Case report

Budd-Chiari syndrome associated with coeliac disease: case report and literature review

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Abstract

We report a case of Budd-Chiari syndrome occurring in a patient with coeliac disease, who presented with symptoms of increased abdominal girth, right upper quadrant pain and shortness of breath for three weeks prior to admission. Initial assessment revealed the presence of moderate ascites, hepatosplenomegaly and right-sided pleural effusion. Further diagnostic work-up established a diagnosis of chronic Budd-Chiari syndrome. Interestingly, complete screening for pro-thrombotic factors was negative. A review of the literature on this association disclosed only 28 similar cases, with the majority of them describing individuals of North African origin. Interestingly, in the majority of cases no specific thrombotic factor could be identified, suggesting that coeliac disease may play a role in this thrombotic disorder.

Key words: coeliac disease; Budd-Chiari syndrome; hepatic vein thrombosis

Introduction

Coeliac disease (CD)—an immune-mediated enteropathy triggered by the ingestion of gluten proteins in genetically susceptible individuals—is known to be frequently associated with a variety of extra-intestinal manifestations [1]. North American and European epidemiological studies have shown that CD is a common disorder, with a prevalence ranging between 1/100 and 1/150 [2]. Similarly, studies from north Africa and the Middle East have shown that the prevalence of CD is comparable to that in western countries [3].

Over the past four decades, several CD-associated hepatobiliary disorders have been documented, including isolated hypertransaminasemia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and non-alcoholic fatty liver disease [4]. Budd-Chiari syndrome (BCS) comprises a heterogeneous group of disorders characterized by hepatic venous outflow obstruction, in the absence of right heart failure, constrictive pericarditis, or sinusoidal obstruction syndrome. BCS is a relatively rare condition, with an estimated prevalence at one case per 100 000 individuals [5]. Several case reports published in the past two decades suggested an association between CD and BCS [6–21]. The aim of this case report and pertinent review is to improve our understanding of the clinical, pathogenic, and epidemiological characteristics of this disease association.

Case Presentation

A 27-year old single female, a known case of CD and on a gluten-free diet (GFD) for the previous 7 years, presented with a 3-week history of increasing abdominal girth, right upper quadrant pain, and shortness of breath. Pertinent physical examination showed a patient in moderate respiratory distress, with dullness to percussion of the right hemithorax and abdomen.
Abdominal ultrasound revealed moderate ascites, enlarged heterogeneous liver with nodularity and irregular margins, and moderate right-sided pleural effusion, in addition to marked splenomegaly (long axis 16 cm). A Doppler ultrasound of the liver showed collapsed suprahepatic veins. The diagnosis of BCS was confirmed by a contrast-enhanced computed tomography (CT) of the abdomen (Figure 1), which showed an enlarged nodular liver, hypertrophied caudate lobe, non-visualization of suprahepatic veins with narrowing of the hepatic segment of the inferior vena cava. At this point a liver biopsy was performed and histopathological examination of biopsies taken from the bulb and the second portion of the duodenum revealed an increase in intraepithelial lymphocytes in the absence of crypt hyperplasia or villous atrophy (modified Marsh type 1). Examination of peritoneal fluid was consistent with transudative ascites and tests for spontaneous bacteremia (modified Marsh type 1). Examination of biopsies taken from the bulb and the second portion of the duodenum revealed an increase in intraepithelial lymphocytes in the absence of crypt hyperplasia or villous atrophy (modified Marsh type 1). Examination of peritoneal fluid was consistent with transudative ascites and tests for spontaneous bacterial peritonitis, neoplasia, and acid-fast bacilli were all negative.

A complete blood count disclosed mild normocytic anaemia and a platelet count of 145 000/mm$^3$ (normal: 150 000–400 000). Liver function tests revealed hypoalbuminaemia (32 g/L; normal: 35–50), normal bilirubin and transaminases, alkaline phosphatase of 274 U/L (normal: 0–240), and a gamma-glutamyl transpeptidase of 86 U/L (normal: 6–42). Pro-thrombin time and international normalized ratio (INR) were elevated at 16.9 seconds and 1.4 seconds, respectively, while partial thromboplastin time was normal. Serum iron levels were low at 3.3 μmol/L (normal: 6.6–26), while ferritin was normal. Vitamin B12 level was low at 113.4 ng/mL (normal: 208–964), and folate level was normal. Vitamin D (25-OH) was decreased at 12.89 ng/mL (normal: >29), while serum calcium levels were within normal limits. Hepatitis C antibodies and HBsAg were both non-reactive. A complete serological screen for autoimmune hepatitis (anti-nuclear antibodies and anti-smooth muscle antibodies) produced normal results. Fasting lipid profile, kidney and thyroid function tests were within normal limits.

A full screen for all known thrombophilic factors was unrevealing. Specifically homocystein level 7.8 μmol/L (normal: 4.9–11.6); wild type (normal) of pro-thrombin mutation by PCR; lupus anticoagulant 39 seconds (normal:32–42); anticardiolipin (IgG and IgA) negative; wild type of factor V Leiden by PCR (normal); anti-thrombin III activity 88% (normal: 80–120); protein C 95% (normal: 75–165); protein S free 91% (normal: 50–120). A bone marrow biopsy—performed to rule out myeloproliferative disorder—was normal. Additionally, a test for V617F JAK2 mutation by real-time polymerase chain reaction (JAK2 MutaQuant kit, Ipsogen, Hilden, Germany) was negative.

The patient was therefore managed conservatively with anti-coagulants, diuretics, and a gluten-free diet in addition to oral vitamin D supplements and vitamin B12 injections. She initially showed some improvement, but unfortunately later developed massive, refractory ascites, requiring multiple therapeutic paracentesis. At that point, she was referred to interventional radiology for porto-caval shunt, which was successfully carried out, with subsequent resolution of ascites. Six years after her shunt procedure, the patient remains well with no recurrence of ascites.

Discussion

This case describes the occurrence of BCS in a female patient with CD. She developed features of BCS despite strict adherence to a GFD and in the absence of any known pro-thrombotic factor. We searched PubMed for full articles, case reports and case series published in English, Spanish, or French-language journals in the period from January 1980 to April 2016 using the following keywords and free text terms alone or in combination: “Budd-Chiari syndrome”, “celiac”, “coeliac”, “gluten-sensitive enteropathy”, “liver abnormalities”, “venous thrombosis”, “coagulation”, and “thrombophilia”. Our literature search revealed the following points: (i) few reports of CD-associated BCS have been published, with most of the cases reported from north African countries in French-language Journals; (ii) many pro-thrombotic mechanisms have been proposed, without definite conclusions on the exact cause–effect relationship between CD and BCS; (iii) a paucity of studies on the effects of a gluten-free diet on the course of BCS and other thrombotic disorders associated with CD.

BCS in CD was first described in 1990 [6]. Since then, scattered case reports of CD-associated BCS have appeared in the literature. Our literature review revealed only 12 case reports and three case series (a total of 27 cases) on the occurrence of BCS in patients with CD [6–20], and one case of BCS detected in a case-finding study using CD serology in patients with various liver diseases (Table 1) [21]. Interestingly, 22 cases were reported from north African Arab countries [7, 8, 11, 13, 15, 17–20], while only six cases were described in other regions of the world [9, 10, 12, 14, 16, 21]. In a prospective study in Algeria, the authors assessed the aetiology of BCS in 116 consecutive patients [22]. In that study, CD was found in 10 (11.4%) of the 88 patients tested, and only 40% of those patients had an underlying thrombophilia associated with CD. Based on their results, the authors proposed a systematic search for CD in the aetiological work-up for BCS.

Our case was the first to be reported from Middle-Eastern Arab countries. It thus seems that the association between CD and BCS is relatively common in north African countries, but rather infrequent in other parts of the world. It has been proposed, by some authors, that genetic and environmental factors (geophagia) explain this predilection for north African individuals, but nothing of this sort has been established [6, 7]. Others have attempted to implicate the passage of hepatotoxic substances, present in north African food, through an excessively permeable intestinal mucosa into the portal circulation [23]. Conversely, the high prevalence of CD in north Africa could also

![Figure 1. Abdominal CT with double contrast showing hepatosplenomegaly and free fluid in the peripancreatic region. The suprahepatic veins are not opacified, while the inferior vena cava appears patent. The liver appears nodular, with hypertrophied caudate lobe.](image-url)
Table 1. Clinical and demographic characteristics of reported BCS in CD patients

| First author; year of publication | Country        | Number of cases | Gender | Presentation of BCS | Pro-thrombotic cause          |
|-----------------------------------|----------------|-----------------|--------|---------------------|-------------------------------|
| Boudhina [6]; 1990               | Tunisia        | 3               | 2F, 1M | Fulminant           | Idiopathic                    |
| Hamdi [7]; 1990                  | Tunisia        | 1               | M      | Fulminant           | ATIII deficiency              |
| Martheau [8]; 1994               | Algeria        | 3               | 2F, 1M | 1 acute;           | 1 MPD;                       |
|                                   |                |                 |        | 2 chronic          | 2 Idiopathic                  |
| Aguirrebarrena [9]; 2001         | Argentina      | 1               | F      | Chronic             | ATIII and protein C deficiency|
| Manzano [10]; 2002               | Spain          | 1               | M      | Acute/sub-acute     | Idiopathic                    |
| El Younssi [11]; 2003            | Mauritania     | 1               | M      | Acute/sub-acute     | Idiopathic                    |
| Danaligou [12]; 2003             | Turkey         | 1               | F      | Chronic             | Idiopathic                    |
| Gelsi [13]; 2004                 | Algeria        | 1               | F      | Acute/sub-acute     | Idiopathic                    |
| Martinez [14]; 2004              | Spain          | 1               | M      | Chronic             | Folate deficiency             |
| Kchaou [15]; 2008                | Tunisia        | 1               | F      | Chronic             | Idiopathic                    |
| Kochhar [16]; 2009               | India          | 1               | F      | Chronic             | Functional deficiency of protein C and protein S |
| Alfredj [17]; 2010               | Algeria        | 9               | 6F, 3M | 1 acute;           | 5 Idiopathic                  |
|                                   |                |                 |        | 2 sub-acute;        | 1 MPD;                       |
|                                   |                |                 |        | 6 chronic          | 1 OCP use;                    |
|                                   |                |                 |        |                    | 1 Protein C deficiency;       |
|                                   |                |                 |        |                    | 1 Factor V Leiden mutation    |
| Ben Hriz [18]; 2010              | Tunisia        | 1               | M      | Acute              | Idiopathic                    |
| Hnami [19]; 2011                 | Tunisia        | 1               | F      | Sub-acute           | Idiopathic                    |
| Karim [20]; 2012                 | Algeria        | 1               | F      | Sub-acute           | Idiopathic                    |
| Drastich [21]; 2012              | Czech Republic | 1               | F      | Chronic             | Idiopathic                    |

BCS – Budd–Chiari syndrome; CD – Celiac disease; F – Female; M – Male; ATIII – Antithrombin III; MPD – Myeloproliferative disorder; OCP – Oral contraceptive pills.
however, other mechanisms have been suggested as explaining the pro-thrombotic potential of CD, including (i) malabsorption of vitamin K causing protein C, S and antithrombin III deficiency, (ii) hyperhomocysteinemia secondary to folate deficiency and/or variants in the methylentetrahydrofolate acid reductase (MTHFR) gene [31], (iii) an association with serum lupus anticoagulant [14], (iv) autoimmune vasculitis [32], (v) magnesium deficiency [33] and and (vi) myointimal proliferation leading to thrombosis/atherosclerosis [34].

It is arguable that multiple factors, both inherited and acquired, are needed to precipitate a thrombotic event in coeliac patients, given that only a minority of them experience clinical thrombosis; for instance, it is believed that gut-derived pro-thrombotic factors in patients with altered intestinal mucosa—such as in inflammatory bowel disease and CD—may contribute to the development of non-cirrhotic intrahepatic portal hypertension [35]. Therefore, additional studies are needed to confirm the relevance of the proposed thrombotic mechanisms and to identify other possible pro-thrombotic factors, including dietary, genetic or environmental aetiologies.

Finally, the effect of a GFD on the course of BCS in CD has not been frequently reported. In our patient, BCS had developed despite strict adherence to a GFD, as shown by the negative endoscopic examination of the duodenum, near-normal histopathology, and coeliac serology. In one study, seven out of nine patients (77%) with BCS-CD exhibited the disappearance of ascites and development of collateral porto-systemic circulation after 6 months on a GFD [17]. On the other hand, the two patients who did not adhere to a GFD had refractory ascites and developed extension of their thrombosis in the HV and the IVC. The findings in Afredji’s study are interesting but the small number of patients does not allow valid conclusions. We believe that factors other than gluten sensitivity \textit{per se} could be involved in the pathogenesis of BCS in CD.

In conclusion, this case report highlights the intriguing association between BCS and CD, and sheds some light on the putative pathogenic mechanisms, although the limited number of cases reported raises the question of whether the CD—BCS association could be fortuitous. An underlying pro-thrombotic condition was detected in less than 50% of the patients, implying a possible thrombogenic role for CD. Factors usually implicated in the occurrence of BCS in CD—including hyperhomocysteinemia, gephagia, special diet, deficiency in proteins C and S, factor V Leyden mutation, and thrombocytosis are not well established. Other pathogenic mechanisms should be searched for in these patients. Although there is, thus far, no proven direct link between CD and BCS, clinicians should maintain a high index of suspicion for this association. We suggest that a diagnosis of CD should be pursued in the setting of BCS of undetermined aetiology. Similarly, CD patients with unexplained manifestations of acute or chronic liver injury should be assessed for BCS.

\textbf{Conflict of interest statement:} none declared.

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