Celiac Disease and Myointimal Proliferation: A Possible Correlation?

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Abstract
Celiac disease (CD) is an autoimmune disorder of the small bowel that occurs in genetically predisposed people of all ages, from middle infancy, and is caused by a reaction to gliadin, a gluten protein. Some patients are diagnosed with symptoms related to the decreased absorption of nutrients or with various symptoms which, although statistically linked, have no clear relationship with the malfunctioning bowel. Classic symptoms of CD include diarrhea, weight loss, and fatigue; bowel symptoms may be limited or even absent. In this article we describe the case of a young woman with CD who presents with myointimal proliferation. However multiple cases of vessel thrombosis have been reported in patients with CD. Despite the fact that no definitive relationship between these diseases could be explained, we think this association must be remembered especially in cases of young and tenuous women with these vascular abnormalities.

Introduction
Celiac disease (CD) is an immune-mediated enteropathy caused by permanent gluten intolerance. It affects genetically susceptible subjects, with a higher prevalence in females (F/M: 2.5/1). Epidemiological studies have shown that the prevalence of CD ranges between 1/100 and 1/150 in both Europe and the USA. The histological hallmarks of CD are villous subtotal or total atrophy, crypt hyperplasia and lymphoplasmacellular infiltrate in the intestinal lamina propria, with an increased production of IgM, IgG and IgA. Moreover, changes in intestinal permeability are related to alterations of tight junctions.
The mechanisms on the basis of the gluten-related damage of small intestinal mucosa and malabsorption are not clarified yet. The immunological hypothesis is the most credited; it is supported by the characteristic histopathologic and serologic alterations, the association with specific genetic markers (HLA-DQ2 and HLA-DQ8), the improvement of intestinal damage after steroid therapy, and the association of CD with other immune-mediated diseases.

The pathogenetic mechanism is an immunological reaction to peptides of the gliadin molecule: their high glutamine and proline content renders them resistant to digestion by intestinal enzymes. Because of a dysregulation of the zonulin system that causes the opening of tight junctions, gliadin peptides cross the intestinal barrier to the lamina propria and are deamidated by tissue transglutaminase. The deamidated gliadin subsequently binds to either DQ2 or DQ8 molecules on antigen-presenting cells, causing MyD88-dependent release of both zonulin and cytokines. Gliadin peptides are also presented to T lymphocytes, initiating an aberrant humoral and cell-mediated immune response, ultimately responsible for the autoimmune process resulting in villous injury.

Regarding the clinical presentation we can have different forms of CD: classical and oligosymptomatic CD, dominated by symptoms and sequelae of gastrointestinal malabsorption, a positive serologic test and villous atrophy on biopsy; silent CD, referring to patients who are asymptomatic but have a positive serologic test and villous atrophy on biopsy; latent CD, defined by positive serological tests but not histological changes on biopsy; and finally, potential CD, characterized by HLA predisposition without clinical, serological or histopathological signs of disease.

The initial clinical appearance of CD is more severe in childhood than in adulthood. The most frequent symptoms are: gastrointestinal symptoms such as diarrhea, abdominal pain, flatulence, weight loss, steatorrhea, anorexia and, less frequently, nausea and vomiting and, in children, impaired growth, short stature and pubertal delay; in females: menarche delay, menstrual irregularities, recurrent abortion, intrauterine fetal growth retardation, infertility and early menopause; in males: infertility with altered spermatic motility and erectile dysfunction [1].

Other extraintestinal manifestations, due to micro- and macronutrient malabsorption, immune-mediated or of unknown origin, are the following: (1) hematological: iron and folate deficiency anemia, splenic atrophy and thrombocytosis, thromboembolism risk; (2) skin: Duhring’s dermatis herpetiformis, psoriasis, clubbing and onychodystrophy, skin hyperpigmentation, alopecia, follicular keratosis, hypertrichosis lanuginosa, peripheral edema, cutaneous elasticity reduction; (3) psychiatric/psychological: irritability, poor school performance, anxiety, depression; (4) musculoskeletal: osteopenia, osteoporosis, fractures, dental enamel hypoplasia, arthritis, myopathy, cramps, tetany; (5) neurological: peripheral neuropathy with paresthesia, tremors and fatigue, cerebellar ataxia, epilepsy with or without cerebral calcifications, migraine, night blindness and hemeralopia, dementia, multifocal leukencephalopathy, chorea, sensorineural hearing loss; (6) laboratory and instrumental abnormalities: hypocalcemia, prolonged PT, aspecific ECG alterations, hypertransaminasemia.

Several CD-associated autoimmune disorders have been described and reported, including Hashimoto’s thyroiditis, type 1 diabetes mellitus, autoimmune hepatitis and cholangitis, primary biliary cirrhosis, Sjogren syndrome, Addison’s disease, peripheral neuropathy, psoriasis, idiopathic dilated cardiomyopathy and autoimmune myocarditis. Untreated CD is associated with several complications: splenic hypotrophy or atrophy, ulcerative jejunitis, enteropathy-associated T cell lymphoma, increased risk for MALT
lymphoma, esophageal and oropharyngeal carcinomas, small bowel adenocarcinoma, collagenous colitis and lymphocytic colitis.

Endoscopic evaluation and small bowel biopsy are the gold standard for CD diagnosis and should always be performed if the clinical suspicion for CD is strong. Multiple biopsies either from the second portion of the duodenum or the proximal jejunum should be obtained because the histological alterations may be focal. Recently, a new endoscopic technology with additional magnification has raised high expectations for a substantial improvement in endoscopic recognition of villous atrophy. Serologic tests are important to identify subjects eligible for biopsy. IgA anti-tissue transglutaminase or endomysial antibody have a high sensitivity and specificity (approx. 90%). In patients with selective IgA deficiency, who are known to be at high risk for CD, IgG class antibodies (for tissue transglutaminase or endomysial antibody) should be determined instead of IgA antibodies. Other hematologic, biochemical and imaging abnormalities may lead to the suspicion and eventually to the diagnosis of CD, such as the following ones: (1) steatorrhea in stool examination; (2) hematologic abnormalities such as the presence of Howell-Jolly bodies and target cells in the peripheral smear, reflecting hypersplenism associated with CD; (3) anemia, thrombocytopenia, leukopenia, and hypoprothrombinemia; (4) decreased levels of serum iron, calcium, folate, vitamin D and albuminemia, and abnormal liver enzymes as the aminotransferases; (5) radiographic changes associated with CD including dilatation of the small intestine and loss of the mucosal folds; (6) computerized bone mineralometry can show diffuse demineralization and decreased bone mineral density.

The treatment of CD patients consists in a lifelong strict adherence to a gluten-free diet, sometimes associated with supplemental therapy (iron, calcium, zinc, magnesium, various vitamins, especially of the B complex). Some CD patients may require steroid therapy to obtain clinical and histological improvement. Immunosuppressive therapy, such as azathioprine, may be used to decrease steroid dosage. The prognosis of CD is usually favorable since the gluten-free diet determines clinical and histological recovery. However, 30% of CD patients do not present clinical and histological improvement after a gluten-free diet. This group of patients is considered affected by ‘refractory sprue’. This condition is rare and its most common cause is the failure to adhere to a strict gluten-free diet. Refractory sprue is associated with uncommon complications of CD, such as intestinal ulceration, mesenteric lymph node cavitation, T cell lymphomas, and collagenous sprue, with an unfavorable prognosis and splenic atrophy, with a consequent increased risk for infections and/or thromboembolic complications.

Case Report

A 34-year-old woman came under our observation due to the appearance of intermittent claudication, initially displayed by a sense of fatigue when walking. Lately her walking autonomy had decreased to about 100 meters. No signs worth noting emerged from the anamnesis: both parents were in good health, as was the patient’s 9-year-old daughter. There were no cases of familiar pathologies, especially cardiovascular. Her menstrual cycle was regular and the patient had never suffered from particular ailments, except for rare cases of diarrhea, meteorism and reported difficulty in ‘gaining weight’. On objective examination the patient was found to be in a good general condition, alert and well oriented in time and space with normal facies, negligible decubitus and no signs of bilateral peripheral edemas, apart from an imposing thinness, despite the fact that the patient claimed she ate a balanced diet and did not pay any special attention to her weight. The skin had a normal blood supply and was normally hydrated, but the subcutaneous panniculus adiposus appeared underrepresented yet normally distributed. The muscular mass was slightly hypotonic and hypotrophic. The superficial lymph node system was undamaged. Locoregional objective examination was negative.
The results of the hematochemical examinations were normal, as were the virological tests, the dysplastic markers and the autoimmune pattern. The culture and parasitological test of the feces was negative, as was the Vidal-Wright serodiagnosis. However the test for antiendomysial and anti-transglutaminase antibodies was positive at 227 U/ml, in addition to minimum serum traces of cryoglobulin. Moreover the antigliadin IgA level was elevated. The thrombophilia evaluation results (factor V Leiden, prothrombin 20210 gene mutation, lupus anticoagulant, anticardiolipin antibodies, protein C, protein S, and homocysteine) were negative. Following these results, the patient underwent an esophagogastroduodenoscopy and an ileoscopy that showed: normal esophagus, hypotonic cardia; normal gastric mucosa with the exception of moderate antral hyperemia, patent pylorus; a normal duodenal bulb with sub-atrophic villi and, especially in the second duodenal portion, marked villous atrophy and flattened folds with a ‘scalloped’ appearance. Histological examination of the duodenal biopsies showed: in the gastric antrum chronic phlogistic process with no evidence of *Helicobacter pylori*, with modest activity levels, and in the second duodenal portion chronic phlogistic process with marked villous atrophy and discreet activity levels, compatible with CD. An abdominal ultrasound scan was practically negative. For the circulatory study the patient underwent a global angio-CT of the chest-abdominal-pelvic vessels and the lower limbs that showed normal thoracic aorta without parietal thrombotic appositions, such as the epiaortic arterial trunks and the intracranial circulation; the calibre of the abdominal aorta, in the suprarenal tract, was at the lowest limit with evidence of mainly right-lateral parietal thrombotic apposition and the celiac tripod displayed a significant reduction in calibre at the origin with poststenotic dilatation; the superior mesenteric artery had a slightly reduced calibre at the origin; the renal arteries were normal; aortic parietal thrombotic apposition with a marked reduction in the vessel calibre of the inferior mesenteric artery and severe stenosis at the level of the carrefour with a residual lumen of 0.3 cm: the stenosis extended to the origin of the common iliac arteries. The inferior mesenteric artery was filiform. Parietal atheromasia, in part calcified, with a moderate degree of stenosis in the mid-istal tract of the iliac arteries. The internal and external iliacs and the common, superficial and deep femorals were of reduced calibre. This diagnosis was also confirmed by color Doppler examination.

On completion of the diagnosis, the patient was put on a gluten-free diet, after positioning multiple stents at the level of the inferior mesenteric artery with excellent hemodynamic compensation, return of the distal flow and elimination of the claudication. At present the patient’s condition is good and we evaluated the regression of myointimal proliferation after the beginning of the gluten-free diet with a new angio-CT of the chest-abdominal-pelvic vessels after one year. Six months and one year later the patient underwent a new esophagogastroduodenoscopy with ileoscopy that showed, especially in the second duodenal portion, reduction of villous atrophy.

**Discussion**

As mentioned in the introduction, CD is caused by a reaction to gliadin, a gluten protein found in wheat. Upon exposure to gliadin, the enzyme tissue transglutaminase modifies the protein, and the immune system cross-reacts with the bowel tissue, causing an inflammatory reaction and leading to flattening of the lining of the small intestine, which interferes with the absorption of nutrients [2]. CD appears to be polyfactorial [3]. About 20–30% of people without CD have inherited an abnormal HLA-DQ2 allele [4], which suggests that additional factors are needed for CD to develop. Furthermore, about 5% of those people who do develop CD do not have the DQ2 gene [3].

The proteins in food responsible for the immune reaction in CD are the prolamins. These are storage proteins rich in proline and glutamine that dissolve in alcohols and are resistant to pepsin and chymotrypsin, the two main digestive proteases in the gut. Gliadin in wheat is the best-known member of this family, but other prolamins exist [3].

Classic symptoms of CD include diarrhea, weight loss, and fatigue; bowel symptoms may be limited or even absent. Abdominal pain and mouth ulcers [5] may be present. The symptoms are frequently ascribed to irritable bowel syndrome and are only later recognized as CD; a small proportion of patients with symptoms of irritable bowel syndrome have underlying CD, and screening may be justified [6].
CD leads to an increased risk of both adenocarcinoma and lymphoma of the small bowel, which returns to baseline with diet. The changes in the bowel make it less capable of absorbing nutrients, minerals and fat-soluble vitamins [7]. CD has been linked with a number of conditions such as IgA deficiency [8, 9], dermatitis herpetiformis [10], epilepsy, ataxia, myelopathy, peripheral neuropathy and schizophrenia [11, 12], infertility, hyposplenism [13], diabetes mellitus type 1 [14], autoimmune thyroiditis [15], primary biliary cirrhosis [16] and microscopic colitis [17].

Serology test is useful both in diagnosing CD with a sensitivity of about 98% and a specificity of over 95%. Several serological blood tests exist for CD, but the most commonly used ones detect an antibody of the IgA type against particular antigens in the small bowel as gliadin, and against endomysium or tissue transglutaminase. It is important that a total serum IgA level is checked in parallel because an IgA deficiency is possible [18–20]. However the gold standard in the diagnosis of CD is endoscopy with multiple biopsies of the duodenum or jejunum [21].

Today the only effective treatment is a life-long gluten-free diet [22] and only a tiny minority of patients suffer from refractory disease. Multiple cases of intra-abdominal venous thrombosis have also been reported in patients with CD [1] in the literature such as a case of nonischemic central retinal vein occlusion associated with CD [23] that suggests that although patients with an inherited or acquired predisposition to thrombosis have a lifelong risk, they only experience clinical thrombosis occasionally, and that additional exogenous insults are necessary to precipitate a clinical event; in fact thrombotic episodes are likely multifactorial events in patients who have an inherent predisposition to thrombosis [24–26].

Francis et al. [27] noted that in their patients dehydration due to diarrhea was associated with central retinal vein occlusion; prothrombotic predisposition is caused by hyperviscosity from the circulating antigliadin antibodies or some other yet unknown cause in patients with CD. The literature also describes an association between the Budd-Chiari syndrome and CD, as in Northern Africa [28] and in Turkey [29]. Here the unexplained hypercoagulable state in CD may affect the hepatic veins, the mesenteric veins or the splenoportal axis, causing different syndromes; it is merely a different expression of the same abnormality related to different sites. The authors believe that the reason for the hypercoagulable state may be hyposplenism, and CD with abdominal venous thrombosis may be more frequently found if carefully researched [30]. In fact other authors [31] said that the Budd-Chiari syndrome, in its secondary form, refers to the syndrome caused by such diseases as myeloproliferative disorders [32–34], including polycythemia vera [35], antiphospholipid antibodies [36, 37], paroxysmal nocturnal hemoglobinuria [38, 39], systemic lupus erythematosus [40], Behçet disease [41, 42], CD [43], hepatocellular carcinoma [44], renal cell carcinoma [45], and those after use of oral contraceptives [46, 47] and pregnancy [48, 49].

Conclusion

The present case report suggests an unusual association of myointimal proliferation (thrombosis/atheromasia) and CD. Despite the fact that no definitive relationship between these diseases could be explained, we think this association must be remembered especially in cases of young and tenuous women with these vascular abnormalities.
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