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ORIGINAL ARTICLE

Coeliac Disease and the Liver: Spectrum of Liver Serology, Histology and Response of Treatment with Gluten-Free Diet

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ABSTRACT

Aim: To evaluate the histological spectrum of "celiac hepatitis" and the likelihood that these features will return after GFD.

Methods: The laboratory tests, Clinical profile, liver and duodenal biopsy were studied with the patients with hepatic derangement and CD among 35 patients. Whenever possible, a histological comparison of before and after GFD treatmenton liver and duodenal biopsies were performed.

Results: In the records of the pathology and gastroenterology departments of our institute, CD and ECM were found in 35 patients. There were twenty-four men and 11 women with a mean age of 24.3 (10-50 range).

Twenty-four patients were primarily identified with celiac disease and later diagnosed with CLD. At diagnosis, this feature was currently associated with small bowel diarrhea in 13 (65%) and CD without diarrhea in the remaining seven patients (35%). 10 of these 20 patients had anemia. Antibodies to TTG were positive in 21 patients (87.5%), AGA in 17 patients (70.8%), and EMA in 4 patients. Severe villous abnormality (Marsh-Oberhuber type 3C) in eleven patients (45.8.3%) on duodenal biopsy, moderate villous abnormality (type 3B) in seven patients (29.2%), 5 patients (20.8%) have mild abnormality of the villi (type 3A). The clinical topographies indicating the progress of liver ailment in these 24 cases are as follows: 8 have ascites (33.3%), 6(25%) patients have jaundice, hepatomegaly in 5 (20.8%) and 5(20.8%) Patients have splenomegaly.

Conclusion: There has been a problematic case of coeliac disease that has undergone an unnoticed distinction. This is one of the few researches that shows the full range of Coeliac Disease liver histopathology, from non-invasive to invasive hepatitis'. Experiment of a GFD may outcome in clinicopathological enhancement of 'coeliac hepatitis'.

Keywords: Gluten-free diet, coeliac disease, duodenal biopsies, hepatomegaly.

INTRODUCTION

The risk of developing an autoimmune disorder is dependent on the prevalence of a genetic mutation known as celiac disease, as well as a reaction to gluten in the diet. After the discovery of the disease's etiology, researchers have looked into a variety of genetic, immunological, and environmental factors on its onset[1-2]. CD can also be seen in a variety of non-alcoholic liver diseases, such as autoimmune disease (A) and cryptogenic or primary biliary cirrhosis (C), as well as liver conditions like primary sclerosing cholangitis/primary PBC and primary sclerosing cholangitis (PSC)to a degree previously unknown[3-4]. In this context, there is a question that needs to be answered: whether intestinal injury is associated with CD ('coeliac disease'). Some scholars use the terms "cryptogenic" and "coeliac" hepatitis interchangeably, but "cryptic" and "cryptic" are distinct entities[5-6]. Each of the words "aetiology," "crypto genesis," and "therapy" will be distinct. Although adult patients with coeliac disease first recorded abnormal liver function in the 1970s and have since shown that when they avoid gluten, their liver function improves, not every child has responded to a gluten-free diet, and much of the improvement in liver function was due to weight loss[7-8]. The range of liver entanglementvariesfrom liver injury to non-induced liver steatosis and isolated fibrosis to advanced liver disease counting cirrhosis, there are several different types of liver damage that can occur[9]. According to a PubMed search conducted between 2000 and 2017, histopathology research in CD is almost non-existent. As a result, prior research has primarily focused on the subject of serology. This study also looked into the histological changes observed in 'coeliac Hepatitispatients, as well as the possibility of recovery in CD patients. Another concern was checking for coeliac disease, as it was thought that certain patients may have had unexplained transaminasaemia, and CD has been shown to affect histology in the past.

METHODS

Data indicating that CLD was present in any patient admitted to the Gastroenterology department of Aziz Fatima Medical and Dental College Faisalabadfor three-years duration from March 2018 to March 2021. The ESPGAN (European Society for the Study of the Problem of Small Intestinal Mucosa were used to make the diagnosis of chronic diarrhea. The second criterion is that the patient be totally free of symptoms while on the GFD. The duodenal-biopsies microscopic investigation was done to assess villous architecture and other characteristics of CD using the Marsh-Oberhuber model. The patients with elevated white blood bilirubinemia, asemia, prolonged prothrombin time, ultrasonographic findings, and symptoms

of portal hypertension (pictures of esophageal varices) were present in 35 as the characteristic feature of CLD. Based on measurable features and apparent laboratory examinations, the patients were alienated into 2groups, contingent on whether they had the CLD or CD at the time of examination. We conducted a comprehensive medical history review of all cases of CLD, including those with prior or current jaundice, hepatomegaly, and gastrointestinal bleeding. A group of patients with classical (regular) CD were divided into two groups: those with diarrhea and those without. Non-diarrheal CDs have extracellular indices, such as refractory iron deficiency anemia, short stature, osteoporosisin the absenteeism of diarrhea. Laboratory tests comprised a complete tests of liver function and serological work with antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), antigliadin antibodies (AGA), tissue transglutaminase (TTG) and endomysic antibodies. The biopsies of Liver were performed to look for a number of histological anomalies, counting the characteristics of chronic hepatitis, autoimmune liver disease, mild reactive hepatitis, cirrhosis and steatohepatitis.

Minimum inflammation of the lobe with no significant interface activity were defined as extra zonal steatosis(<5%) or as “mild reactive hepatitis”. Interface activity with “chronic hepatitis” and inflammation of the lobe with or without necrosis were fluctuatinggrades of portal inflammation. Inflammatory activity in both of these groups was measured using the modified Ishak Histological Activity Index (Necro-inflammatory Score).

What we now know is that steatohepatitis normally includes hepatic steatosis and hepatic damage without the occurrence of fibrosis (based on clinical and pathological studies). Histological score (NAS score) was allocated to these cases. Fibrosis was observed in all liver biopsies using the ISS. Liver histology data were accessible in 28 of the 35 cases; Liver biopsy was monitored after initiating a GFD in eight patients. Immunohistochemistry of CD8 could be paired with liver biopsies before and after treatment to inspect for post-GFD reduction in CD8-positive cells.

RESULTS

In the records of the pathology and gastroenterology departments of our institute, CD and ECM were found in 35 patients. There were 24 males and 11 females with a mean age of 24.3 (range 10-50).

Table 1:

Findings	CD	CLD	Total
Liver biopsy indicated	24	11	35
Liver biopsy available	20	8	28
Mild reactive hepatitis with steatosis	6(30%)	3(37.5%)	9/28(32.1%)
Chronic hepatitis	8(40%)	5(62.5%)	13/28(46.4%)
Steatohepatitis	2(10%)	2(25%)	4/28(14.3%)
AILD	2(10%)	4(50%)	6/28(21.4%)
Patient demographics			
Age (years), mean (range)	23.0(12-45)	27.1(14-52)	
M:F	2.4:1.1	3.1:5	
Signs and symptoms of CD			
Non-diarrheal CD	7(35%)	3	
Diarrhea – small intestinal	13 (65%)	8	
Anemia	10(50%)	4(50%)	
Positive serology for CD			
IgA TTG	21(87.5%)	6(54.5%)	
IgA AGA	17(70.8%)	5(45.4%)	
EMA (n=4)	4(16.6%)		
Duodenal biopsy (Marsh-Oberhuber classification)			
Marsh 3C	11(45.8.3%)	7(63.6%)	
Marsh 3B	7(29.2%)	2(18.2%)	
Marsh 3A	5(20.8%)	2(18.2%)	
Marsh 1	1(4.2)	0	
Signs and symptoms of CLD			
Ascites	8(33.3%)	6(54.5%)	
Jaundice	6(25%)	4(36.4%)	
Gastrointestinal bleed	2(8.33%)	3 (27.3%)	
Splenomegaly	5 (20.8%)	7 (63.6%)	
Hepatomegaly	5 (20.8%)	5 (45.5%)	
Biochemistry for CLD			
Raised liver enzymes (ALT/AST/ALP)			
Reduced albumin	12 (50%)	7 (63.4%)	
Hyperbilirubinemia	2 (8.3%)	4 (36.4%)	
Positive autoimmune serology			
AMA	3	2	
ASMA	2	1	
ANA	2	1	

CD as first presentation: Twenty-four patients were primarily identified with celiac disease and later diagnosed with CLD. At diagnosis, this feature was currently associated with small bowel diarrhea in 13 (65%) and CD without diarrhea in the remaining seven patients (35%). 10 of these 20 patients had anemia. Antibodies to TTG were positive in 21 patients (87.5%), AGA in 17 patients (70.8%), and EMA in 4 patients. Severe villous abnormality (Marsh-Oberhuber type 3C) in eleven patients (45.8.3%) on duodenal biopsy, moderate villous abnormality (type 3B) in seven patients (29.2%), 5 patients (20.8%) have mild abnormality of the villi (type 3A). The clinical topographies indicating the progress of liver ailment in these 24 cases are as follows: 8 have ascites (33.3%), 6(25%) patients have jaundice, hepatomegaly in 5 (20.8%) and 5(20.8%) Patients have splenomegaly. Laboratory irregularities observed were decreased serum albumin in 12 (50%), deranged liver enzymes (ALP/ AST/ ALT) in 10 (41.6%) and hyperbilirubinemia in 2 (8.3%) cases(Table 1). To classify liver disease, the CTP score ranged from six to eleven with an average value of eight. The interval between two analyses vacillated from four months to two years. Seven patients had autoimmune serological labels.

AILD, autoimmune liver disease; AGA, antigliadin antibody; ALT, alanine aminotransferase; alkaline phosphatase as ALP; antinuclear antibody as ANA; antimitochondrial antibody as AMA, AST, aspartate aminotransferase; ASMA, anti-smooth muscle antibody; CLD, chronic liver disease; CD, coeliac disease; PBC, primary biliary cirrhosis; EMA, antiendomysial antigen antibody, TTG, anti-tissue transglutaminase antibody.

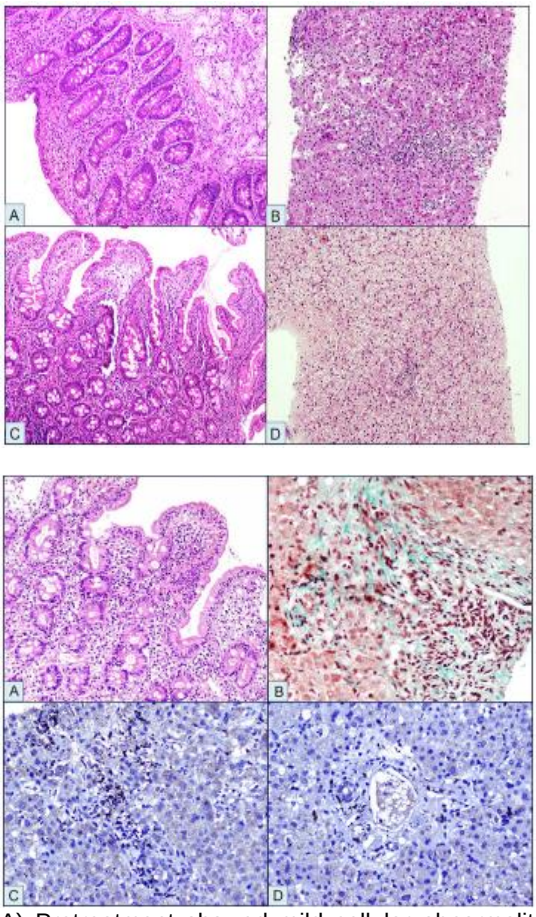
However, no topographiesevocative of autoimmune hepatitis such as plasma cell infiltration, interface hepatitis, bridge necrosis, centrifugal necrosis, or hepatocytic rosacea were observed. Isaac increased histological activity index score from 1 to 3 for mild reactive hepatitis, while chronic hepatitis increased from 5 to 8 (Table 2)

Table 2: Histological valuation of inflammation (NAS and HAI) in the CD and CLD groups

Histological category	CD	CLD
Chronic hepatitis (range, median HAI)	6 (5–8)	5 (5–6)
Patients Number	7	5
Steatohepatitis (NAS score)	7	4
Patients Number	2	2
Minimal reactive hepatitis (median HAI, range)	2 (1–3)	1
Patients Number	5	2

After a GFD; on Follow-up shows an improvement in BMI levels in all cases of hemoglobin and albumin. In these patients, the increase in body mass index increased between 1.4 and 7.3 kg / m2, hemoglobin increased between 1.4 and 5.3 g / dl, and serum albumin increased from 0.4 to 1.5 g / dl. Biopsy monitoring agents revealed improvement of faded cast with a decrease in IEL.

A Pretreatment show severe cellular abnormality, crypt hyperplasia (Marsh 3C) and increase intraepithelial lymphocytes (IEL). (B) Liver biopsy (same patient) shows sign of chronic hepatitis through lymphocytes expansion of portal pathways and a few plasma cells, foci of lobular inflammation and polymorphs (C) Continued duodenal gluten-free diet (GFD) biopsy. The recovery of vicious models has been revealed with the decline of IELs. (D) Liver biopsy after GFD, showing clear resolution of inflammation (eosin and hematoxylin stain, 100x)



A) Pretreatment showed mild cellular abnormality, cryptic hyperplasia (Marsh 3A) and free intraepithelial lymphocytes (eosin and hematoxylin spots, 100x). (B) Liver biopsy (same patient) shows sign of chronic hepatitis with fibrous spur (Ishak score: F4) (Masson's trichrome point, 200x). (CD). CD8 immunohistochemistry and liver biopsy before and after treatment reduced CD8 positive lymphocytes (200x) in the gluten-free diet, respectively.

CLD as first expression: First appearance CLD in patients was 11/35 (31.4%). Later, in the research, the CD was found. These patients who suggest that they have characteristic liver disease on admission; splenomegaly 7 (63.6%), hepatomegaly 5 (45.5%), ascites (54.5%), jaundice 4 (36.4%) and gastrointestinal intestine disease 3 (27.3%). Liver function studies decreased serum albumin in 7/11 (63.4%) patients, elevated liver enzymes in 9/11 (80.8%) and hyperbilirubinemia in 4/11 (36.4%) patients. CTP scores range from five to nine, with an average value of 7. Autoimmune serology was present in 5/11 patients. For hepatitis B and C, viral serology was negative in all patients. Eight of these 11 patients had liver biopsy findings.

In the case of mildly reactive hepatitis, the histological activity index was 1 and in the case of chronic hepatitis it was 5 to 6 (Table 2).

Liver biopsies before and after SGD in CD / CLD patients are shown in Table 3.

Case no.	Diagnosis at presentation	The first biopsy score of Fibrosis	Durationbetween biopsies in months	The second biopsy score of Fibrosis	Comments
1	Celiac disease	F4	6	F2	Declineinfibrosis, lobular and portal tenderness
2	Celiac disease	F1	9	F1	Decline in fibrosis, lobular and portal tenderness;on follow-up no steatosis
3	Chronic Liver disease	F3	3	F4	Patient expired; ASMA
4	Celiac disease	F2	10	F0	No substantial lobular inflammationor fibrosis on follow-up
5	Chronic Liver disease	F4	11	F1	Less lobular inflammation and Mild decrease in fibrosis; ANA
6	Chronic Liver disease	F6	13	F2	Obviousreduction in hepatic injury, no steatosis

Fibrosis stage> 2 occurs in seven cases according to the Ishak staging (Table 4).

Fibrosis stage (Ishak's) in liver biopsies of coeliac disease (CD) and chronic liver disease (CLD)

Fibrosis stage (Ishak)	Celiac disease (n=20)	Chronic Liver disease (n=8)
F0	7	1
F1	4	2
F2	3	0
F3	2	2
F4	2	2
F5	1	0
F6	1	1

DISCUSSION

Hepatic symptoms that may be related with celiac disease include asymptomatic increases in liver enzyme, steatosis, autoimmune liver disease and non-specific hepatitis[9-10]. One proposed pathogenesis mechanism, CLD in combination with CD, is reduced intestinal mucosal integrity, resulting in malabsorption and augmented permeability of mucosa, or liver toxin-mediated injury. An autoantigen recognized as antiendomysial IgA antibodies is also due to mucosal inflammation in CD due to tissue transglutaminase exposure in endomysium. TTG IgA antibodies may also be a risk factor in other autoimmune diseases, which suggests the autoimmune cause of CD and CLD[11]. The pathophysiologic function of autoimmune hepatitis (AIH) and CD is thought to have overlapping HLA molecules, particularly HLA-DR3 and are thus predisposing for coexistence of both diseases (AIH). In a major study involving young adults and 909 children with CD it was found that the incidence of autoimmune diseases was substantially greater in CD patients than in the control group. In 1.1% of the students, the AIH was also identified, without any cases in a stable control group. Researchers concluded that autoimmune disorders in celiac disease rely on the time of the revelation to gluten. Patients with CD have a 15% to 61% prevalence of hypertransaminasemia (68.5% for our trial). The prevalence of CDs is consistent. It needs to be answered if a distinct entity or part of a broader 'co-liver disease' spectrum are cryptogenic hepatitis / 'coeliac hepatitis' and the AILDs occurring in patients with CD. Are these coincidences of CDs and liver insults just coincidences, on the other hand? Mounajjed et al1 identified five CD patients with non-specific liver biopsy abnormalities, and no apparent cause other than CD for liver disease[12-13]. Because after a GFD, the liver's biochemistry has changed, these cases may indicate celiac hepatitis. In 4 out of 20 patients with a primary diagnosis of C D, autoimmune or other causes of liver disease were not found. Chronic hepatitis, steatohepatitis, and cirrhosis were mild in these patients. These cases have shown a biochemical improvement on a GFD as well as a histological improvement to help diagnosis of coeliac hepatitis in all three cases in which follow-up biopsies are accessible. In this population, the histology of the liver mentioned is very common and shows a number of changes depending on how long gluten exposures are. The main reason is that most patients receive a gluten-free diet for a long time, due to celiac disease. As a result, CLD patients with suspected symptoms of liver involvement, liver-related transaminemia, or manifestations of tissue dysfunction should be evaluated individually to diagnose "coeliac hepatitis[14-15]."

According to studies, about 10% of patients with hypertyrosinemia may have a positive serological screening for Coagulation Factor V deficiency[16].On the same GFD-treated patients, there were changes in both negative and positive small intestinal blood test outcomes, as well as in the small biopsies from these patients. In this group of patients, the procedure of repeating a GFD had little to no effect on liver pathology and non-specific liver function tests. As a result, CLD was found in 9 of the 11 patients who were eventually diagnosed with the disease in our study. Agnostics were found to be positive in 70% of the patients, while Agnomens were found to be positive in 60%. A duodenal biopsy was performed in each of the duodenal biopsies. Microscopy revealed severe villous disease and moderate villous disease. There is evidence that autoimmune disorders are a significant risk factor for AIH and PBC, so the authors hypothesized that these two conditions may be seen more often in patients who are also predisposed to them. In our sample, people with CD had serological evidence of chronic hepatitis, and one with characteristic histology had PBC; in the other study, people with CD had characteristic histopathology[16-17]. Since completing a GFD, two patients were seriously affected, one with mild biochemical and histological (pathological) benefits, and the other with moderate biochemical and histological (pathological) benefits. Cholesterol tends to play a role in the prevalence of autoimmune disease, which

affects between 3.5 percent and 33.3 percent of the population[18-19]. People who demonstrate that CLD or hypertransaminasinemia exists in cases of AILD, patients, other people with AILD, and people who have no clear or apparent reasons for AILD should all be included in the screening process, according to current and previous studies[20-21].

CONCLUSION

Finally, Celiac disease might be a probable cause ofceliac hepatitis or cryptogenic liver disease.AILDs occurring in patients with "celiac hepatitis" and CD may be different immunopathogenesis, histology, clinical presentation, and therefore entities that respond differently to GFD. Celiac hepatitis patients can be a curable group that responds to GFD. Liver histology in this group is non-specific and displays changes (chronic hepatitis, mildly reactive hepatitis, cirrhosis, steatohepatitis) as a function of the duration of gluten exposure because patients can follow GFD when initially diagnosed. For effective treatment, evaluation of patients with unexplained transaminases, AILD, organomegaly or anemia should be recommended to determine the possible presence of CD.

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