patients. The most

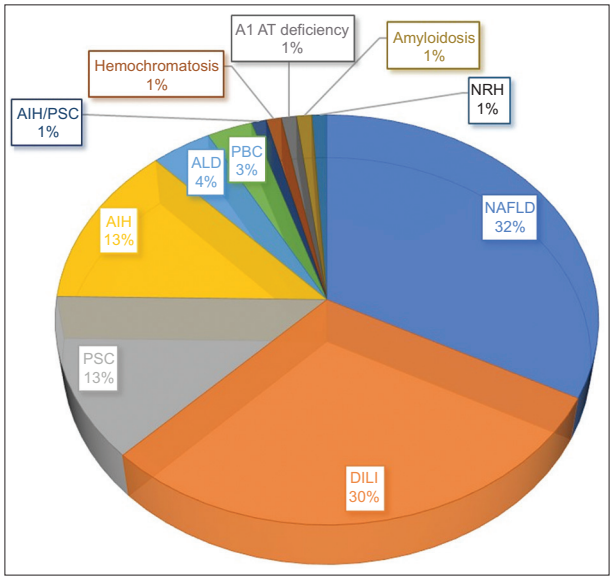

Figure 1 Overall distribution of hepatobiliary disorders
NAFLD, nonalcoholic fatty liver disease; DILI, drug-induced liver injury; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; ALD, alcoholic liver disease; PBC, primary biliary cholangitis; A1 AT, α1 antitrypsin; NRH, nodular regenerative hyperplasia

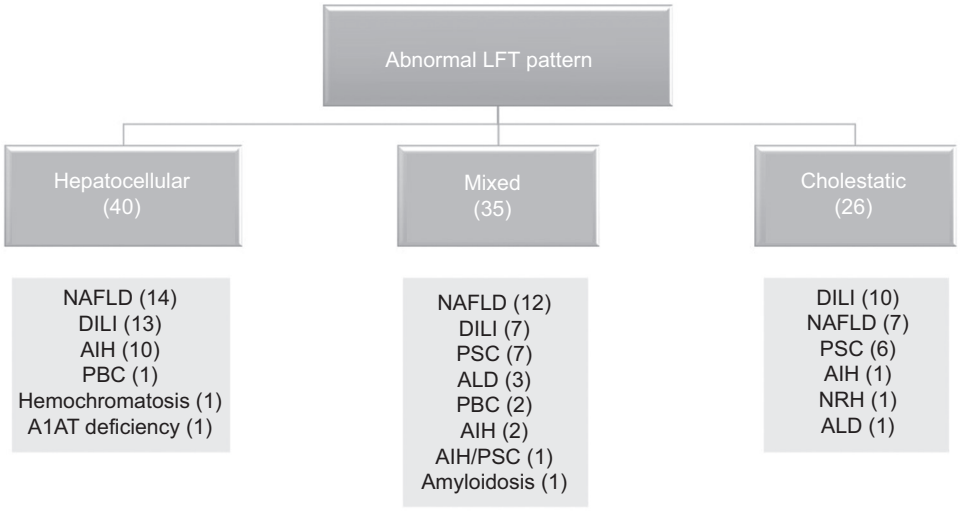

Figure 2 Distribution of hepatobiliary disorders according to predominant pattern of abnormal liver function tests
LFT, liver function tests; NAFLD, nonalcoholic fatty liver disease; DILI, drug-induced liver injury; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; ALD, alcoholic liver disease; PBC, primary biliary cholangitis; A1 AT, α1 antitrypsin; NRH, nodular regenerative hyperplasia

commonly implicated drug was azathioprine in 13 (43.3%) cases, followed by infliximab in 9 (30.0%). There were also 4 (13.3%) cases associated with isoniazid during pre-biological treatment of latent tuberculosis, and 1 (3.3%) case each was associated with adalimumab, ustekinumab, 5-ASA, and herbal products. In 17 patients, the inciting drug was stopped with normalization of liver biochemistries in all, whereas in 13 a decision to maintain the drug was taken after considering the benefit-to-risk ratio, with spontaneous resolution of abnormal LFT in 11 and maintenance of liver enzyme elevation in 2.

A diagnosis of PSC was established in 13 patients; 7 (53.8%) were male and 9 (69.2%) had UC. Large-duct PSC was diagnosed in 8 (61.5%) and liver biopsy was required in these to exclude overlap with AIH because of significant cytolysis and/or hyperglobulinemia and/or elevated antinuclear antibody (ANA)/anti-smooth muscle antibody (ASMA) titers or to adequately stage liver disease after inconclusive transient elastography. In contrast, 5 (38.5%) had small-duct PSC and liver biopsy was essential for diagnosis. All patients started ursodeoxycholic acid (UDCA), although only 5 (38.5%) had significant biochemical improvement. Importantly, 2 (15.4%) were diagnosed in the cirrhotic stage and were referred for liver transplantation. One patient required endoscopic retrograde cholangiopancreatography for dominant biliary stenosis.

AIH was identified in 13 patients; 7 (53.8%) were male and 10 (76.9%) had CD. A hepatocellular pattern of abnormal LFT was identified in 10 (76.9%); less commonly they presented with mixed (15.4%) or cholestatic (7.7%) patterns. ANA were present in 10 (76.9%), ASMA in 3 (23.1%), and hyperglobulinemia in 6 (46.2%). Liver biopsy was, by definition, essential to establish this diagnosis. AIH occurred in association with infliximab in 2 patients and its suspension was effective. In the others, conventional therapy with steroids and azathioprine resulted in biochemical improvement.

PBC was also diagnosed in 3 patients, all female, including 2 with CD and 1 with UC. All had positive anti-mitochondrial antibodies and liver biopsy was needed to exclude overlap with AIH because of significant cytolysis. One patient was diagnosed in the cirrhotic stage. All started UDCA with significant improvement.

The patient with amyloidosis was a 39-year-old female, with a 10-year history of CD under azathioprine, who developed cholestasis. After negative autoimmune panel and ultrasound, she underwent liver biopsy, which revealed amyloid deposition. She started infliximab and, with improved control of IBD, there was normalization of liver enzymes.

The patient with NRH was a 41-year-old male with CD who, 1 year after starting azathioprine, developed cholestasis. Magnetic resonance cholangiopancreatography (MRCP) revealed multiple nodules and liver biopsy confirmed the diagnosis of NRH. LFT did not improve after azathioprine was stopped.

A panel of viral markers (HBsAg, anti-HBc, anti-HBs, anti-HCV) was performed in 88 patients in total, most commonly during evaluation of cytolytic rather than cholestatic abnormal LFT. One case of HBV infection was detected in a 38-year-old female with mild ulcerative proctitis, during a diagnostic workup for mild cytolysis. Viral markers were positive for HBsAg, anti-HBc and anti-HBs and serum HBV DNA level was 5506 copies/mL, consistent with chronic HBV infection. Since transient liver elastography was inconclusive regarding the presence of fibrosis, the patient underwent liver biopsy, which revealed ground-glass hepatocytes in the absence of liver fibrosis. All the other patients had negative HBV and HCV screening.

Transient liver elastography was also performed in 31 patients, with a median liver elastography of 6.20 kPa and a median controlled attenuation parameter (CAP) of 256.0 dB/m. The median liver elastography was significantly higher in patients with histological evidence of liver cirrhosis

compared to patients who did not have histological evidence of liver cirrhosis (32.40±15.70 vs. 6.78±2.74, P<0.001). Median CAP was also significantly higher in patients with histological evidence of steatosis compared to patients who did not have evidence of steatosis (259.67±44.60 vs. 184.25±50.82, P=0.007).

Discussion

In this study, we present a retrospective analysis of a large cohort of IBD patients who underwent liver biopsy for sustained abnormal LFT. Notably, we demonstrated that liver biopsy may play an essential role during the diagnostic workup of sustained liver enzyme elevation, with important diagnostic, staging and therapeutic implications.

NAFLD was the most commonly diagnosed hepatic manifestation of IBD in our study, consistent with the published literature. In fact, NAFLD is more common and occurs at a younger age in IBD patients compared with the general population [6,7], and it is currently considered the most frequent hepatobiliary manifestation in these patients [8]. Importantly, metabolic syndrome does not appear to be the only triggering factor for NAFLD in IBD patients and the prevalence of risk factors such as obesity, hypertension, diabetes mellitus and dyslipidemia is significantly lower in patients with coexisting IBD and NAFLD compared to patients who only have NAFLD [9,10]. Advanced age, endoscopic activity, IBD duration and history of intestinal resection have been described as additional risk factors for NAFLD in IBD patients [6,7,11]. Although controversial, there is also some evidence that steroids, immunomodulators and anti-tumor necrosis factor (TNF) agents may predispose to NAFLD [12,13]. Management is mainly based on control of metabolic risk factors, lifestyle changes (particularly diet and physical exercise) and maintenance of IBD remission [14].

Abnormal LFT may also represent adverse effects of the drugs used in the treatment of IBD, as illustrated in our series, where DILI was the second most common cause. Almost all drugs used in the treatment of this condition may be associated with hepatotoxicity. Azathioprine can be associated with different types of liver injury, including hypersensitivity reactions, idiosyncratic acute cholestatic or hepatitis pattern, or long-term dose-dependent endothelial injury presenting as sinusoidal dilatation, peliosis, NRH and sinusoidal obstruction syndrome [15]. Most cases are mild and transient, rarely (4%) requiring drug withdrawal in cases of severe cholestasis, jaundice, non-improvement after 50% dose reduction, or development of chronic endothelial injuries [16]. Anti-TNF agents can also result in liver injury, more commonly with infliximab but also adalimumab, golimumab and certolizumab [17]. Abnormal LFT are typically mild and transient although, less commonly, cases of AIH have been described [18]. Discontinuation is recommended if transaminase elevation is >3 times the normal value and monitoring LFT are required when anti-TNF therapy is started and routinely every 4 months [19]. In rare cases, vedolizumab may also result in liver toxicity that is usually reversible when the drug is discontinued [20]. Rarely, 5-ASA may also result in severe hepatitis [21]. In contrast, ustekinumab and corticosteroids appear to be safe regarding hepatotoxicity, although the latter may induce NAFLD and reactivate viral hepatitis after prolonged use [22,23].

PSC is considered the most specific manifestation of IBD. The prevalence of IBD in patients with PSC is 70-80%, most frequently UC, while only approximately 5% of patients with IBD develop PSC [24]. It is hypothesized that PSC is a consequence of the sustained inflammatory response as a product of bacterial and viral translocation typical of IBD, with its subsequent release to the portal system contributing to an exaggerated inflammatory response of the cholangiocytes and possible evolution into fibrosis [25]. The most frequent clinical manifestations include abdominal pain, itching, jaundice, cholangitis and decompensated cirrhosis, although patients are often asymptomatic. Laboratory tests exhibit a predominantly cholestatic pattern and MRCP may demonstrate the typical beaded appearance, with multifocal segmental stenosis of the intra- and extra-hepatic biliary trees. Liver biopsy is used for diagnostic uncertainties or suspicion of small duct involvement, the classic finding being the presence of "onion-skin" periductal fibrosis leading to ductopenia and cholestasis. UC represents 80% of IBD-associated PSC cases, while indeterminate colitis and CD constitute the remaining 20%. UC usually follows a milder clinical course, although with more frequent extension to the right colon and significantly higher risk of colorectal cancer. The clinical course of CD also tends to be more benign, with the predominant phenotype being inflammatory [26].

AIH has a classic autoimmune behavior, and diagnosis consists of the combination of epidemiological factors, hypergammaglobulinemia, serology with ANA, ASMA and/or anti-LKM autoantibodies and liver biopsy, mandatory for diagnostic and prognostic purposes and demonstrates lymphoplasmacytic infiltration, pseudorosette formation and emperipolesis [27]. Its association with IBD is of low prevalence and it is more commonly associated with UC than CD. However, this association has clinical significance, as patients with AIH and IBD develop liver disease at a younger age, have a lower remission rate, a higher rate of treatment failure and more progression to cirrhosis [28].

The association between IBD and PBC is less common and concerns mostly patients with UC. Compared with classical PBC, patients seem to be more often young males with usually mild and non-extensive mucosal lesions, such as proctitis [29].

An important finding in our study is that a significant proportion of patients (70.3%) already had some degree of fibrosis at the time of liver biopsy and 5.9% already had liver cirrhosis. Studies assessing liver stiffness with transient elastography report a lower prevalence, with moderate fibrosis in 4% and severe fibrosis in 1% [30,31], suggesting that liver biopsy may be more sensitive and therefore advantageous for

detecting liver disease at an early stage. Importantly, there is evidence that active IBD at baseline is associated with a higher rate of liver fibrosis during follow up [32].

Interestingly, we found an association between histological findings of steatosis and fibrosis and elevated CAP and median elastography, respectively. Although only 31 patients underwent transient liver elastography, this raises the hypothesis that it may also play a role in the evaluation of IBD patients with sustained abnormal LFT. According to a study involving patients with IBD and HCV infection who achieved sustained viral remission, removal of the insulting factor may result in regression of liver fibrosis as measured by transient elastography, suggesting that it could also be useful in follow up [33]. Prospective studies are needed to define its role in the diagnosis and follow up of IBD patients with sustained abnormal LFT.

The pattern of liver enzyme elevation also provided important clues in guiding the differential diagnosis. Importantly, an algorithm guiding diagnostic tests according to the predominant pattern of abnormal LFT has been proposed: for patients with hepatocellular pattern the medication history, viral markers and ultrasound are recommended as first-line tests, followed by ANA, ASMA, anti-LKM and immunoglobulins if the former were negative, whereas a cholestatic pattern mandates medication history evaluation, AMA and ultrasound/MRCP. Liver biopsy is recommended when all previous evaluations were negative, regardless of the predominant pattern [34], and our results support the importance of liver biopsy in this setting.

The main limitation of this study was its retrospective single-center design. In addition, the fact that we only included patients who underwent liver biopsy may have resulted in selection bias, as our cohort mostly comprised more severe patients; this would affect the global picture of hepatobiliary manifestations of IBD, as they not always require histopathological examination for diagnosis. For example, cholelithiasis, reported as the second most common hepatobiliary manifestation of IBD [35], is classically diagnosed by imaging and liver biopsy does not play a role, so these cases were not included in our study. Nevertheless, our study also has strengths, as it includes a large cohort of IBD patients and, to the best of our knowledge, is the first study to specifically address the role of liver biopsy in patients with CD and UC, which can improve management of these patients.

In conclusion, abnormal LFT in IBD had a wide range of possible etiologies and liver biopsy was often essential for reaching a correct diagnosis. The most frequently detected conditions were NAFLD, DILI, PSC, and AIH. Advanced fibrosis, and even liver cirrhosis, was already present by the time of diagnosis in a significant proportion of patients. Therefore, liver biopsy is an important diagnostic tool that should be considered early during the diagnostic work-up of IBD patients with sustained abnormal LFT after inconclusive immunological and imaging studies.

Summary Box

What is already known:

- It is estimated that approximately 50% of patients may present abnormal liver function tests during the course of inflammatory bowel disease (IBD)
- The pathogenesis of hepatobiliary manifestations of IBD may be related to common immunological mechanisms or adverse events from drugs used in its treatment
- The clinical spectrum is wide, ranging from incidental findings to more severe manifestations

What the new findings are:

- Abnormal liver function tests in IBD had a wide range of possible etiologies and liver biopsy was often essential to reach a correct diagnosis
- This suggests there may be advanced fibrosis, and even cirrhosis, in a significant proportion of patients by the time of diagnosis
- Liver biopsy should be considered early during the diagnostic workup of abnormal liver function tests in IBD patients with inconclusive immunological study and imaging methods

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