Role of Radiology in a Celiac Disease's Patient Assessment

Dr. Eman Mazyad Alruwaili

General practitoner

Dr. Abdalrahim Mohammed Siralkhatim Alhassan

Senior Registrar

Diagnostic Radiology

Abstract:

Celiac disease (CD) is defined as a chronic autoimmune inflammatory disorder triggered by the ingestion of gluten-containing cereals in individuals who are genetically predisposed. The symptoms of celiac disease can vary widely from person to person and may manifest differently in children and adults. The high prevalence rate of CD worldwide has necessitated efficient diagnostic and management strategies. Radiology plays a pivotal role in the comprehensive assessment of CD patients, thus aiding in early detection, disease staging, and treatment evaluation. This review article aims to provide a comprehensive overview of the diverse radiological modalities employed in the assessment of CD. The primary focus of this review lies in elaborating on the strengths and limitations of different radiological investigations in CD patients. The well-established techniques, such as plain radiography and barium studies, are explored in conjunction with the evolving technologies, such as magnetic resonance enterography (MRE), computerized tomography enterography (CTE), ultrasonography, and nuclear medicine. These advanced imaging modalities offer high-resolution visualization of the small bowel and associated structures, facilitating the identification of characteristic CD features, such as villous atrophy, mural thickening, and mesenteric lymphadenopathy. The amalgamation of conventional and cutting-edge imaging modalities empowers clinicians with valuable insights into disease progression, therapeutic response, and potential complications. As CD continues to present a diagnostic challenge, radiology stands as an indispensable ally, contributing significantly to improved patient outcomes and paving the way for personalized and effective management strategies.

1. Introduction:

Celiac disease (CD) is a T-cell mediated autoimmune inflammatory enteropathy induced by dietary gluten ingestion in individuals who are genetically predisposed. This chronic disease is characterized by villous atrophy in the proximal small bowel mucosa, crypt hyperplasia, and gastrointestinal malabsorptive enteropathies that occur as a result of infiltration of CD4+ T lymphocytes in the small bowel [1]. CD tends to first start in the duodenum and with time, it extends distally to the ileum. This results in the hypertrophy of crypts (product fluid) and the loss of villi (absorb fluid), leading to the presence of excess chronic fluid in the small bowel [2].

Gluten describes a group of alcohol-soluble proteins found in some cereals, including rye, barley, wheat, kamut, and spelt [3]. CD occurs when the body's immune system mistakenly identifies gluten as a threat, which results in injury of the small intestine, thus leading to the malabsorption of nutrients [4]. The first ever clinical description of CD was demonstrated by Samuel Gee in 1887. Later in 1953, Dicke described a wheat-free diet to successfully manage the disease [5].

As a gluten intolerance disorder, CD affects approximately 1% of the worldwide population [6]. However, this prevalence rate is not representative of the actual number of CD cases because many cases of CD, as reported by various studies, are asymptomatic and go undiagnosed. A research study conducted in Italy found that the ratio of symptomatic to asymptomatic CD cases is 1:7 [7]. The prevalence rate of CD is relatively high among White population. While it was believed that only the

population of European descent is affected by CD, about 5.6% of the population in North America has been shown to be affected with this illness [8]. CD has been reported to be quite rare in Pacific Islanders and East Asia because these populations have a lack of specific HLA haplotype (responsible for the occurrence of CD) and consume a diet low in gluten [9,10]. First and second-degree relatives accompanied by people with autoimmune diseases show a high incidence rate of CD [3,11]. Studies have reported that the prevalence of CD has increased four to five times over the last few decades [12].

There are two peaks of onset of CD, one occurs at the age of two years (childhood) and the second occurs at any age, mainly in the second and third decade of life [13]. According to Oslo's definitions, there are seven categories used to describe CD: classic, non-classic, refractory, potential, overt, and silent. CD is also classified according to the histological appearance and location [14].

Females are more commonly affected with CD with an F:M ratio of 2:1. Females are primarily diagnosed with at a young age and exhibit symptoms of iron deficiency anemia and constipation [15,16]. The clinical manifestations of CD involve one or more than one organ systems [17]. Classical symptoms of CD in the pediatric population include short stature, malabsorption, delayed puberty, loss of appetite, failure to thrive, diarrhea, and abdominal detention [4]. Predictably, 50% of children present with vomiting, nausea, weakness, diarrhea, or weight loss and about 90% endorse abdominal pain [18]. Children experience gastrointestinal symptoms predominantly under the age of three, while they experience typical complaints of alopecia, mood disorders, short stature, and iron deficiency anemia when they are in older age [14]. Just like pediatrics, the adult populations exhibit diverse symptomatology. Although adults present with typical GI symptoms like chronic diarrhea, bloating, steatorrhea, and postprandial abdominal pain, they often experience extraintestinal symptoms. Chronic malabsorption of micronutrients (fat-soluble vitamins) is the primary reason behind these symptoms [19,20]. The main reason for the hospitalization of CD patients is considered to be cachexia and electrolyte imbalance [17,19]. Sometimes, some cases of CD also experience systemic manifestations in addition to gastrointestinal symptoms. It is because CD is a chronic condition involving multiple organs. Some musculoskeletal symptoms of CD include myopathy, osteoporosis, rickets, and poor growth. Anemia is another hematological manifestation of CD. Some individuals also experience endocrinological symptoms, such as infertility and delayed puberty. Manifestations of CD in the central nervous system include peripheral neuropathy and gluten ataxia [21].

1.1 Role of Genetics, Immunology, and other Trigger Factors:

CD is a chronic autoimmune disorder involving environmental trigger (gluten), the auto-antigen (tissue transglutaminase (tTG)), and the genetic component (HLA)-DQ2 or HLA-DQ8). Genetic predisposition is evidenced by its high concordance of 70% in monozygotic twins [22]. The heritability of CD must include specific genetic markers specifically HLA-DQ2 and HLADQ8 belonging to the HLA (human leukocyte antigen) class II heterodimers. About 95% of patients with CD have HLA-DQ2, and the remaining majority have HLA-DQ8 [17]. These genes play a crucial role for presenting modified gliadin peptides to the immune cells, specifically CD4+ T cells. In individuals with genetic susceptibility (HLA-DQ2/DQ8), CD4+ T cells recognize the modified gliadin peptides as foreign antigens, leading to an abnormal immune response [23].

In addition to genetic susceptibility, gluten ingestion is another risk factor for the development of CD. Studies suggest that CD occurrence may be influenced by the amount of gluten exposure, the timing of gluten ingestion, and breastfeeding patterns [24,25].

Gluten proteins are not completely digested by intestinal, pancreatic, and gastric proteases. Other peptides enter the lamina propria by crossing the epithelial wall of the small bowel. This stimulates innate immune response in CD patients, leading to intestinal inflammation [25]. The gluten peptides

presented with disease-associated HLA-DQ2/DQ8 are recognized by CD4+ T cells present within the lamina propria. The tissue transglutaminase 2-modified gliadin peptides are also identified by the T cells [25,26]. This results in cross-linking of gluten proteins and deamidation of gliadin peptides, leading to alteration in the conformation and charge of gliadin. This results in the binding of gliadin to HLA-DQ2/DQ8 with much higher affinity, leading to the stimulation of T-cells. This activation results in the formation of proinflammatory cytokines (interferon-γ) and autoantibodies (tTG), resulting in tissue injury. This results in villous blunting and hyperplasia [27].

Diagnosing celiac disease involves a combination of clinical evaluation, serological testing (Tissue Transglutaminase Antibodies (tTG-IgA) testing and Endomysial Antibodies (EMA) testing), confirmation through small intestine biopsy, and genetic testing. The only effective treatment for celiac disease is a strict, lifelong gluten-free diet. Following a gluten-free diet helps prevent the immune response triggered by gluten ingestion and allows the small intestine to heal, leading to symptom relief and improved overall health [1,17].

2. Role of Radiology in Patient Assessment of Celiac Disease:

When it comes to the diagnosis and assessment of CD, radiology plays a vital role. It can also help assess the severity of celiac disease by evaluating the extent of intestinal damage. Moreover, radiological imaging can be used to monitor the response to gluten-free diet (the primary treatment for celiac disease). Sometimes, celiac disease symptoms can overlap with other gastrointestinal disorders. Radiological imaging can be useful in ruling out other conditions and aiding in the differential diagnosis process. Radiological procedures use various imaging technologies, such as X-rays, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound to create detailed images of the internal structures of the body, including the small bowel, colon, and mesenteric lymph nodes, which are all affected by celiac disease. These images are used for diagnostic purposes and to assess the presence of abnormalities, such as tumors, fractures, or other pathologies. Celiac disease is associated with various other medical conditions, including osteoporosis, anemia, and certain autoimmune diseases. Radiology, such as DEXA scans for osteoporosis assessment, can be used to detect and evaluate these associated conditions [28]. Early and accurate diagnosis facilitated by radiology can lead to timely treatment, reducing the associated morbidity and mortality resulting from delayed diagnosis.

Various radiological imaging techniques are used in the assessment of celiac disease. These imaging modalities provide valuable information about the small intestine and associated structures, helping in the diagnosis, evaluation, and monitoring of the condition. The following are some different types of radiologic modalities:

2.1.Ultrasound:

Ultrasound is a non-invasive imaging technique that uses sound waves to create images of the small bowel wall structure having an abnormal appearance. Radiologists most frequently use transabdominal ultrasonography (US) to diagnose CD in pediatrics because ultrasound does not require the use of anesthesia or needle sticks. If CD is fully developed, typical indications include continuous peristalsis occurring during fasting in the segments of the small bowel and fluid-filled intestinal loops [29]. Increased gallbladder volume, enlarged mesenteric lymph nodes, intestinal dilatation, and the presence of abdominal fluid are some markers of CD as investigated by ultrasound [30]. These abnormalities can reverse upon the exclusion of a high gluten diet. One limitation of using ultrasound is that it cannot detect any malignancies or sensitivities for bowel wall thickening.

2.2.Small Bowel Follow-Through and Enteroclysis:

A small-bowel series involves the ingestion of a barium solution, which coats the lining of the small intestine. X-ray images are then taken to visualize any abnormalities, such as strictures or ulcers, in the small bowel. Enteroclysis is a more invasive procedure where a tube is inserted through the nose or mouth into the small intestine. Barium solution and air are then injected through the tube, allowing for detailed imaging of the small bowel [31]. Small bowel follow-through (SBFT) and enteroclysis are some fluoroscopic examinations that are referred to as the standard radiological approaches for the successful assessment of the small bowel intraluminal pathologies associated with CD [32]. Small bowel barium studies, however, are not considered for the successful CD diagnosis, but it can help with the changes, such as moulage sign, jejunoileal fold pattern reversal, and small intestinal dilatation.

Low sensitivity for deep or flat mucosal lesions, inaccuracies about extraluminal pathologies, and exposure to high radiation doses are some of the limitations of fluoroscopic examinations. However, substantial evidence has reported that SBFT is still used in the setting of inflammatory bowel disease (IBD) and related illnesses [33].

2.3.Computed Tomography Enterography/Enteroclysis (CTE):

CTE is a more advanced, cross-sectional radiological technique used to evaluate abdominal symptoms and detect complications of CD. This imaging method involves the administration of a small amount of luminal contrast agent by means of a nasoduodenal tube, and a series of CT images are taken to create detailed cross-sectional images of the abdomen. CT enterography provides high-resolution images that can reveal intestinal abnormalities, such as strictures, dilations, thickened bowel walls, malignant transformation, lymphadenopathy, or signs of malabsorption [2]. It can be helpful in identifying complications of celiac disease or in cases where endoscopy is inconclusive. In order to achieve bowel distention, barium (positive enteral contrast) or methylcellulose (neutral enteral contrast) are administered directly into the small bowel or the dose of contrast medium is increased [34].

Research data has suggested that CTE can successfully aid in distinguishing between CD/type 1 RCD and RCD2/EATL. However, they have been proven to be a diagnostic tool to differentiate only between uncomplicated RCD2 and CD [30].

2.4 Magnetic Resonance Imaging (MRI) Enterography:

MRE is another imaging technique used to assess the study of the small bowel wall. Similar to CT enterography, this method also involves the ingestion of a contrast solution. MRE uses magnetic fields and radio waves to create detailed images of the abdomen and small intestine [32]. When it comes to the detection of small bowel alterations, MRE has been studied to be highly specific and sensitive [33]. Recent data has also illustrated that MRE can show higher performances in the detection of suspected small bowel neoplasm [35]. It can provide excellent soft tissue contrast, allowing for the visualization of inflammation, strictures, and other abnormalities in the gastrointestinal tract. MRE is particularly useful in cases where exposure to ionizing radiation (as in CT scans) needs to be minimized, such as in pregnant patients or those with a history of radiation exposure [36].

1. Nuclear medicine:

When other radiologic modalities are unsuccessful, nuclear medicine can help. 18F-FDG PET CT (18F-fluorodeoxyglucose positron emission tomography) [37], metaiodobenzylguanidine and octreotide studies for detecting neuroendocrine tumors, labeled red cell studies for detecting bowel hemorrhage, white blood cell inflammatory imaging, and scintigraphy for the detection of Meckel's

diverticulum are some of the nuclear medicine testing techniques that can successfully assess small bowel diseases [30]. PET CT can not only evaluate the small intestine but also assess suspected neoplasms [38]. The results of PET CT are often compared with endoscopy and MRI in Crohn's disease patients' assessment, though some issues, such as accessibility and high radiation exposure may still arise. Evidence from one study has revealed that 18F-FDG PET CT shows 100% sensitivity and 90% specificity in identifying and localizing lymphoproliferative disorders associated with CD, including EATL [39].

3. Conclusion:

Radiology plays a pivotal role in the comprehensive assessment of patients with celiac disease. As a complex autoimmune disorder affecting the small intestine, celiac disease requires accurate and timely diagnosis, evaluation of disease severity, monitoring of treatment response, and detection of potential complications and associated conditions. Abdominal ultrasound is particularly useful for patients with gastrointestinal symptoms. MRE enables the visualization of bowel and extraluminal findings, providing valuable insights into the disease. Small-bowel series, enteroclysis, and CT scans are also important radiographic examinations for diagnosing celiac sprue. However, it is important to note that while radiological findings can support the diagnosis, a combination of other tests is necessary for an accurate diagnosis of celiac disease.

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