

Case Report

Gluten-Free Hepatomiracle in "Celiac Hepatitis": A Case Highlighting the Rare Occurrence of Nutrition-Induced Near Total Reversal of Advanced Steatohepatitis and Cirrhosis

Kavita Gaur, Puja Sakhuja, Amarendra S. Puri¹, Kaushik Majumdar

Departments of Pathology and ¹Gastroenterology, GB Pant Institute of Postgraduate Medical Education and Research (GIPMER), New Delhi, India

Address for correspondence:

Prof. Puja Sakhuja, Department of Pathology, GB Pant Institute of Postgraduate Medical Education and Research (GIPMER), New Delhi, India.
E-mail: pujasak@gmail.com

ABSTRACT

Regression of hepatic fibrosis is increasingly becoming a reality, both in clinical as well as experimental models. Reversal or near-total regression of marked liver steatohepatitis and fibrosis, however, remains a rare event. We report the case of a 20-year-old female presenting with diarrhea due to celiac disease and biopsy proven cirrhosis with portal hypertension who had a remarkable clinical improvement in response to a gluten free diet (GFD). A follow-up liver biopsy 9 months after the initiation of GFD revealed a remarkable regression of both fibrosis as well as steatosis. Villous atrophy, as seen in patients with celiac disease, could lead to a deprivation of trophic factors leading to liver injury and subsequent cirrhosis. A gluten-free dietary regimen can produce a reversal of fibrosis leading to the amelioration of symptoms associated even with advanced liver disease.

Key Words: Celiac disease, fibrosis, gluten free diet, liver

Received: 21.03.2016, Accepted: 14.06.2016

How to cite this article: Gaur K, Sakhuja P, Puri AS, Majumdar K. Gluten-Free hepatomiracle in "celiac hepatitis": A case highlighting the rare occurrence of nutrition-induced near total reversal of advanced steatohepatitis and cirrhosis. Saudi J Gastroenterol 2016;22:461-4.

Liver changes in celiac disease (CD) range from asymptomatic elevation of transaminases^[1] to severe alterations including cirrhosis.^[2] Institution of gluten free diet (GFD) is known to reverse hepatic dysfunction, even though its effect in cirrhosis has only rarely been reported.^[2] Strict adherence to GFD in this reported case led to an improvement in clinical and biochemical parameters, along with reversal of steatocirrhotic change on histology. To the best of our knowledge this is the first case in which dietary intervention alone has resulted in near-total reversal of cirrhosis.

CASE REPORT

A 20-year-old female presented with complaints of abdominal pain and intermittent diarrhea for 6 months. Examination revealed pedal edema, ascites, and hepatosplenomegaly. The patient had a normal body mass index (20.16) for her age

and was not malnourished at presentation (Subjective Global Assessment of Nutritional Status class A). Investigations revealed a borderline low platelet count ($110 \times 10^9/L$), elevated erythrocyte sedimentation rate [ESR] (36mm/h), and prolonged international normalized ratio [INR] (1.8). Mild elevation of the transaminases (aspartate aminotransferase [AST]:68 IU/L, alanine aminotransferase [ALT]:38 IU/L), hypoproteinemia (5.6 g/dl), and hypoalbuminemia (2.9g/dl) were noted. Ascitic fluid revealed a high serum ascites albumin gradient [SAAG] (1.8g/dl). Ultrasonography (USG) confirmed hepatosplenomegaly with coarse liver echotexture and presence of collaterals suggesting portal hypertension. Upper gastrointestinal endoscopy showed grade 2 esophageal varices. Serological tests for Human Immunodeficiency Virus, hepatitis viruses, and cytomegalovirus were negative. Iron profile, autoimmune, and metabolic workup (including Wilson's) was non-contributory.

IgA tissue transglutaminase (TTG) done as a part of the diarrhea workup was strongly positive (542 IU/L). Duodenal biopsy

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Access this article online	
Quick Response Code: 	Website: www.saudijgastro.com
	DOI: 10.4103/1319-3767.195554

showed moderate villous blunting, increased intraepithelial lymphocytes (IEL), and crypt hyperplasia [Figure 1]. In view of the radiological and biochemical derangements, a percutaneous liver biopsy was also performed which showed parenchymal nodules separated by fibrous septae. Diffuse moderate-to-severe macrovesicular steatosis (65–70% of the hepatic parenchyma), hepatocyte ballooning, mild portal inflammation, and 2–4 foci of lobular inflammation/10 × were also noted [Figures 2a-b and 3a-b]. Piecemeal necrosis was not seen. A histopathological impression of cirrhosis with moderate activity and steatosis was suggested. The patient was put on a gluten free regimen, diuretics, and vitamin supplements. Complete resolution of ascites and near-normal transaminase levels was noted 6 months later when the patient presented again with the complaint of abdominal pain. Examination was unremarkable and investigations revealed a minimal elevation of AST (43 IU/L), other biochemical parameters being normal. Hematological parameters including platelet count ($170 \times 10^9/L$) were within normal limits. ESR, however, was elevated at 50 mm/h. USG displayed normal liver echotexture, minimal free fluid, but without any evidence of portal hypertension. An occasional subcentimetric mesenteric lymph node was noted. Ascitic fluid (AF) showed lymphocyte predominance and a low SAAG (0.8 g/dl). AF adenosine deaminase level was 57 U/L suggesting peritoneal tuberculosis. Peritoneal biopsy done for confirming tubercular pathology revealed epithelioid cell granulomas; however, acid fast bacilli (AFB) were not detected. The patient was put on antitubercular therapy in view of the above findings. She was religiously following the gluten free dietary regimen and was asked to continue the same.

Three months subsequently (i.e., 9 months after initial presentation), follow-up liver biopsy revealed complete disappearance of the steatosis and reversal of the fibrosis with

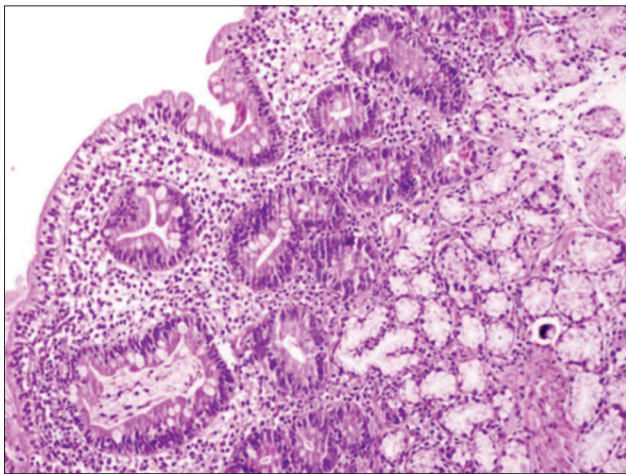


Figure 1: Duodenal biopsy showing moderate villous blunting increased intraepithelial lymphocytes and crypt hyperplasia (Marsh class 3b) (H and E, $\times 40$)

minimal expansion of the portal tracts [Figure 3c and d]. Only an occasional focus of lobular inflammation was noted. Biochemical, clinical, and hematological parameters including platelet count ($180 \times 10^9/L$) were normal. USG at this juncture displayed normal liver echotexture, no organomegaly, free fluid, or evidence of portal hypertension. A fibroscan unfortunately could not be performed in this case. Currently, the patient is asymptomatic and is doing well 3 years after her initial presentation and is completely adherent to the GFD.

DISCUSSION

Liver dysfunction in CD is attributed to increased intestinal permeability brought about by the induction of zonulin—a molecule involved in tight junction regulation.^[3] Accompanying mucosal damage promotes an increased access of a cocktail of toxins, antigens, and cytokines to the portal circulation. The result is liver disease of varying degrees.

Two main categories of liver disease have clinically been described in CD, that is, cryptogenic and autoimmune.^[4] While there is substantial literature on the clinical aspects of celiac liver disease, studies on histomorphological changes are few. Findings are generally non specific^[1] and include periportal inflammation, bile duct injury, increased number of Kupffer cells, steatosis, and fibrosis very rarely including cirrhosis.^[2]

In the current case, the patient had advanced liver disease with extensive steatosis in a setting of CD. We hypothesize that the small bowel is responsible for some unknown trophic factors for the liver which are transported by the portal circulation. Villous atrophy, as seen in patients with CD, could lead to a deprivation of the trophic factors leading

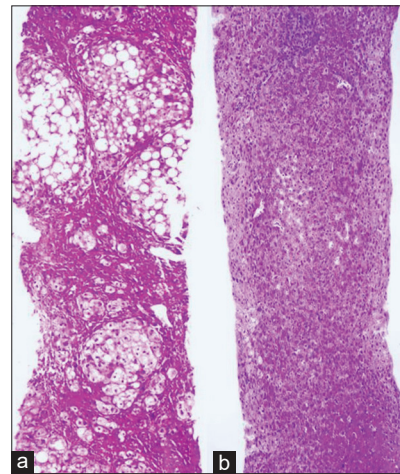


Figure 2: Low power magnifications of (a) Pre-GFD and (b) post-GFD liver biopsies highlighting the marked disappearance of fibrosis and steatosis after nutritional therapy (H and E, $\times 40$)

to liver injury and subsequent cirrhosis. The disease fitted into a cryptogenic category because infectious, autoimmune, and metabolic etiologies were ruled out after thorough work-up. Notably, a dramatic response to GFD was noted with histological evidence of near-total regression of fibrosis and steatosis.

Fibrosis regression has been documented in a range of chronic liver diseases.^[5] Friedman and Bansal^[5] mentioned that reversal and regression of liver fibrosis were distinct terminologies. The term “reversal” is preferred over “regression,” as in this case there is a complete restoration of normal architecture after the establishment of cirrhosis. Reversal is more likely to occur in young patients with a relatively short duration of illness,^[6] both factors being seen in this case.

Kaukinen *et al.*,^[2] in the year 2002, described 4 patients of CD with severe liver injury displaying improvement after GFD.

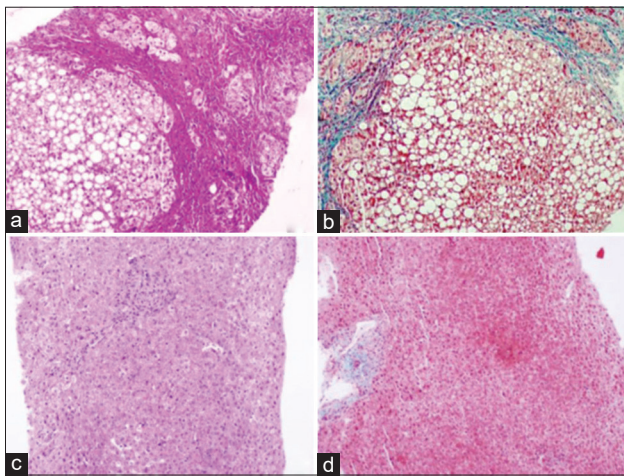


Figure 3: (a) Liver biopsy showing parenchymal nodules separated by fibrous septae, with diffuse macrovesicular steatosis on Hematoxylin and eosin (H and E $\times 200$) and (b) Masson's Trichrome ($\times 200$). (c) Post-GFD biopsy showing near total reversal of fibrosis and steatohepatitis (H and E $\times 200$);(d) Masson's Trichrome stain ($\times 200$)

One of these patients had early cirrhosis, and even though institution of GFD led to disappearance of the ascites, the micronodular cirrhosis persisted. In contrast, the present case witnessed resolution of cirrhosis. This remarkable clinical, biochemical, and histological reversal of advanced cryptogenic liver disease may be explained by the religious adherence of the patient to GFD.

As radiological and biochemical improvement was noted in this patient before the diagnosis of tuberculosis and subsequent antitubercular therapy, tuberculosis is unlikely to be responsible for the liver injury.

It may be argued that, in the absence of fibroscan results, the needle biopsy may be prone to sampling errors. Though we acknowledge this limitation, the significant difference in fibrosis in pre and post-GFD treatment biopsies correlated both with clinical improvement and reduction in noninvasive fibrosis indices—AST to platelet ratio index (APRI),^[7] Forn's,^[8] and FIB4^[9] after therapy [Table 1].

To conclude, CD is a potentially treatable cause of chronic liver disease. It is possible that dietary therapy alone could be of some benefit in the management of advanced celiac hepatitis. Further studies on larger cohorts, however, will be required to corroborate these results.

Ethical adherence

The present work was performed after taking informed consent from the patient and a sincere effort has been made to uphold patient confidentiality.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Table 1: Noninvasive fibrosis markers assessed in the current case

Fibrosis Index	Formula for calculation	Cut off scores for significant fibrosis/cirrhosis ⁽¹⁰⁾	Pretreatment	Post-treatment	%change
APRI	$\text{AST/UPPER LIMIT AST (IU/L)} \times 100$ $\text{Platelet count (10}^9\text{/L)}$	A score of at least 1.0 has a sensitivity of 61 to 76% and specificity of 64 to 72% in predicting significant fibrosis/cirrhosis	1.766	0.683	-61.32%
Forn's	$7.811-3.131 \times \ln(\text{Platelet count}[10^9\text{/L]})$ $+0.781 \times \ln(\text{GGT}[\text{IU/L}]) + 3.467 \times \ln(\text{age})$ $-0.014 \times \text{cholesterol (mg/dl)}$	At a score of <4.25 , a negative predictive value of 96% for excluding significant fibrosis, and at a score of >6.9 , a positive predictive value was 66% for significant fibrosis has been described	4.84	3.126	-35.41%
FIB 4	$\text{Age (years)} \times \text{AST (IU/L)}$ $\text{Platelet count (10}^9\text{/L)} \times \sqrt{\text{ALT (IU/L)}}$	At a score <1.45 , a sensitivity of 74% and specificity of 80% to exclude significant fibrosis. A score >3.25 has a specificity of 98% in confirming cirrhosis.	2.01	0.87	-56.7%

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, APRI: AST to Platelet Ratio Index, FIB-4, Fibrosis-4, GGT: Gamma-glutamyl transferase, IU: International units, ln: Natural logarithm

REFERENCES

1. Rubio-Tapia A, Murray JA. The liver in celiac disease. *Hepatology* 2007;46:1650-8.
2. Kaukinen K, Halme L, Collin P, Färkkilä M, Mäki M, Vehmanen P, *et al.* Celiac disease in patients with severe liver disease: Gluten free diet may reverse hepatic failure. *Gastroenterology* 2002;122:881-8.
3. Clemente MG, De Virgiliis S, Kang JS, Macatagney R, Musu MP, Di Pierro MR, *et al.* Early effects of gliadin on enterocyte signalling involved in intestinal barrier function. *Gut* 2003;52:218-23.
4. Zali MR, Rostami Nejad M, Rostami K, Alavian SM. Liver complications in celiac disease. *Hepat Mon* 2011;11:333-41.
5. Friedman SL, Bansal MB. Reversal of hepatic fibrosis-Fact or Fantasy. *Hepatology* 2006;43 (2, Suppl 1):S82-8.
6. Bortolotti F, Guido M. Reversal of Liver Cirrhosis: A desirable clinical outcome and its pathogenic background. *J Pediatr Gastroenterol Nutr* 2007;44:401-6.
7. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, *et al.* A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003;38:518-26.
8. Forns X, Ampurdanès S, Llovet JM, Aponte J, Quinto L, Martinez-Bauer E, *et al.* Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. *Hepatology* 2002; 36:986-92.
9. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, *et al.* FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection comparison with liver biopsy and fibrotest. *Hepatology* 2007;46:32-6.
10. Cox-North PP, Shuhart MC. Hepatitis C online. Core Concepts. Evaluation and Staging of Liver Fibrosis [Internet]. Washington (US) [Last Updated: 2015 October 22, Cited 2016 Jan 6]. Available from: <http://www.hepatitisc.uw.edu/go/evaluation-staging-monitoring/evaluation-staging/core-concept/all>.