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Capsule endoscopy in nonresponsive celiac disease

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Abstract

Background—Nonresponsive celiac disease (CD) is defined by persistent or recurrent symptoms, common after treatment with a gluten-free diet (GFD).

Objective—To evaluate the utility of capsule endoscopy (CE) in nonresponsive CD.

Design—Case-control study.

Setting—Tertiary-care center.

Patients—Forty-two consecutive patients with nonresponsive CD and 84 age- and sex-matched CD-free controls who underwent CE were included. In addition, capsules taken after treatment with a GFD were retrospectively evaluated in 30 patients with uncomplicated CD.

Intervention—CE.

Main Outcome Measurements—Diagnostic accuracy of CE for the detection of mucosal abnormalities in nonresponsive CD.

Results—Macroscopic features of villous atrophy were detected in 13 of 42 patients (31%) with nonresponsive CD compared with none among 84 CD-free controls and 14 of 30 patients (47%) with uncomplicated CD. Among nonresponsive CD cases, the overall sensitivity and specificity of CE for the detection of any degree of villous atrophy as graded by histology were 56% and 85%, respectively. Single or multiple erosions/ulcerations of the gut were observed in 19% of nonresponsive CD patients, 18% of CD-free controls, and 31% of patients with uncomplicated CD ($P = .35$). The presence of erosions/ulcerations was associated with increased aspirin/nonsteroidal anti-inflammatory drug use in nonresponsive CD ($P = .05$). Two severe complications (ulcerative jejunitis and adenocarcinoma) were detected by CE in nonresponsive CD.

Limitations—Single-center, retrospective study.

Conclusions—Mucosal abnormalities were observed by CE in patients with both nonresponsive CD and uncomplicated CD. CE can detect severe complications in patients with nonresponsive CD.

Celiac disease (CD) is a permanent intolerance to gluten that causes intestinal injury characterized by villous atrophy.¹ Clinical response is evident after strict adherence to a gluten-free diet (GFD) in most patients with CD.² A minority of patients with treated CD may have persistent or recurrent symptoms despite declared gluten exclusion (nonresponsive

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CD).^{3, 4} Persistent or recurrent symptoms are most often caused by gluten contamination.^{3–5} Other causes of nonresponsive CD include microscopic colitis, small-bowel bacterial overgrowth, pancreatic insufficiency, refractory CD, and lymphoma.^{3, 4, 6–11}

Classic endoscopic features of villous atrophy are scalloping, fissures, reduced or absent Kerckring's folds, and the "mosaic" pattern.^{12–14} Until recently, the evaluation of patients with small-bowel disorders was limited by the relative inaccessibility of the midgut.¹⁵ Double-balloon enteroscopy can permit endoscopic evaluation of the entire intestine, but it is invasive and not widely available.^{16, 17} Capsule enteroscopy (CE) allows painless and magnified imaging of the entire small bowel.¹⁸ It has proved to be far more sensitive than other conventional imaging techniques of the intestinal mucosa.^{15, 19} Obscure GI bleeding of presumed small-bowel origin is the principal indication for CE.^{20, 21}

CE can readily detect the villous atrophy in CD, having better sensitivity than conventional upper GI endoscopy.^{22–24} Finally, CE has been used to determine both the extent of enteropathy and the response to a GFD,²³ thus, supporting the suggestion that CE could be an alternative to biopsy in patients unwilling or unable to undergo upper GI endoscopy.²⁵

The utility of CE has been explored in patients with nonresponsive CD and refractory CD.^{24–28} Villous atrophy or ulcerations are often features reported in complicated CD.²⁸ Intestinal ulceration can indicate severe complications such as refractory CD, ulcerative jejunoileitis, and lymphoma.^{11, 27, 29, 30} Therefore, it is crucially important to know whether ulceration of the gut discovered by CE is truly related to CD or could be an nonspecific finding related to other factors such as the use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).³¹

The aim of this study was to determine the prevalence of mucosal abnormalities and accuracy of findings detected by CE in patients with nonresponsive CD compared with those found in CD-free controls and a group with treated uncomplicated CD.

METHODS

Study population

We included 42 consecutive patients with biopsy-proven CD. CE was performed because of nonresponsive CD defined by persistent or recurrent symptoms (such as diarrhea, weight loss, and abdominal pain) after at least 6 months on a GFD.³ The control group consisted of 84 age- and sex-matched subjects with normal duodenal histology who underwent CE concurrently with the evaluation of nonresponsive CD patients. Blind review of images was achieved by mixing the CE videos and assigning a numeric code only known by 1 investigator (C.V.D.). Unexplained GI bleeding or anemia were the most frequent indications in the control group (n = 64, 76%). In a post hoc analysis, a blinded retrospective re-review of CE in 30 consecutive asymptomatic patients with biopsy-proven CD who underwent follow-up CE after at least 6 months of treatment with a GFD was undertaken to address the rate of erosion/ulceration in patients with treated uncomplicated CD. Details of this group were previously published.²³

Capsule enteroscopy

The study used the Wireless Endoscopy Imaging System (Given M2A; Given Imaging Ltd, Yoqneam, Israel).^{18, 32} No bowel preparation other than fasting or prokinetic drugs were used.

Image analysis

The video images of each patient were blindly reviewed by an experienced investigator (J.A.M.) with > 100 capsules reviewed before this study and extensive GI endoscopy experience (>25 years). The following characteristics on CE were considered indicative of CD (villous atrophy): (1) mucosa (scalloping, fissuring, mosaic pattern) and (2) absence of villi (Fig. 1). The time until the appearance of the first villi and time with features of atrophy were also recorded, expressed in hours and fraction of hours. Other abnormalities such as erosions (defined as small mucosal break with or without exudates or surrounding red color), ulcers (defined by a large pale or yellow base with a pink or red surrounded border of elevated mucosa), submucosal lesion, and stenosis were also recorded (if present). It is difficult to accurately distinguish erosions from ulcers by CE because images are magnified, and it is a challenge to judge the size (eg, the conventional endoscopy rule of 5 mm to differentiate erosion from ulcer does not apply).^{33, 34} Thus, for analytical purposes, ulcers were combined with erosions.

Clinical and laboratory data

Clinical and laboratory data were retrospectively collected from the medical record with special emphasis on the history of aspirin or NSAID use that includes data from the medication reconciliation process (a systematic process implemented at the Mayo Clinic for drug history and safety in which health care providers obtain and review current medication information before each visit and/or procedure). Of note, medication reconciliation standards require direct inquiry about aspirin/NSAID use before each endoscopic procedure. Patients with nonresponsive CD underwent a systematic sequential evaluation as previously described by our group.³

Histology

At least 4 biopsy specimens were taken from the distal duodenum in patients with nonresponsive CD and CD-free controls. Histological lesions were summarized according to the modified Marsh classification.³⁵

Statistics

Data pertaining to patient demographics, clinical factors, and CE characteristics were summarized with descriptive statistics. These included counts and percentages for categorical data and means and standard deviations for continuous data. To examine a difference in CE characteristics, comparative analyses were performed using the group of nonresponsive CD patients and the set of 2:1 matched CD-free controls. In addition, a previously assembled cohort of CD patients who underwent CE after clinically responsive GFD treatment was included to serve as a disease-similar control group to the nonresponsive CD patients. Among the 3 groups, we assessed for associations with baseline demographics and clinical factors using standard one-way tests, including the χ^2 test for categorical factors and analysis of variance for continuous factors. To test for associations between group and CE findings, each performance characteristic was modeled as a dependent variable via analysis of variance regression (or logistic regression if the characteristic was binary). In addition to the 3-level CD group variable, each model also included age and sex as adjusting covariates because group comparisons revealed borderline to significant differences (ie, the matched case and control groups tended to be older and more predominantly female than the uncomplicated CD group). All analyses were carried out using the SAS statistical software package version 8.2 (SAS Institute Inc, Cary, NC). $P < .05$ was considered statistically significant.

Ethical issues

The study was approved by the Institutional Review Board of Mayo Clinic.

RESULTS

Patients

Forty-two consecutive patients with nonresponsive CD and 84 age- and sex-matched CD-free controls were studied. In addition, we did a retrospective re-review of CE in 30 patients with treated uncomplicated CD who underwent CE evaluation after treatment with a GFD for approximately 6 months or more (Table 1).

CE findings

All 126 patients swallowed the capsule successfully, and no capsule failed to leave the stomach. Small-bowel transit time was significantly longer in nonresponsive CD patients compared with CD-free controls (5.0 ± 1.6 hours vs 4.3 ± 1.7 hours, $P = .019$), although not significantly different compared with uncomplicated CD patients (4.9 ± 1.4 , $P = .79$), adjusting for age and sex. No capsule retention was observed (Table 2).

Villous atrophy—Macroscopic features of villous atrophy were detected in 13 patients (31%) with nonresponsive CD compared with none of the CD-free controls and 14 patients with uncomplicated CD (47%) (Fig. 1). The time to the appearance of first villi was significantly longer in nonresponsive CD patients (0.4 ± 1.3 hours) compared with both CD-free controls (0.01 ± 0.03 hours; $P = .007$) and patients with uncomplicated CD (0.26 ± 0.88 hours, $P = .019$), adjusted for age and sex. Among 13 patients with nonresponsive CD with atrophy detected by CE, the mean time with features of atrophy tended to be longer compared with 14 patients with treated uncomplicated CD (1.52 ± 2.14 hours vs 0.26 ± 0.30 hours, $P = .086$), although this result did not reach statistical significance.

Villous atrophy was confirmed by histology in 16 patients with nonresponsive CD (13 had partial villous atrophy and 3 had total villous atrophy). Results of CE and histology agreed on examinations with negative findings in 22 patients and examinations with positive findings in 9 patients. Seven patients with negative findings on CE had histological atrophy and 4 patients with positive findings on CE had negative findings on histology. All 3 patients with total villous atrophy had positive findings on CE compared with 6 of 13 patients with partial villous atrophy. In total, CE and histology findings agreed in 74% of nonresponsive CD cases ($\kappa = 0.44$), suggesting weak agreement. The overall sensitivity and specificity of CE for the detection of any degree of villous atrophy as graded by histology were 56% and 85%, respectively. The most frequent diagnosis in nonresponsive CD was gluten contamination suspected in 20 patients with positive CD-specific serology during follow-up. Among those 20 patients, CE showed features of atrophy in 11 (8 had abnormal histological findings and 3 had normal histological findings). In addition, features of atrophy on CE were observed in 2 patients with refractory CD (both had abnormal findings on histology).

Erosions/ulcerations—Single or multiple erosions/ulcerations of the gut were observed in 19% of patients with nonresponsive CD, 18% CD-free controls, and 31% of patients with uncomplicated CD (Fig. 2). Neither the rate nor quantity of erosion/ulcerations was significantly different among the study groups (Table 3).

Thirty-eight of the 156 patients included in this study have histories of concurrent use of aspirin or NSAIDs at the time of CE, including 9 of the 42 patients (21%) with nonresponsive CD, 21 of the 84 CD-free controls (25%), and 8 of the patients (27%) with

uncomplicated CD. There was a borderline association between aspirin/NSAID use and the presence of any erosions/ulcerations among patients with nonresponsive CD (rate for any lesion: 44% in aspirin/NSAID users vs 12% in nonusers, $P = .05$).

Other relevant findings—Deep ulceration of the jejunum suggestive of either ulcerative jejunitis or lymphoma was identified by CE in 1 patient with nonresponsive CD (Fig. 3). No overt lymphoma was evident by histology after extensive biopsy sampling of the affected segment by enteroscopy, but a T-cell clone was confirmed by demonstration of T-cell receptor- γ clonal rearrangement by polymerase chain reaction characteristic of refractory celiac disease type II.³⁶ This patient was not taking aspirin or NSAIDs. A tumor with active bleeding was detected on CE in the jejunum of another patient with nonresponsive CD. The histology demonstrated grade 4 adenocarcinoma with metastasis to 2 regional lymph nodes. No cases of ulcerative jejunitis, lymphoma, or cancer were detected in either the CD-free controls or patients with uncomplicated CD.

DISCUSSION

This study yielded 3 major findings. First, macroscopic features of villous atrophy were detected by CE in 31% of patients with nonresponsive CD and 47% of patients with treated uncomplicated CD, suggesting persistent mucosal damage despite a GFD. Second, small-intestine erosions/ulcerations are no more frequent in nonresponsive CD than in either the CD-free controls or patients with treated uncomplicated CD, but those with nonresponsive CD are associated with increased aspirin/NSAID use. Third, CE can detect severe complications (eg, malignancies) in patients with nonresponsive CD.

Features of villous atrophy were observed on CE in patients with both nonresponsive CD and uncomplicated CD, consistent with other previous reports.^{23, 28} Positive CD-specific serology was observed in 51% of patients after GFD, suggesting that dietary transgressions may underlie nonresponsive CD.^{3, 4, 37} The high rate of features of villous atrophy detected in uncomplicated CD could be explained by the short time between the onset of GFD and the follow-up CE (0.9 0.44), suggesting weak 0.4 years). This observation is consistent with extensive evidence that suggests low rates of mucosal recovery despite clinical response in adult-onset CD years after starting a GFD.^{38–40} Patients with uncomplicated CD had shorter time to the appearance of first villi and the time with features of atrophy when compared with nonresponsive CD supporting mucosal response to gluten exclusion in uncomplicated CD. The sensitivity (56%) and specificity (85%) of CE for detection of villous atrophy as graded by histology in this real clinical scenario of nonresponsive CD were lower than those previously reported in patients with untreated CD.^{22, 23, 25} The principal reason that may explain this discrepancy is that the majority of patients with both nonresponsive CD and biopsy-proven villous atrophy had partial villous atrophy likely reflecting partially treated CD.³⁸ CE may have a lower accuracy to detect partial villous atrophy.^{14, 41} Villous atrophy was accurately detected by CE in the 3 patients with total villous atrophy. The low specificity (increased false-positive rate) found in this study compared with studies in untreated CD requires further comment because the utility of the intestinal biopsy as a reference standard is confined to the evaluation of the proximal small intestine.^{26, 42} It is possible that CE could detect more distal changes beyond the reach of the sampling area of conventional endoscopy. Thus, in the appropriate clinical context, some supposedly false-positive CE findings may be indeed diagnostic yield gains over an imperfect criterion standard of duodenal biopsies. This view is supported further by the absence of false positives in the CD-free control group.²³ However, the poor sensitivity of CE is still an issue, and duodenal histology should remain the standard for assessment of mucosal damage in CD.^{43, 44}

Despite similar prevalence of erosions/ulcerations among study groups, the presence of erosions/ulcerations was associated with concurrent aspirin/NSAID use in patients with nonresponsive CD. The spectrum of small-bowel NSAID-associated enteropathy is extensive.^{45–48} Endoscopically visible erosions/ulcers can be seen in as many as 71% long-term NSAID users.^{33, 49} CE was highly accurate for detecting indomethacin-induced enteropathy.⁵⁰ Small inflammatory lesions could be observed by CE in 14% of healthy subjects.³⁴ Thus, a careful clinical-endoscopic correlation (eg, presence of T-cell clones) and detailed history of drug use are advisable before assuming that erosions/ulcerations seen on CE are attributable to CD.³⁶ In this series, CE detected 2 patients with severe CD-associated complications located in the mid small intestine beyond the reach of conventional upper GI endoscopy, consistent with other reports.^{27, 28} It is the authors' practice to use CE in parallel with other imaging modalities (eg, CT enterography) to exclude malignancy as part of the workup in patients with refractory CD associated with aberrant and/or clonal intraepithelial lymphocytes (type II).³⁶ CE may be indicated in treated patients who have alarm symptoms such as weight loss, fever, and severe abdominal pain. CE evaluation is not necessary when a cause for nonresponsive symptoms is evident such as intentional gluten contamination or microscopic colitis.⁵¹ Balloon-assisted enteroscopy may be helpful for sampling abnormal areas located beyond the reach of conventional endoscopy to exclude (or confirm) enteropathy-associated T-cell lymphoma, ulcerative jejunitis, and/or adenocarcinoma in patients with complicated CD.⁵²

Two particular strengths of this study are the use of a biopsy-negative control group and blinded CE evaluation. This study showed that mucosal abnormalities by CE could be observed in both nonresponsive CD and uncomplicated CD. It remains to be demonstrated whether the use of CE may improve patient outcomes in nonresponsive CD.⁵³

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Abbreviations

CD	celiac disease
CE	capsule enteroscopy
GFD	gluten-free diet
NSAID	nonsteroidal anti-inflammatory drug

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Take-home Message

- Capsule endoscopy could be useful to detect severe celiac disease-related complications located beyond the reach of conventional upper GI endoscopy in patients with nonresponsive CD.

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Figure 1. Examples of macroscopic features of atrophy detected by CE in nonresponsive CD: normal villi (**A**), scalloping of the mucosa on circular folds (**B**), fissuring of the mucosa (**C**), mosaic pattern (**D**).

Figure 2.
Examples of a single erosion (A), multiple erosions (B), and ulceration of the jejunum (C).

Figure 3. Ulcerative jejunitis detected by capsule endoscopy in a patient with nonresponsive celiac disease. A T-cell clone was confirmed by demonstration of T-cell receptor- γ clonal rearrangement by polymerase chain reaction characteristic of refractory celiac disease type II. No overt lymphoma was evident.

TABLE 1

Summary of demographics, clinical characteristics, histology, and endoscopic findings

	Nonresponsive CD	Control group	Uncomplicated CD	
Characteristic	(n = 42)	(n = 84)	(n = 30)	P value
Female sex, no. (%)	32 (76)	64 (76)	17 (57)	.10
Age at time of CE, y, $\pm$ SD	55.8 $\pm$ 13.0	54.1 $\pm$ 13.1	47.7 $\pm$ 11.4	.023
Age at time of CD assessment, $\pm$ SD	49.0 $\pm$ 14.6	52.7 $\pm$ 12.7	46.8 $\pm$ 11.5	.07
Years between diagnosis and CE, $\pm$ SD	6.8 $\pm$ 10.6	0.6 $\pm$ 1.7	0.9 $\pm$ 0.4	<.001
Years between GFD and CE, $\pm$ SD	6.8 $\pm$ 10.6	—	0.8 $\pm$ 0.4	.008
Positive serology at time of CD assessment, * no. (%)	16/17 (94)	2/29 (7) [†]	23/26 (88)	<.001
Positive serology after GFD, * no. (%)	20/39 (51)	—	—	
Aspirin/NSAID use, no. (%)	9 (21)	21 (25)	8 (27)	.86
Histology at time of CE, no. (%)				
Normal	26 (62)	84 (100)	—	
Partial VA	13 (31)	—	—	
Total VA	3 (7)	—	—	

CD, Celiac disease; CE, capsule endoscopy; SD, standard deviation; GFD, gluten-free diet; NSAID, nonsteroidal anti-inflammatory drug; VA, villous atrophy.

* Positive serology refers to either IgA tissue transglutaminase or endomysial antibodies.

[†]The 2 patients with positive serology in the control group had low titers of IgA tissue transglutaminase antibody (21 U and 21.7 U, respectively; normal <20 U) and negative endomysial antibodies.

TABLE 2

Capsule endoscopy performance characteristics and prevalence of villous atrophy

	Nonresponsive CD	Control group	Uncomplicated CD	
Performance characteristic	(n = 42)	(n = 84)	(n = 30)	P value*
Complete small-bowel examination, no. (%)	32 (76)	69 (82)	28 (93)	.424 [†]
Duodenal entry time, $\pm$ SD	0.80 $\pm$ 0.92	0.80 $\pm$ 0.95	0.54 $\pm$ 0.45	.254
Cecal entry time, $\pm$ SD	5.8 $\pm$ 1.7	5.1 $\pm$ 1.6	5.5 $\pm$ 1.5	.050 [‡]
Small-bowel transit time, $\pm$ SD	5.0 $\pm$ 1.6	4.3 $\pm$ 1.7	4.9 $\pm$ 1.4	.046 [‡]
Time until first villi, $\pm$ SD	0.40 $\pm$ 1.31	0.01 $\pm$ 0.03	0.26 $\pm$ 0.88	.028 [§]
Capsule atrophy present, no. (%)	13 (31)	0 (0)	14 (47)	.132 ^{//}
Time with atrophy, $\pm$ SD	1.52 $\pm$ 2.14 (n = 13)	—	0.26 $\pm$ 0.30 (n = 14)	.086 ^{//}

CD, Celiac disease; SD, standard deviation.

* Adjusted for sex and age at time of capsule endoscopy.

[†] Comparison of nonresponsive CD and control groups only.

[‡] Significant association ($P < .05$) detected between nonresponsive CD and control group.

[§] Significant associations detected between nonresponsive CD and control group ($P = .007$) and also uncomplicated CD group ($P = .019$).

^{//} Comparison of nonresponsive and uncomplicated CD groups only.

TABLE 3

Prevalence of erosions/ulcerations detected by capsule endoscopy

Performance characteristic	Nonresponsive CD (n =42)	Control group (n =84)	Uncomplicated CD (n =30)	P value *
Erosions/ulcerations, no. (%)				.282 [†]
None	34 (81)	69 (82)	20 (69)	
1	3 (7)	8 (10)	2 (7)	
2–4	4 (10)	4 (5)	6 (21)	
5	1 (2)	3 (4)	1 (3)	
Any erosions/ulcerations	8 (19)	15 (18)	9 (31)	.351 [‡]

CD, Celiac disease.

* Adjusted for sex and age at time of capsule endoscopy.

[†] Linear trend across the ordinal levels among the 3 groups.[‡] The rate of having any (vs no) lesions among the 3 groups.