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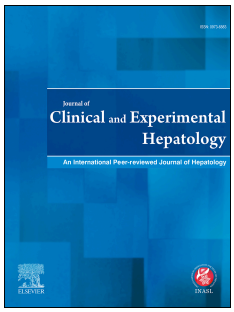

Frequency of non-cirrhotic portal fibrosis in patients with celiac disease: A single centre experience from northern India

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Frequency of non-cirrhotic portal fibrosis in patients with celiac disease: A single centre experience from northern India

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Running title: NCPF in patients with celiac disease

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To the editor,

Portal hypertension is well-known in patients with celiac disease (CeD). However, only a few reports of non-cirrhotic portal fibrosis (NCPF) are reported in patients with CeD [1]. The association of NCPF with CeD is uncommon, and the data on this issue is sparse. Accordingly, we undertook a study to know the frequency of NCPF among patients with CeD. The present study included 150 patients with CeD whose data were prospectively maintained on a questionnaire including demographic, clinical, biochemical and histological parameters during a five-year period (2016 to 2021) in the Department of Gastroenterology at Sanjay Gandhi Postgraduate Institute of Medical Sciences. All patients underwent necessary tests to look for the presence of portal hypertension. Patients with portal hypertension who had normal liver ultrasonography, patent splenoportal axis and low liver stiffness value (<10 kPa) underwent liver biopsies and hepatic venous pressure gradient (HVPG) measurement. Asia pacific association for the Study of the Liver (APSAL) criteria were used to diagnose NCPF [2]. Among 150 patients three patients (2%) had NCPF. Their clinical, biochemical, and histological features are described here (Table 1). On examination, all of them had clinically palpable splenomegaly. Liver biopsies revealed periportal fibrosis in two patients and normal in one patient, suggesting NCPF. Following a gluten-free diet (GFD), their symptoms improved.

NCPF has been now classified as porto-sinusoidal vascular disease (PSVD) [3]. PSVD encompasses a group of disorders which is characterized by lesions involving small vasculature of the liver or sinusoids because of underlying immune disorders, infections, or thrombophilia. A liver biopsy is mandatory to diagnose PSVD [3]. Non-specific duodenal biopsies findings are common in patients with portal hypertension and false positive celiac serology is also reported in patients with cirrhosis [4]. But the combination of high anti-TTG,

villous atrophy and response to gluten therapy point towards the diagnosis of CeD.

In our study, 2% of patients had NCPF. Similar results were found in a study from India. A study by Nijhawan et al. showed that of 363 patients with CeD, 12 (3.3%) had NCPF [5]. Other reports from India have shown similar presentations [6]. Following GFD, symptomatic improvement was noted however improvement of portal hypertension was not documented in most of the studies. The prevalence of autoimmune liver diseases like autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis are high among patients with CeD (4-11%) [7][8]. The association between CeD and autoimmune liver diseases can be explained by underlying genetic predisposition and immunogenic mechanisms [9][10]. Interestingly patients with CeD and other autoimmune liver diseases share common HLA which was shown by Kaukinen et al [9]. In that study, 39% of patients with PBC with celiac disease and 58% of patients with PSC and celiac disease shared HLA DR3 DQ2 or DR4-DQ8. Hence, a gluten-free diet can reverse liver dysfunction in celiac disease which has been reported in earlier studies [9]. NCPF is uncommonly associated with CeD and the presence of splenomegaly should prompt a physician to look for portal hypertension.

Abbreviation

CeD: Celiac disease

GFD: Gluten-free diet

HVPG: Hepatic venous pressure gradient

HLA: Human leukocyte antigen

LSM: Liver stiffness measurement

NCPF: Non-cirrhotic portal fibrosis

PSVD: Porto-sinusoidal vascular disease

TTG: Tissue transglutaminase

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Table 1: Clinical**,** biochemical, and histological profile of all the patients with non-cirrhotic portal fibrosis (NCPF)

Patient characteristics	**Patient 1**	**Patient 2**	**Patient 3**
Age (years)	27	33	19
Sex	Female	Female	Female
Presenting complaints	Easy fatigability and recurrent iron deficiency anemia	Easy fatigability and left hypochondrium pain	Chronic diarrhea
Clinically palpable splenomegaly	++	++	+++
Hemoglobin (12-16 g/dL)	7.6	8.5	10.2
Total leukocyte count (4500-11000/ mm^3)	3500	2450	4100
Platelet count (1.5-4.5/ mm^3)	80,000	1.41	76,000
Bilirubin mg/ dL (total/conjugated)	1.4/0.7	2.3/1.3	1.2/0.4
SGOT/SGOT (U/L)	40/35	18/32	34/24
Alkaline phosphatase (U/L)	254	115	59
Albumin (g/dL)	3.7	3.4	4.0
INR	1.62	1.43	1.63
Anti TTG (Normal <3Unit/mL)	>100	78	112
Concomitant autoimmune disease	Hypothyroidism	Nil	Subclinical hypothyroidism
LSM (kPa)	11	9.1	9.8
HVPG (mm of Hg) (Normal < 5)	9	8	7.5
Varices	Small esophageal varices	Small esophageal varices	Small esophageal varices
Spleen size (7.6-13 cm) **PV diameter (<13 mm)**	22 16	25 15	20 18
Liver biopsy	Inconspicuous portal tract with fibrosis	Normal liver biopsy	Peri-portal tract fibrosis
Response to GFD	Died of intestinal perforation after eight	Yes Gained weight, anemia improved	Yes Diarrhea improved

	months of diagnosis after transient response		

SGOT: Serum glutamic-oxalacetic transaminase; SGPT: Serum glutamic-pyruvic transaminase; INR: International normalized ratio; TTG: Tissue transglutaminase; kPa: kilopascal; ANA: Antinuclear antibody; AMA: Anti-mitochondrial antibody; LKM1: Liver kidney microsomal antibody 1; HVPG: Hepatic venous pressure gradient; U/L: unit per liter