Multimodal approach aids diagnosis of celiac disease

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Celiac disease (sprue) is a gluten-sensitive enteropathy of the gastrointestinal tract that affects the small intestine in individuals who are genetically susceptible. It is characterized by small intestinal malabsorption after the ingestion of gluten, villous atrophy of the small intestinal mucosa with increased intraepithelial lymphocytes, clinical and histologic improvement when a strict gluten-free diet is adhered to, and clinical relapse when gluten is reintroduced.

Although celiac disease can occur at any age, the peak adult incidence occurs between the ages of 50 and 59 years old. One in every 200 to 300 individuals in Western Europe will be affected. Prevalence is three times higher in the female population than among men. Diagnoses of celiac disease have increased with the advent of serological methods to aid identification, including use of tissue transglutaminase and endomysial antibodies (IgA). Symptoms are frequently unspecific, but complications are not uncommon and may result in significant morbidity and mortality. Clinical suspicion should consequently be high.

The disease may manifest clinically in many ways. The classical manifestations of diarrhea and steatorrhea are found in a minority of cases. Atypical features include fatigue, weight loss and bloating, anemia, neuropathy, infertility, myopathy, and osteomalacia.

Permanent withdrawal of dietary gluten remains the essential treatment. Most patients show a rapid clinical response, with improvement of symptoms within weeks. Histological improvement is slower, and complete mucosal recovery can take months or years. Celiac disease is generally considered to be a precancerous condition, and it has been suggested that a gluten-free diet may play a protective role against the complications of malignancy.

Small intestinal biopsy is essential to confirm the diagnosis of celiac disease. An accurate radiological examination should be performed as well to visualize any morphological abnormalities. Radiological investigation also helps to exclude complicating lesions, such as lymphoma, carcinoma, intussusception, and stricture, in those who present with atypical symptoms. Imaging is not sufficiently sensitive or specific to confirm a diagnosis of celiac disease. It is, however, especially useful in the presence of abdominal pain to exclude complicating lesions. Current methods of investigation include:

- barium follow-through examination of the small bowel;
- barium small bowel enteroclysis (jejunal intubation allowing controlled and rapid infusion of contrast agents);
- MRI follow-through of the small bowel; and
- CT.

Barium studies have traditionally been used to document radiological abnormalities. CT findings of celiac disease have also been described. CT can additionally help identify complications and extraintestinal features. MRI is the latest method to be advocated as a possible diagnostic modality for small bowel imaging owing to its excellent soft-tissue contrast and multiplanar imaging capabilities.

Approximately 25% of patients with untreated celiac disease have no radiological abnormalities. For the 363 such patients assessed at our institution over a five-year period, no abnormalities were seen in 77.8% of cases when using any imaging method.

BARIUM BENEFITS

Follow-through studies of the small bowel can be performed after administration of a liter of barium (60% weight per volume). Prone abdominal plain films are obtained every 20 minutes until contrast reaches the colon. Spot views are obtained of the duodenum, jejunum, and terminal ileum.
For enteroclysis, the small bowel is best imaged by distending the lumen before flocculation of barium occurs. Jejunal intubation allows controlled and rapid infusion of contrast. A 14-F Bilbao-Dotter catheter is typically used to infuse 600 to 800 mL of barium (40% w/v). The infusion rate is adjusted to allow adequate filling of small bowel loops without complete elimination of peristalsis.

A number of criteria have been used to assess images from small bowel barium studies in patients with celiac disease (Figure 1). The most frequent finding is diffuse small bowel dilatation. This occurs when increased peristalsis causes rapid transit of small bowel contents, resulting in distention of the ileum. Other findings include atrophy (loss of folds), fold thickening (due to increased intestinal secretion), flocculation (indicating increased intraluminal fluid and delayed transit time), reversal of the jejunoileal fold pattern (ileal jejunization), and the presence of complications. Findings on small bowel followthrough studies are often nonspecific. Enteroclysis results may be more conclusive. Small bowel enteroclysis can allow practitioners to make a confident diagnosis of celiac disease in nearly 75% of patients who have the disease. Many patients exhibit a decreased number of folds per inch in the jejunum and an increased number of folds per inch in the ileum. For instance, three or fewer folds per inch in the jejunum is strongly suggestive of celiac disease, whereas if five folds per inch are observed in the jejunum, then celiac disease is unlikely.

ALTERNATIVE OPTIONS

CT findings of celiac disease are similar to those seen on small bowel series in which barium imaging techniques were used. Small bowel dilatation, usually involving the duodenum or jejunum with loss of the normal valvulae conniventes, is often seen. Jejunization of the ileum is a key feature and is characterized by the presence of jejunum-like folds in the ileum. CT can also identify complications associated with celiac disease, including lymphoma (Figure 2A), intussusception, ulcerative jejunulieitis, and cavitary mesenteric lymph node syndrome.

MRI is also emerging as a method for diagnosing small bowel pathology. A number of approaches can be adopted for imaging the distended bowel using either positive or negative contrast agents. At our institution, we administer 600 mL of an isosmotic and nonabsorbable polyethylene glycol solution to distend the bowel and act as an oral contrast agent. Images are obtained coronally and axially every five minutes using T2-weighted half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequences. Imaging continues for up to 30 minutes maximum until the cecum is filled with oral contrast. Documented abnormal MRI findings include small bowel caliber (>30 mm in adults, >24 mm in children), wall thickening (>3 mm), reduction of intestinal folds in the proximal jejunum (>five folds/inch), and an increase of folds in the distal ileum (>five folds/inch). Qualitative evaluation may include the identification of jejunoileal fold pattern reversal (Figure 2B) and the evaluation of extraintestinal findings, including mesenteric lymphadenopathy.

COMPLICATIONS

Patients with celiac disease are at an increased risk of malignant lymphoma, adenocarcinoma of the small bowel, squamous carcinoma of the esophagus and pharynx, intussusception, ulcerative jejunoileitis, and cavitary mesenteric lymph node syndrome. Malignant tumors are the most common cause of death in celiac disease. The possibility of malignancy should be considered in any celiac patient who has recurrent symptoms after a period of dietary control. The risk of neoplasm increases with longstanding celiac disease. Enteropathic malignancies, namely lymphoma and esophageal carcinoma, are recognized associations of celiac disease.

- lymphoma. Small intestine lymphoma accounts for more than half of the malignancies associated with celiac disease. Most small bowel lymphomas in the general population are of B-cell origin (60%), whereas intestinal lymphoma as a complication of celiac disease is more commonly of T-cell origin and the prognosis is poor.

This malignancy typically affects older patients (those 50 years and above) who have experienced more than 20 years of celiac disease. Such intestinal lymphomas usually involve the small bowel in either a multifocal or a diffuse distribution (Figure 3). A short segment will occasionally be involved (Figure 4). Lymphoma is encountered more frequently in the ileum than the jejunum, owing to the increased frequency of lymphoid follicles in this location. Approximately 33% of patients have liver, spleen, or
lymph node involvement. Peripheral lymphadenopathy is uncommon.\textsuperscript{15} Clinical onset may be insidious, and the initial presentation may mimic that of untreated celiac disease. Radiographic distinction of lymphoma from ulcerative jejunoileitis may be difficult. Characteristic radiological signs include luminal narrowing with mucosal destruction, shouldering of the margins and stricture formation, broad-based ulceration, thickening of valvulae conniventes, discrete intraluminal filling defects, extraluminal mass, and focal aneurysmal dilatation. Complications include perforation and cavitation. Fistulas may form if a cavitating mass invades other ileal loops.

The recurrence of gastrointestinal symptoms in patients whose disease has previously been controlled on a gluten-free diet should raise the clinical suspicion of lymphoma. The average life expectancy of these patients following diagnosis is approximately nine months. The five-year survival rate for individuals with primary intestinal lymphoma, by comparison, is 50%. It has been suggested that strict adherence to a gluten-free diet reduces the risk of all malignancy.

We reviewed the incidence of malignancy in patients at our institution with a histological diagnosis of celiac disease over a five-year period (2000 to 2005). A total of 19 cancers were diagnosed in the population of 363 (5.2%). Five of these patients were diagnosed with esophageal cancer (1.4%), and six (1.7%) had lymphomatous involvement of the gastrointestinal tract. All diagnosed lymphomas were T-cell-type non-Hodgkins lymphomas, while all esophageal cancers were squamous cell carcinomas. The total number of malignancies, instances of lymphoma, and instances of esophageal carcinoma were significantly higher in our patient population than would be expected in the general population.

- **Intussusception.** Transient intussusceptions are identified on small bowel barium follow-through examinations in approximately 20% of celiac patients. This finding is not specific for celiac disease, though.\textsuperscript{16} Most are asymptomatic and possibly related to uncoordinated peristalsis in dilated small bowel loops (Figure 5).\textsuperscript{12}

- **Chronic ulcerative jejunoileitis.** These multiple chronic, benign ulcers of the small intestine occur most frequently in adults who are in their fifth and sixth decades. The lesions are uncommon but, when present, are frequently fatal.\textsuperscript{17,18} The risk of perforation is high. Ulcerative jejunoileitis is difficult to differentiate from underlying malignant lymphoma. Radiologists should look out for irregular diffuse thickening of the bowel wall and folds. Patients may complain of fever, acute abdominal pain, distention, and weight loss (similar symptoms to those of celiac disease complicated by neoplasm).\textsuperscript{12} Associated complications include hemorrhage, perforation, and obstruction. Some patients have concurrent lymphoma or may develop lymphoma.

- **Cavitary mesenteric lymph node syndrome.** This is a rare, usually fatal, disorder. It is characterized by mesenteric lymph node cavitation, splenic atrophy, and villous atrophy of the small intestinal mucosa.\textsuperscript{19} Clinical features include diarrhea, malabsorption, abdominal mass, and small bowel obstruction. The cavitating lymph nodes appear on CT as enlarged masses of low attenuation with or without fat/ fluid levels.

**CONCLUSIONS**

Celiac disease is common in developed countries, but the condition is often underdiagnosed. This is due, in part, to the absence of any obvious radiographic abnormality. Certain imaging features are, however, characteristic of the disease. A multimodal approach may consequently aid diagnostic confidence.

Barium and MRI follow-through of the small bowel and barium enteroclysis are valuable methods for assessing the extent of celiac disease and, potentially, the response to treatment. These studies can also help exclude complications such as lymphoma, carcinoma, ulceration, and/or stricture. Findings are often nonspecific and yield few positive diagnoses, though a high proportion of complications, including lymphoma, may be identified. Patients with celiac disease whose symptoms recur or worsen after treatment with a gluten-free diet should undergo small bowel investigation in order to exclude malignancy or other complications.

**Disclosures:**

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