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Case Report

Occurrence of Chronic Budd-Chiari Syndrome in a Patient with Coeliac Disease

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A B S T R A C T

The association of Budd-Chiari Syndrome (BCS) with coeliac disease has been understudied and underreported. Majority of the cases of this association have been reported from North Africa and Southern Europe, due to a higher prevalence of coeliac disease. BCS can present as acute, subacute, or chronic form and is characterised by hepatic venous obstruction, either thrombotic or non-thrombotic without any evidence of sinusoidal obstruction syndrome, right heart failure or constrictive pericarditis. Unlike patients with BCS alone, an underlying hypercoagulable state cannot be identified in most patients if coeliac disease is associated with BCS. Its incidence is found to be low in the rest of the world. Here, we present a case of coeliac disease and BCS from an Indian setting in a patient who was previously diagnosed with coeliac disease six years back, maintained on a gluten-free diet, and now presented with complaints of chronic Budd-Chiari Syndrome without any identifiable hypercoagulable aetiology.

Keywords: Coeliac Disease, Gluten-free Diet, Budd-Chiari Syndrome, Haematemesis

Introduction

Coeliac disease is a chronic, small intestinal, immune-mediated enteropathy that is precipitated by dietary gluten in genetically predisposed individuals. A large number of diseases occur more commonly among patients with coeliac disease. Dermatitis herpetiformis, type 1 diabetes mellitus, Down syndrome, epilepsy with cerebral calcification, fibrosing alveolitis, hypothyroidism or hyperthyroidism, idiopathic pulmonary hemosiderosis, IgA deficiency, inflammatory bowel disease (IBD), and recurrent pericarditis have a definite association with coeliac disease.[1] Coeliac disease may be implicated in deep venous thrombosis, but it is rarely responsible for hepatic vein thrombosis.[2-4] Budd-Chiari syndrome (BCS) is a relatively rare condition, characterised by hepatic venous obstruction, either thrombotic or non-thrombotic without any evidence of sinusoidal obstruction syndrome, right heart failure, or constrictive pericarditis. Its prevalence is estimated at approximately one case per 100,000 inhabitants.[5] Here, we present a case report of a young 18 years old Asian female who was diagnosed with coeliac disease six years back and now presented with symptoms of BCS. However, despite being on a gluten-free diet, on evaluation, no obvious aetiology for such a prothrombotic state was found.

Case Report

An 18-year-old Asian female, who was a known case of coeliac disease, and was on a gluten-free diet for the past 6 years, presented to our hospital with chief complaints of multiple episodes of haematemesis and melena for 15 days. There was no history of fever, abdominal distension, jaundice, pedal oedema, altered sensorium, menorrhagia, bleeding from any site, alcohol consumption or any drug intake, pruritis, joint pain, or abnormal bowel habits. A general physical examination revealed pallor. On per abdominal examination, splenomegaly was appreciable without any evidence of ascites and rest of the systematic examination was unremarkable. Initial resuscitation with intravenous fluids and transfusion of 3 units of packed cell volume (PCV) was done which was later followed by further investigations to delineate the aetiology. On the day of presentation, biochemical and haematological investigations revealed a haemoglobin level of 5.4 g/dL, platelet count of 48000 /mm^3, total leukocyte count of 3300 cells/mm^3 and International Randomised Ratio (INR) of 1.5. Peripheral smear showed pancytopenia with a microcytic hypochromic picture with a reticulocyte production index (RPI) of 1.9. Serologies for HIV, hepatitis B, C, A, E and leptospirosis were all negative. Antiphospholipid antibody profile (APLA), serum homocysteine levels, protein C, S, anti-thrombin 3 levels and prothrombin mutation, and factor V Leiden mutation were all within normal limits. In addition, testing for V617F JAK 2 mutation was also negative. Her autoimmune markers (antinuclear antibodies, anti-smooth muscle antibody, anti-liver kidney muscle antibody) were negative.

Further, a bone marrow biopsy was planned to investigate the aetiology of pancytopenia with reduced RPI and rule out myeloproliferative disorder. The biopsy revealed features of iron and vitamin B12 deficiency anaemia with a hypocellular marrow without any evidence of myeloproliferative disorder. Serum ceruloplasmin level was normal and Kayser–Fleischer ring was not observed on the slit lamp examination.

Ultrasound of the abdomen was suggestive of splenomegaly with small-sized liver and mild free fluid in the abdomen. Ascitic fluid analysis showed a transudative picture. Upper GI endoscopy revealed grade 3 oesophageal varices.

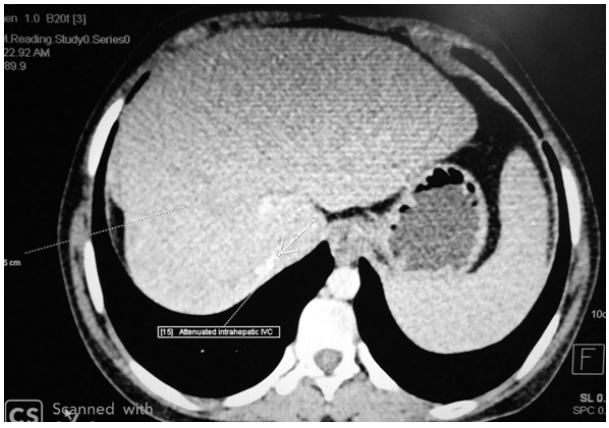

Figure 1.CECT Abdomen showing Attenuation of Intrahepatic IVC

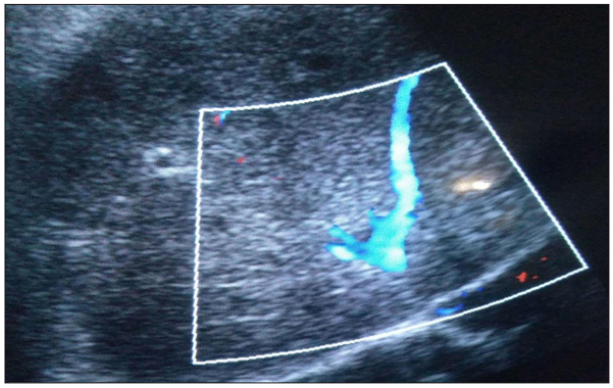

Figure 2.USG SP Axis Doppler showing Prominent Left Hepatic Vein and Non-visualisation of Right and Middle Hepatic Vein

A contrast-enhanced computed tomography (CECT) scan of the abdomen showed a small-sized liver with an irregular nodular surface, hypertrophy of the caudate lobe of the liver with non-visualisation of all the three hepatic veins, a dilated portal vein and attenuation of the intrahepatic inferior vena cava, as shown in Figure 1. Doppler ultrasound showed enlargement of the caudate lobe of the liver and a prominent left branch of the portal vein with an attenuated right branch, as shown in Figure 2.

Table 1.Characteristic Findings of Different Case Reports of Coeliac Disease with BCS from South-East Asian Region

Variables	2009 India	2018 India	2019 India	2020 Pakistan
Age (years)/ gender	19/ male	11/ female	18/ female	15/ female
Previous diagnosis of coeliac disease	No	No, but history of recurrent loose stools for the last 5 years	Yes, diagnosed 2 years back and well, controlled on a gluten-free diet	Yes, diagnosed 6 years ago and well-controlled on a gluten-free diet

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Presentation	Variceal bleeding	Anasarca, ascites, hepatomegaly	Progressive ascites	Progressive abdominal distension, diffuse abdominal pain, shortness of breath
Pro-thrombotic markers	Low levels of protein C and protein S	No	Elevated serum homocysteine and low serum folate levels	No
Prognosis/ outcome	Responded to a gluten-free diet	Clinical and radiologic evidence of recovery on day 5	Clinical recovery after 4 weeks of anticoagulation and gluten-free diet	Clinicopathologic recovery in 4 weeks

The patient underwent endoscopic variceal ligation and was started on low molecular weight heparin therapy along with a gluten-free diet. The patient improved symptomatically. She was discharged and referred to a gastroenterology unit on a gluten-free diet, oral anticoagulants, and oral hematinics. She is asymptomatic since the discharge and is on regular outpatient follow-up in a gastroenterology unit. Written consent was taken from the patient to use the clinical data for this report.

Discussion

As per the latest systematic review, the pooled global prevalence of coeliac disease is estimated to be 1.4% based on seroprevalence (i.e., positive anti-tissue transglutaminase and/ or anti-endomysial antibodies) and 0.7% among biopsy-proven cases.[6] The pooled prevalence in the Asia-Pacific region among the low-risk group is 1.2%.[7] The occurrence of BCS in a patient with coeliac disease is a very rare association with an annual incidence of this association being less than 5 per million.[8] This association was first reported in 1990.[9] In more than 80% of cases with BCS, an underlying hypercoagulable state could be recognised, however, when found in association with coeliac disease, no specific aetiology could be identified in most of the cases.[10] A review from Jordan illustrated that only 28 similar cases have been reported, with the majority being from Northern Africa.[11] Majority of the cases of BCS with coeliac disease have been reported from North Africa and Southern Europe.[12] Reports have attributed this to genetic, environmental, and dietary substances in the North African diet.[9,13,14] The annual incidences of BCS in Asian and European populations are 0.469 and 2 per million respectively.[15] As per the literature, four cases have been reported from the rest of the world where the occurrence of BCS was seen in patients with coeliac disease.[16,-19] Case reports of coeliac disease with BCS association from various parts of South-East Asian countries have been shown in Table 1.

The first case identified in India was in 2009; a 19-year-old teenager who presented with variceal bleeding as a complication of chronic BCS and on evaluation was found to have coeliac disease with low levels of protein C and S causing a prothrombotic state.[16] The second case reported from India was in 2018 - an 11-year-old female diagnosed to have coeliac disease with transient hepatic vein obstruction, suspected to be due to a thrombus or hemangioma.[17] The third case was reported from India in 2019 in an 18-year-old female with a diagnosis of coeliac disease, well-controlled on a gluten-free diet, who presented with progressive ascites. On further evaluation, she was found to have elevated homocysteine levels and low serum folate.[18] In the present case, the patient was diagnosed with coeliac disease 6 years back and was on a regular gluten-free diet. However, she presented with features of chronic BCS. In a similar report from Pakistan in 2020, the patient was a diagnosed case of coeliac disease for 3 years and presented with cardinal features of BCS. It is noteworthy to mention that the patient was not adherent to a gluten-free diet for the past several months preceding the diagnosis.[19] Although in our case, the patient gave a history of adherence to a gluten-free diet which had a temporal association with symptomatic improvement, evidence showed that history, clinical assessment of symptoms, and serologic tests had limited role in establishing patient compliance. More accurate measures to confirm adherence include the detection of gluten immunogenic peptides in faeces and urine.[20] These tests couldn't be performed in the present case due to financial constraints.

No cause of hypercoagulable state could be identified in our case. Various theories have been proposed for the occurrence of a prothrombotic state including malabsorption of vitamin K causing protein C, S and antithrombin III deficiency, hyperhomocysteinemia secondary to folic acid deficiency or methylenetetrahydrofolate reductase (MTHFR) gene mutation, myeloproliferative disorders,

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lymphoma, magnesium deficiency, autoimmune vasculitis, thrombocytosis, association with serum lupus anticoagulant, and thrombocytopenia secondary to hypersplenism.[21-23] We could not find any aetiology for this hypercoagulable state in our case.

Conclusion

There are multiple extraintestinal manifestations of coeliac disease. However, the occurrence of BCS in such patients is rare. Clinicians should be aware of the clinical presentation of such an association even in patients with coeliac disease who are relatively doing well on a gluten-free diet and a differential of BCS should be ruled out in such patients.

Conflict of Interest: None

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