ORIGINAL ARTICLE

The value of wireless capsule endoscopy in patients with complicated celiac disease CME

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Background: Celiac disease may be complicated by symptoms that raise the suspicion of small-intestinal malignancy. The objective is to evaluate wireless capsule endoscopy (WCE) in complicated celiac disease.

Methods: This is a prospective study at a university referral center. There were 47 patients. The indications for WCE were abdominal pain (57%), cancer surveillance (23%), blood in the stool, or persistent iron deficiency (19%).

Results: Findings were consistent with celiac disease in 87%: atrophy (68%), fissuring (62%), and mosaic pattern (19%), extending to the ileum in 34%. Unexpected findings were ulceration in 45% (n = 21), cancer (1), polyps (1), stricture (1), submucosal mass (1), ulcerated nodular mucosa (2), and intussusception (1) were seen in 60%.

Conclusions: WCE has a high yield in complicated celiac disease, by identifying mucosal abnormalities and by excluding adenocarcinoma. (Gastrointest Endosc 2005;62:55-61.)

Celiac disease is a gluten-sensitive enteropathy that occurs in genetically predisposed individuals.[1] Patients with the disease must adhere to a strict gluten-free diet. However, not all patients respond promptly to the diet,[2] and some develop symptoms while on the diet. The presence of persistent abdominal pain and blood detected in the stool raise the possibility of complications such as small intestinal malignancy[3-5] and ulcerative jejunitis.[6,7]

Until recently, the evaluation of patients with small-intestinal diseases was limited to endoscopy and biopsy, push enteroscopy, small-intestinal barium studies, and CTs. Because these studies are not sensitive at detecting small-intestinal lesions, the diagnosis of small-intestinal malignancies[8,9] is often delayed.

Wireless capsule endoscopy (WCE) of the small intestine[10] has been used to detect and to localize small-intestinal bleeding sites in patients with obscure GI bleeding. It has proven to be far more sensitive than other available techniques.[11-16] More recently, WCE has been used to detect small-intestinal lesions not identified by radiologic techniques in patients with inflammatory bowel disease.[11,12,17] Therefore, we used WCE to evaluate patients with celiac disease who had abdominal pain or other symptoms suggestive of an associated malignancy, or those with an increased risk of malignancy. We regarded these patients as having complicated celiac disease.

See CME section; p. 116.

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PATIENTS AND METHODS

Patient selection

Patients were evaluated in the Celiac Disease Center at Columbia University Medical Center (CUMC). All the patients had serology- and biopsy-proven celiac disease.

WCE was performed in patients we considered to have complicated celiac disease. This was defined as patients with worrisome symptoms, especially abdominal pain that was not explained by previous evaluation or with a high risk of small-intestinal malignancy. Patients were prospectively assigned into 3 categories: group A, persistent abdominal pain, weight loss, with and without diarrhea; group B, history of small-bowel cancer or adenoma, or patients with long-standing celiac disease as defined by a diagnosis of celiac disease during childhood, with failure to maintain a gluten-free diet until rediagnosis as an adult (surveillance for cancer); group C, heme-positive stool or iron deficiency anemia nonresponsive to oral iron therapy.

Exclusion criteria included swallowing disorders, pacemaker, pregnancy, and suspicion or known small-bowel stricture.

WCE procedure

WCE was performed by using the Given M2A (Given Imaging Ltd, Yoqneam, Israel) capsule. Patients fasted

from midnight of the day of the test. No bowel preparation was used. Eight abdominal leads were placed in the upper, the mid, and the lower abdomen, and a belt that contained the data recorder and a battery pack was affixed around the waist of the patient. Two hours after ingestion, liquids were permitted, and, 4 hours after capsule ingestion, the patient was permitted to resume eating light meals. Approximately 8 hours after ingestion, the belt data recorder was removed, and the data was downloaded to the computer workstation.

Data collection

The indication for the procedure and the previous studies to evaluate these patients were prospectively recorded. All patients filled out a basic questionnaire about current medication use, past medical and surgical history, date of diagnosis of celiac disease, and length of time on a gluten-free diet.

All studies were reviewed by a gastroenterologist with experience in interpreting WCE who was aware that the patient had celiac disease but was unaware of the indication for the procedure.

The findings were characterized as (1) those specific for celiac disease (villous atrophy, fissuring, and nodularity), and (2) unexpected findings (ulcers, tumors, stricture, and intussusception).

All patients consented for the study that was approved by the institutional review board of CUMC. Groups were compared by using the chi-square test and the Fisher exact test.

RESULTS

Patients

Between August 2002 and November 2003, we evaluated 47 patients (22 men, 25 women) with complicated celiac disease. They ranged in age from 22 to 80 years old, with a mean age of 54.8 $\pm$ 15.1 years. All of the patients were on a gluten-free diet for a mean of 5.1 years $\pm$ 5.6 years (range 3 months to 22 years). Two patients were taking aspirin or nonsteroid anti-inflammatory drugs (NSAID).

Evaluation before WCE

Patients underwent extensive evaluation of their symptoms of abdominal pain, persistent iron deficiency, blood in the stool, or increased risk of cancer, before WCE. These evaluations included the following: 99 upper-GI endoscopies, 74 abdominal CTs, 70 small-bowel barium studies, 37 abdominal US, 13 enteroscopies, 10 enteroclyses, and 3 position emission tomography scans. Diagnostic laparoscopy was performed in two patients and laparotomy in one, because of the concern of the presence of an occult malignancy. None of these studies revealed a cause of patient symptoms, apart from an intussusception that also was seen on an abdominal CT.

Capsule Summary

What is already known on this topic

- Celiac disease is a chronic inflammatory small-bowel disorder.
- Patients are at risk for complications that include small-intestinal adenocarcinoma, lymphoma and ulcerative jejunitis.
- Radiologic evaluation of the small intestine is not sensitive.

What this study adds to our knowledge

- Capsule endoscopy provides a method of visualization of the entire small-intestinal mucosa.
- The changes of celiac disease may extend the entire length of the small intestine.
- Capsule endoscopy excludes small-intestinal cancer in patients at risk.
- Patients with celiac disease and abdominal pain or blood in the stool have a high rate of intestinal ulceration detected by capsule endoscopy.

An aberrant, clonal T-cell population that defines patients with refractory sprue or enteropathy T-cell lymphoma, was identified in the duodenal biopsy of 3 of the patients of 17 in whom it was sought.[18]

WCE

WCE findings are listed in Tables 1 and 2. Mucosal abnormalities, which we associate with celiac disease, readily identified in the duodenum at endoscopy, were identified at WCE. These included the following: villous atrophy (n = 32), scalloping and fissuring (n = 29), and mosaic pattern (n = 9) (Figs. 1 and 2). No lesions were identified in 13% (n = 6) of WCE examinations. Abnormalities extended into the ileum in 16 (34%) of the patients. These findings in the ileum included villous atrophy (n = 8), fissuring (n = 3), and nodularity (n = 3). We identified a previously unreported observation, that of ''layering'' of folds (Fig. 3). This was identified in 40% of the patients and extended into the ileum in 9%.

Unexpected findings were ulceration (n = 21), nodularity (n = 6), cancer (n = 1), polyp (n = 1), stricture (n = 1), intussusception (n = 1), and submucosal mass (n = 1) (Figs. 4 to 8).

The findings in relation to the different groups of patients are shown in Table 3. There were no significant differences in the occurrences of the findings between each group, though overall there was a high yield of unexpected findings in group A patients (abdominal pain); 52% had ulceration, stricture, or intussusception.

Small-bowel transit time was recorded as the time interval between entrance into the duodenum and passage through the ileocecal valve. Small-bowel transit time ranged from 94 to 460 minutes, with an average

TABLE 1. Wireless capsule endoscopy: findings consistent with celiac disease

Capsule findings	% (n)
Villous atrophy	68.1 (32)
Fissuring	61.7 (29)
Layering	40.4 (9)
Mosaic pattern	19.1 (9)
Any ileal findings	34.0 (16)
No findings	12.8 (6)

TABLE 2. Unexpected findings at capsule endoscopy

Finding	% (n)
Ulceration	44.7 (21)
Nodularity	12.8 (6)
Cancer	2.1 (1)
Polyp	2.1 (1)
Stricture	2.1 (1)
Intussusception	2.1 (1)
Submucosal mass	2.1 (1)

transit time of 297 minutes. The capsule did not pass the ileocecal valve in 10 of the patients (21.3%). No capsules were retained in the GI tract. In one patient, the capsule did not traverse a stricture during 7.5 hours of recorded video. Follow-up abdominal radiographs 3 days later, however, demonstrated passage of the capsule out of the GI tract.

Intestinal ulceration

Ulceration of small-bowel mucosa was identified in a similar percentage from each group of patients: group A, 44%; group B, 36%; group C, 56%. Ulcers were multiple in all cases and were identified in both the jejunum and the ileum. The findings of ulceration prompted a change in the medical management of 60% of patients. Treatment included cessation of aspirin and NSAIDs, the use of Pepto-Bismol (Procter & Gamble, Cincinnati, Ohio), and the initiation of the anti-inflammatory agents (mesalamine and budesonide).

Adenocarcinoma

Carcinoma was found in one patient from group C. This patient was an 81-year-old man who had a 5-year history of celiac disease and was on a strict gluten-free diet. He was found to have occult blood in his stool. Initially, he underwent a colonoscopy, upper endoscopy, and enteroscopy, which revealed changes of celiac disease only. He also underwent a CT of his abdomen and a negative enteroclysis. WCE revealed the carcinoma in the mid jejunum. At laparoscopy, a palpable lesion was identified and surgically removed. Adenocarcinoma with serosal and lymph-node involvement was confirmed by pathologic examination of the resected specimen. The patient has done well since. Importantly, adenocarcinoma was excluded in the other patients in whom there was a suspicion because of either a previous history of either adenocarcinoma or adenoma, celiac disease untreated since childhood, or occult bleeding.

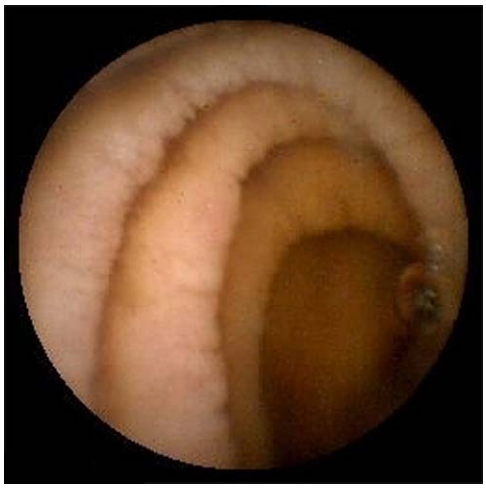

Figure 1. Scalloping and mucosal fissures.

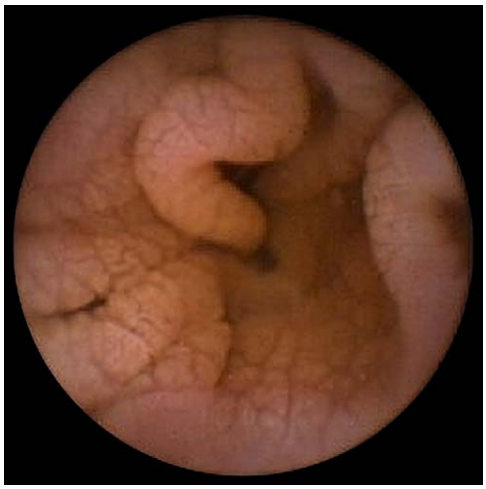

Figure 2. Mosaic pattern of mucosa.

Lesions suspicious for lymphoma

Lesions suspicious for lymphoma were seen in two patients. Both these patients had clonal T-cell populations detected by polymerase chain reaction in duodenal biopsy specimens. These patients had ulcerated nodular areas in the distal jejunum and the ileum. Both patients had

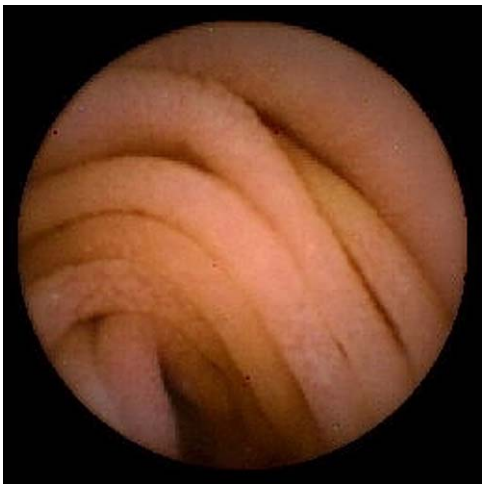

Figure 3. Layering of folds.

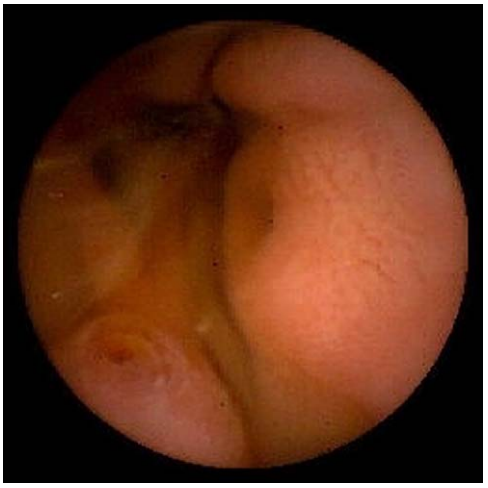

Figure 4. Ulcerated nodular mucosa in a patient with T-cell clonal population in duodenal biopsy specimens.

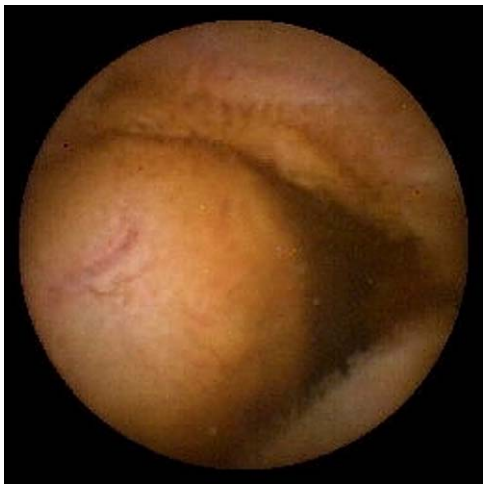

Figure 5. Submucosal mass in a patient with chronic lymphatic leukemia.

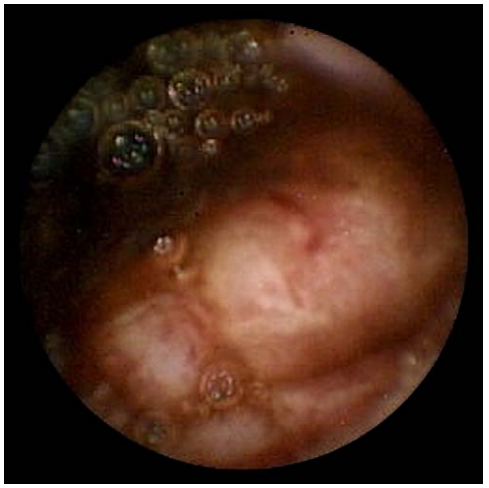

Figure 6. Adenocarcinoma that was not detected by enteroclysis.

undergone evaluation for persistent abdominal pain. They have refused laparoscopy/laparotomy because of resolution of symptoms with Pepto-Bismol (1) and budesonide (1).

Stricture and intussusception

Stricture and intussusception were identified in patients with recurrent episodes of abdominal pain. The stricture was identified in a woman with long-standing celiac disease who had recurrent episodes of severe, mid epigastric, abdominal pain. Evaluation had included endoscopy, enteroscopy, EUS of the pancreas, CTs, and laparoscopy. At WCE, an obstructing stricture was identified. There was, however, no retention of the capsule. The patient declined operative intervention. The intussusception was identified in a 23-year-old man who presented with recurrent episodes of abdominal pain. There was no evidence of a tumor at the site of the intussusception. The intussusception also was identified on an abdominal CT. Since starting a gluten-free diet, he has had no further episodes of abdominal pain.

Submucosal mass

An ileal submucosal mass was identified in a 54-year-old woman with celiac disease and chronic lymphatic leukemia who was evaluated for persistent iron deficiency. At WCE, as well as changes of villous atrophy extending into the ileum, a submucosal mass that did not appear to be ulcerated was identified. A small-intestinal series and a CT of the abdomen and the pelvis were normal. Follow-up WCE is planned.

Patients with normal WCE

All patients with normal WCE had abnormal findings at EGD, including loss of duodenal folds, mucosal fissures, and scalloping of folds. This observation suggests that

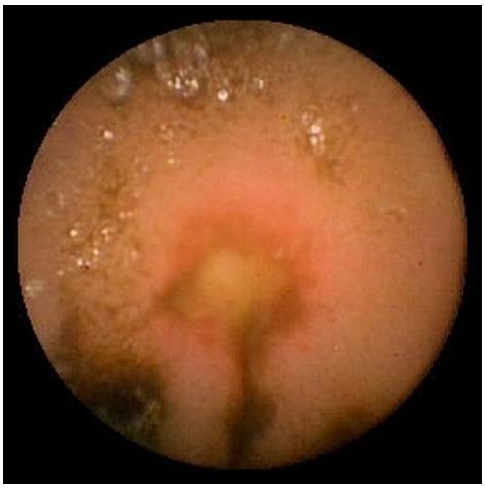

Figure 7. Ulceration in distal jejunum.

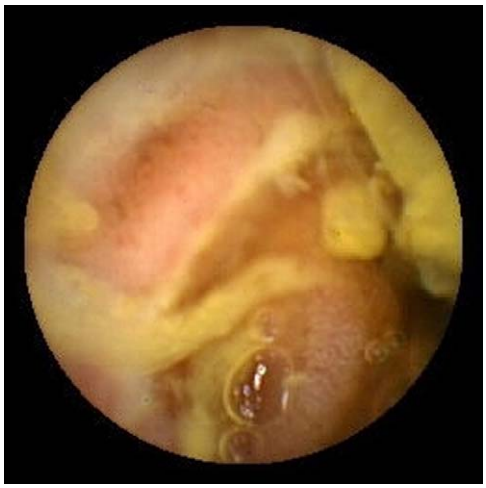

Figure 8. Ulceration, nodularity, and adherent mucus.

TABLE 3. Findings in relation to indication for WCE

Finding	% of patients overall (n)	Group A n = 27, 57%	Group B n = 11, 23%	Group C n = 9, 19%
Villous atrophy	68.1% (32)	70.4	45.5	88.9
Fissuring	61.7% (29)	66.7	36.4	77.8
Mosaic pattern	19.1% (9)	22.2	18.2	11.1
Layering	40.4% (19)	37.0	36.4	55.6
Ulcers	44.7% (21)	44.4	36.4	55.6
Nodularity	12.8% (6)	7.4	18.2	22.2
Cancer	2.1% (1)	0	0	11.1

Group A, Persistent abdominal pain and weight loss; *Group B*, cancer surveillance (prior small intestinal cancer or adenoma, or history of childhood celiac disease rediagnosed as an adult; *Group C*, heme-positive stool or refractory iron deficiency.

WCE is not as sensitive for detecting abnormalities in the descending duodenum, an area examined by EGD.

DISCUSSION

Celiac disease may be complicated by a variety of conditions, including small-intestinal adenocarcinoma,[3,4,19] small-intestinal lymphoma,[19-23] and ulcerative jejunitis, which are often not identifiable by conventional imaging modalities.[24] The presence of persistent or recurrent abdominal pain, as well as occult GI bleeding raises the possibility of these complications. We used WCE to study this high-risk group of patients with celiac disease who, despite maintenance on gluten-free diet, had abdominal pain, occult blood loss, or refractory iron deficiency anemia. All patients underwent extensive conventional investigations before WCE.

We noted changes consistent with celiac disease (atrophy, fissures, mosaic pattern to the mucosa) in the majority of the patients. These changes extended to the ileum in 34% of the patients. These changes were present despite the patients being maintained on a gluten-free diet, a finding that we had noted during follow-up EGD in patients with celiac disease while on a gluten-free diet.[25] A frequent observation was that of layering or stacking of folds. We have rarely recognized this in other patients who underwent WCE and have attributed this finding to atrophy of the mucosa. In some patients, the capsule study was normal, suggesting that the WCE does not uniformly visualize the descending duodenum, an area that is examined by EGD.

A major finding in our study is the high rate of detecting ulceration in the distal intestine, both jejunum and ileum. Only two of these patients gave a history of

concurrent or recent NSAID use. Ulceration occurred in each of the groups we studied. In each case, the ulcers were discrete and multiple, and would satisfy a diagnosis of ulcerative jejunitis or ileitis. Crohn's disease was excluded by negative colonoscopy and biopsy. Recent studies have shown that WCE detects ulceration in the intestine in patients with inflammatory bowel disease, which had not been detected by other studies, including small-intestinal series, enteroclysis, and contrast-enhanced CT.[11,17,26] In our study, the detection of ulcers led to clinical interventions, including the following: discontinuation of NSAIDs, as well as initiating specific treatment with 5-aminosalicyclic acid–containing drugs, budesonide, and Pepto-Bismol. Whereas we have not performed follow-up WCE, patients with complaints of abdominal pain and ulceration have had resolution of their abdominal pain. There, however, is a lingering concern that the patients may harbor a low-grade enteropathy T-cell lymphoma. This is especially a worry in those patients who have an aberrant T-cell clone in duodenal biopsy specimens.[21,27] In addition, the submucosal mass in the patient with chronic lymphatic leukemia is worrisome.

Only one patient who presented with occult blood in his stools had an adenocarcinoma detected by WCE. State-of-the-art radiologic studies had failed to reveal this tumor. This is not uncommon, because the detection of small-bowel cancers generally is delayed.[28-30] Most importantly, cancer was excluded in the all other patients, especially those at risk with a previous history of small-intestinal cancer or adenoma, or with a history of childhood celiac disease and ingestion of gluten until rediagnosis as adults.[4]

Overall, patients with celiac disease and abdominal pain had a high yield of unexpected findings, they included ulceration, stricture, and intussusception. Intussusception has been reported previously and may be a more common cause of abdominal pain in patients with celiac disease[31,32] than previously thought. While uncommon, a tumor as a lead point of the intussusception needs to be excluded. The demonstration of intussusception and the lack of a tumor would obviate the need for a laparotomy or laproscopy.

In summary, WCE has a high yield in patients with celiac disease that is complicated either by persistent symptoms of abdominal pain, evidence of blood loss, or a greater than expected risk of a small-intestinal malignancy. These patients typically have an extensive series of evaluations to exclude a small-intestinal malignancy. All the patients that we studied had multiple investigations before WCE, including laparoscopy and laparotomy. These investigations did not result in a diagnosis, apart from a jejunal intussusception that also was seen at WCE. While several of the abnormalities that we have detected require further follow-up to determine their significance, it is clear that these patients undergo an extensive series of tests that have minimal yield. In fact, our findings show that standard radiologic studies are too insensitive to detect mucosal abnormalities and appear to have little role in the evaluation of these patients. Our study suggests that WCE should be performed early in these patients, before embarking on an extensive evaluation. Furthermore, this new diagnostic modality, WCE, allows initiation of specific therapies when another diagnostic finding is established. WCE is a valuable tool in the assessment of complicated celiac disease, especially in excluding small-intestinal cancer. The limitation of our study is the nature of our referral center with a large number of patients who are not doing well on the diet. However, we anticipate more studies of the use of WCE in patients with this common condition.

DISCLOSURE

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