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RESEARCH ARTICLE

Rare Complications of Celiac Disease: Clinicopathologic Features

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ABSTRACT

Celiac disease (CD) is an immune mediated disorder characterised by intolerance to glutens in certain grains like wheat, barley, and rye. The exposure to gliadin protein component in the susceptible individuals leads to an inflammatory reaction damaging small bowel mucosa with progressive disappearance of intestinal villi. The damaged intestinal mucosa leads to malabsorption. The usual symptoms of celiac disease include diarrhea, steatorrhea, weight loss, fatigue, and abdominal pain. Diagnosis is based on clinical features, duodenal biopsy, elevated levels of anti-gliadin antibodies and response to gluten free diet. Contrary to common belief, celiac disease is a protein systemic disease rather than merely a pure digestive alteration. Celiac disease is closely associated with genes that code HLA -II antigens mainly of DQ2 and DQ8 classes, production of disease specific antibodies (i.e., endomysial antibodies), multiorgan involvement, comorbidity with other autoimmune diseases (shared autoimmunity), familial aggregation, and immune system dysregulation.

The clinical presentation of celiac disease can be variable. In mild form, patients can be almost asymptomatic whereas in the most severe form, the patients are at increased risk of life-threatening complications. Celiac disease has a well-known association with other autoimmune diseases such as autoimmune liver diseases (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis), diabetes mellitus, autoimmune thyroid diseases, skin diseases such as dermatitis herpetiformis, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, psoriasis, sarcoidosis, immune thrombocytopenic purpura, and pancreatitis. In addition, celiac disease may be associated with rare but potentially serious complications such as, collagenous sprue, ulcerative jejunoileitis, refractory celiac disease (RCD), enteropathy associated T-cell lymphoma, small bowel adenocarcinoma (SBA), hyposplenism, and cavitating mesenteric lymph node syndrome (CMLNS). The present article describes clinicopathologic features of these rare but serious complications of celiac disease.

Introduction

Celiac disease (CD) is an immune mediated disorder characterised by intolerance to glutens in certain grains like whet, barley, and rye. The exposure to gliadin protein component in the susceptible individuals leads to an inflammatory reaction damaging small bowel mucosa with progressive disappearance of intestinal villi. The damaged intestinal mucosa leads to malabsorption. Contrary to common belief, celiac disease is a protein systemic disease rather than merely a pure digestive alteration. CD is closely associated with genes that code HLA -II antigens of DQ2 and DQ8 classes, production of disease specific antibodies (i.e., endomysial antibodies), multiorgan involvement, comorbidity with other autoimmune diseases (shared autoimmunity), familial aggregation, and immune system dysregulation.[1] The key elements of CD, an autoimmune disease are genetics HLA-DQ2 and HLA-DQ8 genotypes, environmental factors (gluten intake), and autoantibodies to tissue transglutaminase (tTG) which are known to play a key role in the pathogenesis.[2] CD is frequently associated with extraintestinal manifestations making it a systemic disease rather than a disease confined to gastrointestinal tract. There are several associated diseases which are present at the time of diagnosis or develop throughout evolution of disease. Significantly increased prevalence of other autoimmune diseases has been reported in individuals with CD and their first-degree relatives compared to controls.[3,4,5,6] It has been suggested that association between CD and other autoimmune diseases may be explained by sharing a common pathogenic basis involving genetic susceptibility, similar environmental triggers, the loss of intestinal barriers secondary to dysfunction of intercellular tight junctions with increased intestinal permeability, and by other undiscovered mechanisms.[7,8,9,10,11,12]

The clinical presentation of celiac disease can be variable. In the mild form, patients can be almost asymptomatic whereas in the most severe form of disease patients may present with many complications which may be life threatening. The current article deals with clinicopathologic features of rare complications of CD.

Complications

Collagenous sprue

Collagenous sprue is characterised clinically by persistent diarrhea associated with malabsorption causing multiple nutrient deficiencies and progressive weight loss that fails to respond to gluten free diet. Pathologic examination of small bowel shows subepithelial band of collagen akin to collagenous colitis. This is often associated with inflammatory infiltrate and surface sloughing.[13,14] Concomitant collagen deposition may also occur in gastric or colonic mucosal sites indicating that this unusual mucosal process may be quite extensive in the intestinal tract.

Refractory celiac disease

Refractory celiac disease is characterized by persistent symptoms and severe villous atrophy not responding to gluten-free diet for at least 6 months.[15] It is a rare CD complication with a variable incidence and prevalence. A systematic review by Rowinski and Christensen showed a cumulative incidence of 1-4% over 10 years and a prevalence of 0.31%-0.38% in CD patients[16], while a study based on a cohort of celiac individuals in Austria reported an incidence over 25 years of 2.6%.[17] Mean age at RCD diagnosis has been reported to be around 63 years. The median time between the diagnosis of CD and the diagnosis of RCD is 21 months, although rare cases of RCD primarily diagnosed at the time of first presentation of malabsorption symptoms have been described.[18] RCD is divided into two subtypes (RCD type 1 and RCD type 2). Cases of RCD type 1 display normal intraepithelial lymphocytes (IEL) phenotypes with CD3+ and CD8+. In RCD type 2, the IEL show aberrant phenotypes in that intracytoplasmic CD3 is present but surface CD3 and often CD8 are not present; additionally, clonal T cell receptor gene arrangement is detected.[12] Patients with type 2 RCD have very poor prognosis with the 5-year survival rate being less than 50%.[19] These patients are at increased risk of life-threatening complications.[20]

Ulcerative jejunoileitis

This rare complication of refractory celiac disease is characterized by extensive ulceration of the intestinal mucosa. The patient may present with intestinal obstruction. Tinguria and Liaconis reported a case of refractory celiac disease presenting with ulcerative jejunoileitis with intestinal obstruction and cavitating mesenteric lymph node syndrome.[57] The intestinal obstruction required bowel resection. The resected segment of jejunum showed severe luminal narrowing associated with extensive mucosal ulceration. The adjacent flattened mucosa showed severe villous atrophy [Figure 1].

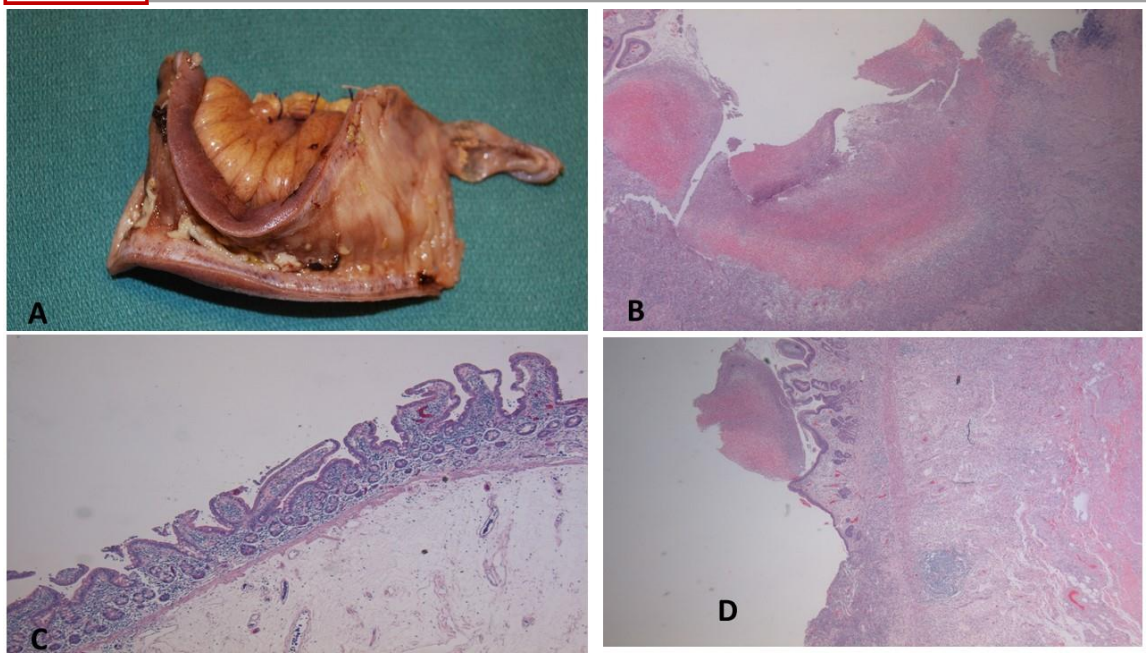

Figure 1.

A. Gross photograph of resected segment of jejunum from the site of intestinal obstruction showing marked luminal narrowing. Mucosal surface of the bowel appears flattened with loss of mucosal pattern and shows large areas of ulceration.
B. Hematoxylin and Eosin section of jejunum from the site of intestinal obstruction. Large area of ulceration is noted covered with necrotic slough (40x).
C. Hematoxylin and eosin section from non-ulcerated area of jejunum showing severe villous atrophy (100x).
D. Hematoxylin and eosin section from the jejunum adjacent an ulcer showing very severe villous atrophy with almost flattened mucosa (40x).

Enteropathy associated T-cell lymphoma

Celiac disease individuals, especially those with longstanding disease, have a relative risk of developing extra-nodal non-Hodgkin lymphoma around 3-4 times higher than general population. Enteropathy associated T-cell lymphoma (EATL) is a rare lymphoma that accounts for less than 1% of non-Hodgkin's lymphoma.[21] There are two types of EATL. Type 1 (80-90% of all cases) often progresses from refractory CD type II.[22,23] The possible explanation for this association is chronic inflammation, which is supported by persistent villous atrophy.[24] Type II EATL arises *de novo*.[25,26] Most EATL cases (70 – 80%) are diagnosed in late stage of the disease.[27] EATL most frequently involves small intestine. However due to extraintestinal dissemination of aberrant lymphocytes, it could also be found in the large intestine, stomach , lymph nodes, bone marrow, skin, and lungs.[28] EATL is characterized by ulcerations, nodules, or large tumor masses. Microscopic examination shows medium-to-large-sized cells with medium-sized, round, darkly staining nuclei with a rim of pale cytoplasm. Malignant cells are CD3, CD7, and CD103 positive and CD5 negative, variable for CD8 and TCRβ, and more than 80% of cells are CD30 positive.[25,29] The prognosis is extremely poor, with a median overall survival of 7.1–10 months.[25]

Small bowel adenocarcinoma

Small bowel adenocarcinoma (SBA) is a rare disease with an incidence of 5.7/1,000,000 persons/year.[30] Many epidemiological studies and meta-analysis suggest that CD patients have a higher risk to develop SBA compared to the general population.[31,32] The tumor is usually diagnosed in the seventh decade of life.[33] High cellular turnover related to chronic inflammation, increased intestinal permeability to oncogenic factors, malabsorption of protective factors such as vitamins A and E, and impaired immunogenic surveillance in CD are considered in the pathogenesis of this complication.[34] SBA is usually diagnosed at an advanced stage because of late-presenting symptoms. Abdominal pain, gastrointestinal bleeding, vomiting, signs of ileus and bowel perforation, weight loss, and anemia are the most frequent symptoms of the disease. The tumor is most frequently detected in the duodenum (55%) and jejunum (30%) and less frequently in the ileum (15%).[35] Prognosis is poor, with median overall survival of 20.1 months and 5-year overall survival of 26%.[36]

Hyposplenism

The spleen plays a key role in mounting the immune response to encapsulated microorganisms. The extent of the association between hyposplenism and CD is not well known, as the reported incidence of hyposplenism in CD is highly variable according to studies and diagnostic modalities.[37,38] It may be associated with other autoimmune comorbidities.[39,40] An association between splenic atrophy and mesenteric lymph node cavitation has been described in over thirty cases.[41] In early studies splenic atrophy was often defined during post-mortem evaluation or abdominal surgery. More recently these changes can be easily identified by imaging studies. Hyposplenic patients are at increased risk for bacterial sepsis, especially with encapsulated organisms such as pneumococcus, sometimes with a fatal outcome.[41] Therefore, vaccination using pneumococcal conjugate has been recommended.[43] The risk of sepsis is more significant if diagnosis of celiac disease is established during adult years rather than in childhood.[44] The World Gastroenterology Organization also recommends vaccination against Haemophilus influenzae and meningococci.[45] Hyposplenism may be reversible with the gluten free diet (GFD), but that remains controversial.[46,47] Celiac disease is frequently associated with several autoimmune disorders, including Hashimoto's thyroiditis, insulin-dependent diabetes mellitus, Sjogren's syndrome, Addison disease, systemic lupus erythematosus, rheumatoid arthritis.[48,49] The evidence that autoantibodies may develop within months of splenectomy together with the demonstration that celiac patients with blood film features of hyposplenism have a higher prevalence of autoantibodies have led to the hypothesis that defective splenic function might predispose the development of autoimmunity in celiac disease.[50,51,52,53]

Cavitating mesenteric lymph node syndrome

The incidence of mesenteric lymphadenopathy is variable in celiac disease and ranges from 0 to 12%. Mesenteric lymph node enlargement may be due to reactive hyperplasia secondary to ulcerative jejunitis, lymphoma or rarely due to cavitating mesenteric lymph node syndrome (CMLNS). Cavitating mesenteric lymph node syndrome (CMLNS) is a rare but potentially fatal complication of celiac disease (CD) associated with extremely poor prognosis and mortality reaching up to 50%. Mortality is related to severe malnutrition, intestinal hemorrhages secondary to ulceration and overwhelming sepsis due to a combination of hyposplenism and malnutrition. The disease is characterized by cystic change in the mesenteric lymph nodes.

The syndrome was first described by Hemet et al in 1969.[54] McBride et al summarized thirty-eight case reports of CMLNS and celiac disease worldwide.[20] The patients characteristically present with refractory symptoms of celiac disease with weight loss, diarrhea, and fatigue. This may be associated with clinical signs of hyposplenism in the form of increased susceptibility to infection. Splenic atrophy or splenic hypofunction is an important although not essential component of CMLNS.[46,55,56] Tinguria and Liaconis reported a case of refractory celiac disease in a patient who presented with intestinal obstruction secondary to ulcerative jejunitis and cavitating mesenteric lymph node syndrome.[57] Imaging studies are useful in suspecting the diagnosis of CMLNS in patients with celiac disease and confirmation is achieved by pathological evaluation of the excised mesenteric lymph nodes. As similar imaging findings can be seen in a variety of other conditions including mycobacterial infection, Whipple's disease, lymphoma associated with necrosis, as well as necrotic metastatic malignancies in the mesenteric lymph nodes, pathological examination of the lymph nodes is an important part of patient work-up.[57]

There are only a few reports describing pathologic features of CMLNS.[20,57,58,59] Grossly, the lymph nodes show central cavitation filled with fluid and peripheral rim of residual lymph node. Microscopic examination of the lymph node shows central cystic cavity filled with pale eosinophilic material surrounded by residual lymph node remnants in the form of reactive lymphoid follicles, sinuses and interfollicular plasmacytosis [Figure 2]. Reactive lymphoid tissue can be further confirmed using immunohistochemical studies on the excised lymph node. The lymphoid cells show positivity for leucocyte common antigen (LCA) and shows mixture of CD 20 positive B cells and CD3 positive T cells. Bcl-2 shows benign pattern of staining with positivity mainly outside the germinal centres [Figure 3]. Flow cytometry can be carried out on the excised lymph node to rule out lymphoma.

The pathogenesis of CMLNS is not known. It has been suggested that excessive antigenic stimulation by damaged intestinal mucosa might lead to depletion of lymphoid elements in the mesenteric lymph nodes and spleen causing cystic changes in the mesenteric lymph nodes in some cases. Alternatively, these cystic changes may represent necrosis of the mesenteric nodes triggered by localized immune-mediated complement activation and intravascular coagulation.[60]

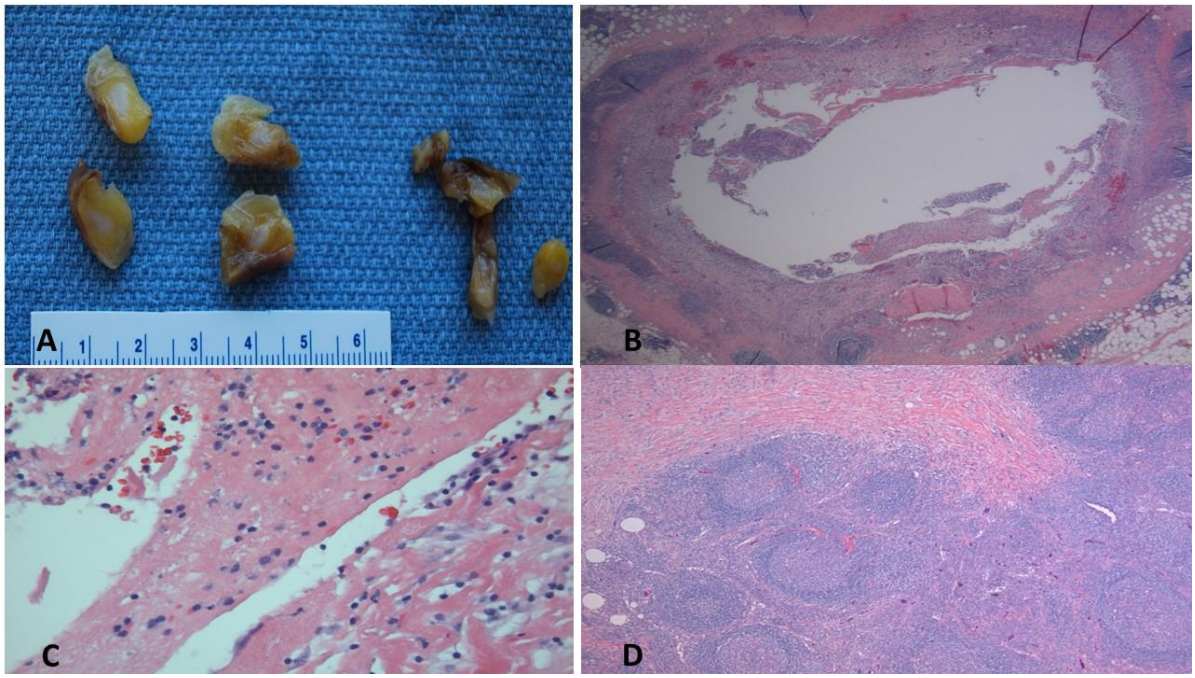

Figure 2.

A. Gross photograph of cut surfaces of mesenteric lymph nodes. Central cyst like appearance can be appreciated in some areas.
B. Hematoxylin and eosin section from one of the mesenteric lymph nodes. Central area of cavitation is noted surrounded by residual lymphoid tissue (40x).
C. Hematoxylin and eosin section from mesenteric lymph node. Eosinophilic fluid like material is noted in central portion of the lymph node in some areas, although most of the material usually gets washed off during processing of the lymph nodes (100x).
D. Hematoxylin and eosin section from mesenteric lymph node. The lymph node in non-cystic areas showing reactive lymphoid follicles with germinal centres (100x).

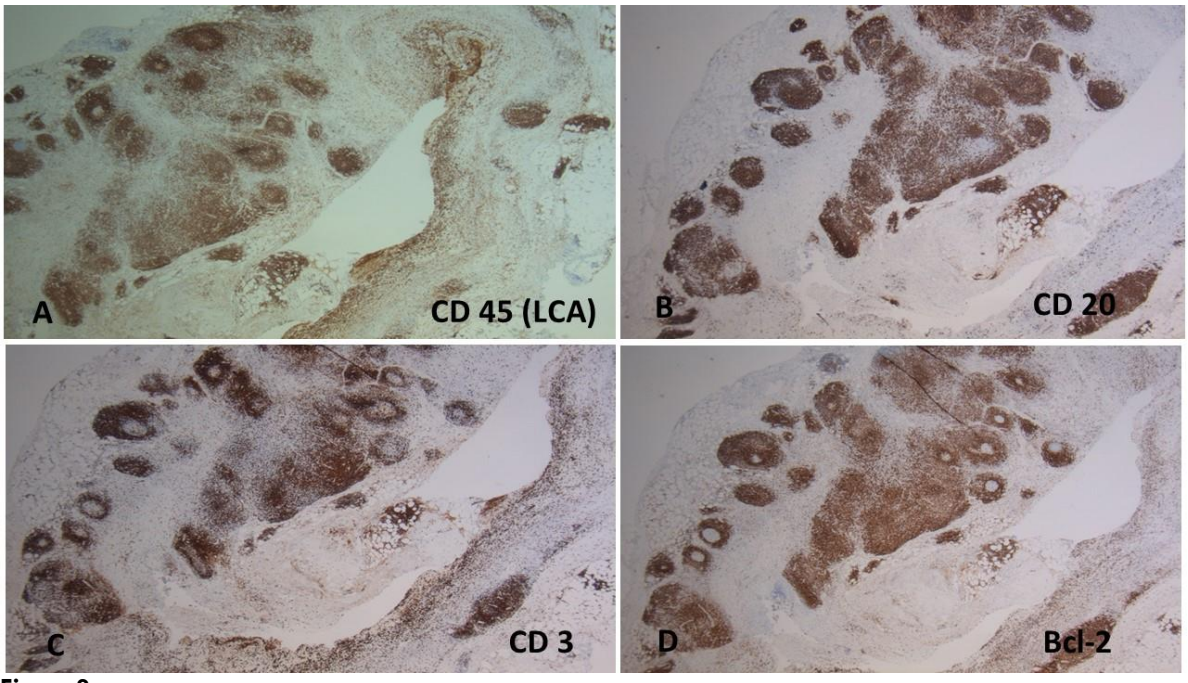

Figure 3.

Immunohistochemical staining (IHC) showing positivity for CD45 (LCA =Leukocyte Common Antigen) (A) with mixture of CD 20 positive B cells (B), CD 3 positive T cells (C) and Bcl-2 (D) showing benign pattern of staining with positivity mainly outside the geminal centres in the reactive lymphoid follicles (A, B, C, D 100X).

Conclusion

The clinical presentation of celiac disease is variable. In the mild form, patients may be almost asymptomatic whereas in the most severe form of disease patients may present with many complications. Although rare (around 1% of patients diagnosed with celiac disease),[61] the complications may be life threatening. Complications should be suspected in all patients in whom symptoms persist or if there are exacerbation of symptoms despite adherence to gluten free diet. The complications occur more frequently when diagnosis of CD is established in elderly.

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Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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