COLON/SMALL BOWEL

Diagnostic Yield of Capsule Endoscopy in Refractory Celiac Disease

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OBJECTIVES: **Capsule endoscopy (CE) allows for the assessment of the small bowel in numerous intestinal diseases, including celiac disease (CD). The main advantage of CE is the complete visualization of the intestinal mucosal surface. The objective of this study was to investigate whether CE can predict the severity of CD and detect complications.**

METHODS: **We retrospectively studied the medical files of 9 patients with symptomatic CD, 11 patients with refractory celiac disease type I (RCDI) and 18 patients with refractory celiac disease type II (RCDII), and 45 patients without CD who were investigated both CE and upper endoscopy or enteroscopy. The type of CD was diagnosed on the basis of a centralized histological review, flow cytometry analysis of intraepithelial lymphocytes, and the analysis of T-cell receptor rearrangement by multiplex polymerase chain reaction.**

RESULTS: **A total of 47 CEs (10, 11, and 26 CEs in the symptomatic CD, RCDI, and RCDII groups, respectively) from the 38 celiac patients and 47 CEs from the 45 nonceliac patients were retrospectively reviewed. Villous atrophy, numerous, or distally located ulcers were more frequent in celiac patients than in controls. Among celiac patients, CE was of acceptable quality in 96% of cases and was complete in 62% of cases. The concordance of CE with histology for villous atrophy was better than that of optic endoscopy (κ coefficient =0.45 vs. 0.24, $P<0.001$). Extensive mucosal damage on CE was associated with low serum albumin ($P=0.003$) and the RCDII form ($P=0.02$). Three cases of overt lymphoma were detected by CE during the follow-up.**

CONCLUSIONS: **CE findings have a satisfactory concordance with histology and nutritional status in patients with symptomatic or refractory CD. Moreover, CE may predict the type of RCD and allows for the early detection of overt lymphoma.**

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INTRODUCTION

Capsule endoscopy (CE) is widely practiced in the assessment of celiac disease (CD) (1). It allows for the prediction of the severity of mucosal lesions, with a sensitivity and specificity for detection of villous atrophy of 70 to 94% and 86 to 100%, respectively (2–5). It has also been proposed that CE could be useful in predicting overt lymphoma when large ulcers are seen (6). More recent research has focused on the value of CE in nonresponsive CD and has highlighted the potential role of aspirin/nonsteroidal anti-inflammatory drug use in mucosal injury of the small bowel (7). Nonresponsive CD is defined by persistent or recurrent symptoms despite gluten exclusion (7). Refractory celiac disease (RCD) is a nonresponsive CD that has been subdivided into two types according to the phenotype of the intraepithelial lymphocytes (IELs) (4) and the presence of T-cell receptor (TCR) rearrangements. RCD type I (RCDI) is defined by persistent villous atrophy despite a strict gluten-free diet and is associated with an increased number of normal–phenotype IELs and polyclonal TCR rearrangement. RCD type II (RCDII) is characterized by the clonal expansion of abnormal IELs lacking

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the surface markers CD3, CD8, and TCR (CD3–, CD8–, TCR–) (8,9). It remains unknown whether CE can predict the type of RCD in the case of nonresponsive CD. We previously described more frequent erosions in RCDII patients than in RCDI patients examined by CE (9). We and others also described more frequent jejunal ulcers in RCDII, but in all cases, the low number of patients precluded statistically significant differences (6,9). Ulcerative jejunitis usually accounts for the severe protein-loss enteropathy and malnutrition observed in patients with clonal RCD. However, it remains undetermined whether the extent of mucosal damage could also impact the nutritional status. CE is the first-line endoscopic examination to assess the extent of the intestinal disease involvement. Therefore, we have taken advantage of a well-characterized RCD patient series investigated by CE and upper endoscopy/enteroscopy to analyze the CE features of RCD patients. We assessed how well CE could predict the type of RCD and detect overt lymphoma.

METHODS

Patients

The medical files of 63 consecutive patients diagnosed with RCD between February 2003 and February 2011 in our specialized clinic were reviewed retrospectively. Twenty-nine of them had been investigated by both upper endoscopy and CE within the same year and could be included in the analysis. Nine supplementary patients with symptomatic CD investigated by the same endoscopies were included in the study as celiac controls. Forty-five patients without CD, who underwent 47 CE and upper enteroscopy for gastrointestinal symptoms or follow-up between 2007 and 2011, were included in the study as control group. Consequently, 83 patients were considered for the study and followed up until February 2011. The study was approved by our Institutional Review Board (Paris- Ile-de-France II, France).

Collection of data

The clinical data recorded for each patient included age, sex, symptoms (abdominal pain, diarrhea), gluten-free diet assessed by a senior dietician (for patients with CD), and current medication. Clinical nutritional status was assessed by the BMI (body mass index). Blood tests included hemoglobin and serum albumin levels, IgA and IgG anti-gliadin, IgA-class endomysial and IgA anti-human tissue transglutaminase antibodies, and HLA-DRB1 and DQB1 genotyping, as previously described (9).

Endoscopic evaluation included upper gastrointestinal endoscopy or enteroscopy with intestinal biopsies (10,11) and CE. CE was performed with the Wireless Endoscopy Imaging capsule system (Given M2A; Given Imaging Ltd, Yoqneam, Israel). Patients received 2l of polyethylene glycol solution the night before CE. They were allowed to eat 6h after capsule ingestion. The quality of the images was classified as "poor," "intermediate," or "good" depending on the presence of bubbles or food debris. All CE studies were re-read blinded to clinical, biological, or radiological data.

Enteroscopies were performed with either double balloon enteroscopes (Fujinon, Sataima, Japan) or Spirus overtubes (Spirus Medical, Stoughton, MA).

For histological assessment among CD patients, a minimum of four duodenal and/or jejunal biopsies were fixed in 10% formalin, embedded in paraffin, sectioned, and stained with H&E. All sections were reviewed by a single expert pathologist (V.V.). Villous atrophy was assessed in accordance with the Oberhuber *et al.* (12) modification of the Marsh classification (13) and graded as absent, partial, or severe (subtotal/total). The percentage of IELs (number of IELs per 100 epithelial cells) was established in well-orientated serial sections by counting at least 500 epithelial cells. Immunohistochemistry was performed on sections from paraffin-embedded biopsies using antibodies (Abs) directed against CD3 (rabbit polyclonal Ab; A0452), CD8 (mouse monoclonal Ab; C8/144B, M703), CD30 (mouse monoclonal Ab; BER-H2), MIB-1 (mouse monoclonal Ab; MIB-1), CD4 (mouse monoclonal Ab; AB12, Thermo Fisher Scientific, Fremont, CA), CD5 (mouse monoclonal antibody; AC7), and granzyme B (mouse monoclonal Ab; 11F1) (Novocastra, Newcastle-Upon-Tyne, UK) and on acetone-fixed frozen tissue sections using antibodies directed against CD103 (2G5.1) (Coulter Immunotech, Marseille, France). A three-stage indirect immunoperoxidase technique was used (14). Flow-cytometric phenotyping of freshly isolated IELs from duodenal biopsies was performed as described (8). Molecular detection of clonal TCRγ chain rearrangements was performed on DNA extracted from intestinal frozen biopsies by multiplex polymerase chain reaction as previously described (9,11).

The results of small bowel imaging (including abdominal CT (computed tomography) scan, CT, or magnetic resonance (MR) enterography) performed during the same year as CE were also recorded.

Diagnosis and classification of CD

The diagnosis of CD was based on HLA-DQ2/8 typing, the detection of celiac-specific antibodies, villous atrophy histology, and increased counts of IELs on a normal diet. The patients were further classified depending on their clinical and histological response to a gluten-free diet. Symptomatic CD patients were CD patients investigated by CE at the time of diagnosis or with a poor observance to a gluten-free diet. Further follow-up of these patients showed a good response to a strict gluten-free diet. Nonresponsive CD was defined by clinical relapse and/or persistent malabsorption syndrome and villous atrophy after 1 year of strict adherence to a gluten-free diet: main causes of nonresponsive CD are onset of overt lymphoma or refractory CD. RCDs were further divided into RCDI in the absence of detectable clonality in duodenal biopsies and when IELs had a normal phenotype or, conversely, into RCD II when duodenal biopsies contained clonal TCRγ chain rearrangements and IELs had an abnormal phenotype (defined as >50% of IELs expressing intracellular CD3ε but not CD8 in formalin-fixed sections or as >25% of $CD103^+$ or $CD45^+$ IELs lacking surface CD3/ complexes on flow cytometry analysis of IELs isolated from fresh biopsies) (8,11). Overt

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Table 1. Patient characteristics

	Symptomatic CD (*n*=9)	RCDI (*n*=11)	RCDII (*n*=18)	*P* value[a]
Sex ratio (F/M)	9/0	8/3	10/8	GLOBAL: *P*=0.05
Age at CD diagnosis (years)	40 (18–71)	40 (12–49)	40 (25–68)	GLOBAL: *P*=0.67
Age at first capsule endoscopy (years)	40 (18–71)	51 (16–62)	48 (31–73)	GLOBAL: *P*=0.62
Serum albumin (g/l)	37.0 (28–44)	39.9 (34–45.4)	30 (13–44)	GLOBAL: *P*=0.003 RCDII vs. I: *P*=0.0007
Hemoglobin (g/dl)	11.7 (9.1–14.6)	13.3 (12.2–15.2)	12.9 (8–15.6)	GLOBAL: *P*=0.09

CD, celiac disease; RCDI, refractory celiac disease of type I; RCDII, refractory celiac disease of type II.
[a]We used the following strategy for each variable. First, we performed a global test (three groups). If the result was not significant, we stopped the analysis. If it was significant, we performed the three 2×2 tests. Only the significant 2×2 tests are mentioned in the table.
Continuous variables are expressed as median [min–max].

lymphoma or enteropathy-associated T-cell lymphoma (EATL) was defined by intestinal infiltration by pleomorphic or anaplastic lymphomatous cells.

Statistical analysis

Continuous data were summarized using medians [min–max]. Continuous variables were compared using a Kruskal–Wallis test followed by a nonparametric Mann–Whitney test. Categorical variables were compared using Fisher's exact test. We used the following strategy for each variable: first, we performed a global test, including the three groups. If the result was not significant, we stopped the analysis. If it was significant, we performed the three 2×2 tests. Associations were studied with ANOVA. Statistical analyses were performed using StatView version 5.0 software and the Vassar stats website for statistical computation (Vassar College, Poughkeepsie, NY). To determine whether the CE findings were better correlated with histology than those of enteroscopy, we used a bootstrap-based method to compare the correlated κ coefficients (15,16). Standard deviations and means were estimated from bootstrap samples created with the same number of records as the original data using the SAS statistical package. Finally, the average difference between κ coefficients was compared to 0 using Student's *t* test. A *P* value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

All CD patients had positive celiac antibodies and the celiac HLA-susceptibility DQ2 haplotype at diagnosis. None of them reported NSAID or aspirin intake at the time of the study. Twenty-nine patients remained nonresponsive to a strict gluten-free diet. Among them, 11 had villous atrophy with increased IELs of a normal phenotype and a polyclonal TCR profile and were classified as RCDI. The other 18 patients had RCDII, characterized as previously described (9) by the expansion of abnormal IELs containing intracellular CD3 but no surface CD3/TCR complexes, generally no or weak CD8, and clonal rearrangement of the γ chain of TCR detectable in duodenal biopsies. Nine patients had symptomatic CD with new or poor adherence to a gluten-free diet and no actual nonresponsive CD. The median follow-up was 20 months (0–128).

Regarding their nutritional status, RCDII patients had a lower BMI than RCDI or symptomatic CD patients. Serum albumin was significantly lower in RCDII patients than in RCDI patients, a finding consistent with the severe protein loss that has been described in RCDII (**Table 1**) (9).

Forty-five nonceliac patients were included in the control group. Their median age and sex ratio did not differ significantly from CD patients (**Table 2**). The indication of CE was obscure gastrointestinal bleeding or anemia in 73% of patients. Other indications were mainly abdominal pain, follow-up of Peutz-Jeghers syndrome, or weight loss. Three patients reported aspirin or NSAID intake.

Technical characteristics of CE

Some patients had undergone several CEs and enteroscopy examinations. A total of 10, 11, and 26 examinations were assessed for the 9 symptomatic CD, 11 RCDI, and 18 RCDII patients, respectively. The median time from the CD or RCD diagnosis to CE was 5 years (0–37), 5.5 (0–28) in the symptomatic CD group, 6 (2–37) in the RCDI group, and 5 (0–16) in the RCDII patient group ($P=0.45$). The technical characteristics of the CEs and enteroscopies are described in **Table 3**. CE reached the caecum in 61% of cases (29/47), with a quality judged as good in 70% of cases (33/47). The small bowel time transit of CE in RCDII patients was notably longer than in RCDI and symptomatic CD patients ($P=0.03$). A complete small bowel examination was performed in all patients with symptomatic CD but only in half of the RCD patients ($P<0.05$).

Forty-seven CEs were performed in the control group. The technical characteristics of the CEs in patients with and without CD are described in **Table 2**. The rate of complete small bowel examination was significantly higher in control patients (87 % vs. 32%, $P=0.008$).

CE findings

We did not find any significant differences in the severity of villous atrophy among the different types of CD. Ulcers were most frequently observed, and strictures were only found in RCDII

Table 2. Capsule endoscopy findings in patients with celiac disease and controls

	Celiac group (n=38)	Control group (n=45)	P value
Patient characteristics			
Sex ratio (F/M)	27/11	24/21	0.12
Age at first capsule endoscopy (years)	48.5 (16–76)	55 (40–63)	0.13
Capsule endoscopy			
Good quality (no. (%))	25 (53.2%)	33 (70%)	0.14
Duration (min)	288 (119–480)	247 (80–520)	0.50
Complete small bowel examination (no. (%))	29 (62%)	41 (87%)	0.008
Villous atrophy (no. (%))	38 (81%)	1 (2%)	<0.0001
Ulcerations			
Size>1 cm	7 (15%)	2 (4%)	0.15
0< n≤5	8 (17%)	5 (11%)	0.55
n>5	11 (23%)	0	0.0005
Distal localization[a]	15 (32%)	3 (6%)	0.003
Intestinal strictures (no. (%))	4 (8.5%)	2 (4%)	0.68
Other lesions (SBVL, polyp)	6 (13%)	35 (74%)	<0.001
Extension of lesions			
Proximal[b]	22 (47%)	23 (49%)	0.99
Extensive[c]	18 (38%)	19 (40%)	0.99

SBVL, small bowel vascular lesions.
[a]Involvement of distal jejunum and ileum.
[b]Proximal: limited jejunal enteropathy.
[c]Involvement of jejunum and ileum.
Celiac group includes patients with celiac disease (either symptomatic or refractory).

patients. Intestinal damage was also more extensive in the RCDII patients. Despite the strictures, no retention of capsules occurred. The CE findings are presented in **Table 4,** and representative CE aspects are presented in **Figure 1**.

Among control patients, CE revealed small bowel vascular lesions in 26 (55%) patients, polyps, or tumors in 9 (19%), and was normal in 5 (11%) patients. Two intestinal strictures and five ulcerations were also diagnosed, none of which occurred in the patients reporting NSAID or aspirin intake. Villous atrophy, distal, or numerous (n>5) intestinal ulcers were significantly more frequent in patients with CD (81% vs. 2 % P<0.0001, 23% vs. 0%, P=0.0005, and 32% vs. 6%, P=0.003, respectively). The results are presented in **Table 2**.

Enteroscopy in celiac patients

An upper enteroscopy with intestinal biopsies was performed in 55% of cases (26/47), mainly in the RCDII patients (81%, 21/26), and the examination was conducted beyond 1 m after the duodenojejunal flexure in almost half of the cases (up to 70% in the type II RCD group). The other patients had an upper endoscopy with duodenal biopsies. The median time between the CE and the enteroscopy was 3 days (1–362). These results are summarized in **Table 3**.

Radiological findings in celiac patients

Thirty-five radiological investigations were done within the same year as the CEs in our patient series. They were CT or MR enterography in 51% (18/35) of cases and CT with simple oral contrast medium administration in 26% (9/35) of cases. The median time between the CE and the radiological procedure was 21 days (1–280). These three types of abdominal imaging helped diagnose and locate intestinal wall abnormalities, such as wall thickening, intestinal strictures, and subsequent dilatation or intussusceptions features in 17% (6/35) of the cases. These findings were mainly observed in RCDII and less frequently in RCDI patients (14% and 3%, respectively). Mesenteric lymphadenopathies were seen in 46% (16/35) of radiologic studies; however, these lymph nodes were larger than 1 cm in 20% (7/35) of cases, all of which were RCDII patients, and were associated with EATL in one case.

Contribution of CE in celiac patients

The accuracy of CE and endoscopy in predicting the degree of histological villous atrophy (partial, subtotal, or total) was evaluated using Cohen's κ coefficient. The concordance between the CE aspect and histology was better (κ coefficient = 0.45, 95% confidence interval (0.23; 0.67)) than that of optical endoscopy (κ coefficient =0.24, 95% confidence interval (0.02; 0.45)) (P<0.001).

Extensive mucosal damage on CE was more frequent in the RCDII patients than in RCDI (P=0.02). Numerous ulcers (>5) and/or distal ulcers were mainly found in RCDII patients.

Among the different parameters of malnutrition evaluated (BMI, hemoglobin level, and serum albumin level), we observed an association between the extent of intestinal lesions on CE and serum albumin level (P=0.003) (**Table 5**). Taken together, these data indicate that extensive mucosal damage on CE was predictive of low serum albumin and the RCDII form.

The onset of EATL was observed in seven RCDII patients during follow-up. Three of them (two F/1M; mean age: 48 years) were explored by CE, which found intestinal strictures and jejunal ulcers in two patients and severe villous atrophy in all three. The lesions were distal in two patients and proximal in one. Enteroscopy, reaching the distal small bowel in the three cases, confirmed the CE findings. Radiological imaging techniques showed localized jejunal wall thickening in two cases and supracentimetric mesenteric lymph nodes in the other case. EATL was confirmed by endoscopic biopsy in the two patients with major mucosal abnormalities and surgical biopsy of a mesenteric lymph node in the last one.

CE had a major clinical impact by diagnosing ulcerated jejunal strictures, which turned out to be intestinal lymphomas in two cases, and ulcerative jejunitis warranting specific treatment in five cases. Furthermore, stopping investigations when CE was normal

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Table 3. Technical characteristics of capsule endoscopy and upper endoscopy

Type of endoscopic examination	Symptomatic CD (*n*=10)	RCDI (*n*=11)	RCDII (*n*=26)	*P* value[a]
Capsule endoscopy				
Quality (no. (%))				
Good	8 (80%)	6 (55%)	19 (73%)	
Intermediate	2 (20%)	5 (45%)	5 (19%)	GLOBAL: *P*=0.45
Poor	0	0	2 (8%)	
Duration (min)	173.5 (135–390)	300 (150–450)	355 (119–480)	GLOBAL: *P*=0.03 CD vs. RCDII: *P*=0.02
Complete small bowel examination (no. (%))	10 (100%)	6 (55%)	13 (50%)	GLOBAL: *P*=0.01 CD vs. RCDI: *P*=0.04 CD vs. RCDII: *P*=0.01
Duration of CD (years)	5.5 (0–28)	6 (2–37)	5 (0–16)	GLOBAL: *P*=0.44
Upper endoscopy				
Enteroscopy (no. (%))	2 (20%)	3 (27%)	21 (81%)	GLOBAL: *P*=0.0003 CD vs. RCDI: *P*=0.02 RCDI vs. II: *P*=0.006
Upper endoscopy (no. (%))	8 (80%)	8 (73%)	5 (19%)	GLOBAL: *P*=0.0003 CD vs. RCDII: *P*=0.001 RCDI vs. II: *P*=0.006
Extensive bowel evaluation[b] (no. (%))	2 (20%)	1 (9%)	18 (69%)	GLOBAL: *P*=0.0006 CD vs. RCDII: *P*=0.01 RCDI vs. II: *P*=0.001

RCDI, refractory celiac disease of type I; RCDII, refractory celiac disease of type II.

[a]We used the following strategy for each variable. First, we performed a global test (three groups). If the result was not significant, we stopped the analysis. If it was significant, we performed the three 2×2 tests. Only the significant 2×2 tests are mentioned in the table.

[b]Over the proximal jejunum.

Continuous variables are expressed as median [min–max].

or unchanged would have spared 17 upper enteroscopies in our patients.

DISCUSSION

This study of the CE studies of 38 well-characterized CD patients confirms the ability of CE to diagnose villous atrophy and the association of extensive intestinal lesions with RCDII. Furthermore, it shows a correlation between extensive mucosal lesions on CE and hypoalbuminemia.

Noninvasive investigations are useful in CD patients, particularly in patients nonresponsive to a gluten-free diet who have been weakened by malnutrition (9). Our data confirm the superior accuracy of CE in predicting villous atrophy, compared with optical endoscopy (4). The higher magnification of CE pictures has indeed been offered to explain the better agreement of CE with histology. Furthermore, besides the diagnosis of persisting villous atrophy, CE allows for the visualization of intestinal ulcers and strictures, which may suggest RCDII before diagnostic confirmation (by performing enteroscopy with biopsies, immunohistochemistry, IEL flow cytometry analysis, and an analysis of TCRγ rearrangements). The risk of retention clearly remains a limitation of CE, particularly in RCDII patients. It requires preliminary radiological imaging of the small bowel in order to rule out stricturing disease. Four patients with intestinal strictures on radiological imaging underwent CE by mistake; fortunately, none of these patients presented capsule retention. Nevertheless, intestinal strictures may have accounted for the significantly longer duration of small bowel CE examinations in RCDII patients; such a finding on CT scan or MR enterography should contraindicate CE and directly lead to upper enteroscopy in these patients. This finding of the relatively slow progression of CE in the pathological gut has been mentioned in previous publications involving patients with complicated CD (7,17). A delayed progression of CE probably explains why only half of the RCD patients completed the examination, in contrast to 100% in the symptomatic CD group and 87 % in the control group.

Extensive lesions, involving the distal jejunum and ileum, were more frequently observed by CE in the RCDII patients (54%) than in the RCDI patients (9%) ($P<0.02$) and symptomatic CD patients (30%) (N.S.). These results confirm the previously reported association between extensive intestinal mucosal damage and RCDII by Rubio-Tapia *et al.* (18). At the same time, a strong correlation was found between extensive intestinal lesions and low serum albumin levels ($P=0.003$). Indeed, it has long been debated whether the severity of intestinal damage could predict the clinical presentation

Table 4. Findings in video capsule endoscopy

	Symptomatic CD (*n*=10)	RCDI (*n*=11)	RCDII (*n*=26)	*P* value[a]
Grade of VA				
Absent	1 (10%)	3 (27%)	5 (19%)	GLOBAL: *P*=0.35
Moderate	4 (40%)	5 (46%)	7 (27%)	
Severe	5 (50%)	3 (27%)	14 (54%)	
Ulcerations				
Size>1 cm	0	1 (9%)	6 (23%)	GLOBAL: *P*=0.31
0< *n*≤5	1 (10%)	2 (18%)	5 (19%)	GLOBAL: *P*=0.88
n>5	0	0	11 (42%)	GLOBAL: *P*=0.003
Distal localization	1 (10%)	2 (18%)	12 (54%)	GLOBAL: *P*=0.06 RCDII vs. CD/RCDI: *P*<0.002
Intestinal strictures				
Prevalence	0	0	4 (15%)	GLOBAL: *P*=0.39
Distal localization[b]	—	—	2 (8%)	—
Extension of lesions				
Proximal[c]	6 (60%)	7 (64%)	9 (35%)	GLOBAL: *P*=0.20
Extensive[d]	3 (30%)	1 (9%)	14 (54%)	GLOBAL: *P*=0.02 RCDII vs. RCDI: *P*<0.02

CD, celiac disease; RCD, refractory celiac disease; RCDI, refractory celiac disease of type I; RCDII, refractory celiac disease of type II; VA, villous atrophy; *n*, number.
[a]We used the following strategy for each variable. First, we performed a global test (three groups). If the result was not significant, we stopped the analysis. If it was significant, we performed the three 2×2 tests. Only the significant 2×2 tests are mentioned in the Table.
[b]Involvement of distal jejunum and ileum.
[c]Proximal: limited jejunal enteropathy.
[d]Involvement of jejunum and ileum.

of CD (19). To date, no evidence of this correlation has been shown (20). In the particular case of CD assessment by CE, Murray *et al.* (4) did not show any relationship between the extent of disease and clinical malabsorption. We suggested that extensive lesions in CD induce malnutrition. Besides ulcerative jejunitis, which is responsible for protein-loss enteropathy (9), the higher prevalence of extensive intestinal involvement in RCDII patients may contribute to the more severe malnutrition observed in these patients.

These data also underscore the role of CE, which represents the sole investigation technique capable of visualizing the whole mucosa of the small bowel. Indeed, enteroscopy does not allow for complete examination of the small bowel surface, and radiological examinations do not precisely evaluate mucosal damage. In contrast, CE shows the extent of the lesions and guides the choice between standard upper endoscopy and enteroscopy, if necessary, to procure intestinal biopsy samples and make a final diagnosis. Outside the setting of CD, CE has already proven higher diagnostic yield than enteroscopy, especially in the diagnosis of inflammatory and vascular intestinal lesions (21). If CE and enteroscopy are required for the initial assessment of all nonresponsive CD patients, once a diagnosis of RCD is made, complete small bowel examination by CE alone may spare follow-up enteroscopy when no mucosal abnormalities are seen. Furthermore, CE is useful for assessing treatment response in refractory CD, by recording changes in the extent or the severity of mucosal lesions; the absence of modifications may lead to intensify therapy without repeating enteroscopy. Our data suggest that CE may also complement radiological imaging in the initial assessment of the extent of intestinal lesions and in the screening for complications of RCD, especially ulcerative jejunitis and EATL, during follow-up (9). However, we still believe that the regular radiological imaging of the small bowel is of major importance during refractory CD to rule out intestinal stricture, especially before each CE examination.

The control group of 47 CE performed in nonceliac patients, mainly to investigate obscure gastrointestinal bleeding, allowed us to assess the significance of the CE findings among CD patients. Indeed, a small number of ulcers (*n*≤5) did not seem to be specific of any kind of CD and may be found as frequently in CE performed for other indications. But numerous or distal intestinal ulcers were significantly more frequent in CD patients.

However, our study has some limitations: first, we performed a retrospective, single-center study; second, as a tertiary care center, the prevalence of RCDII patients or severe clinical presentations of RCD in our department is unusually high. This last point may account for the higher proportion of RCDII patients (47%) in our study, as compared to others (18).

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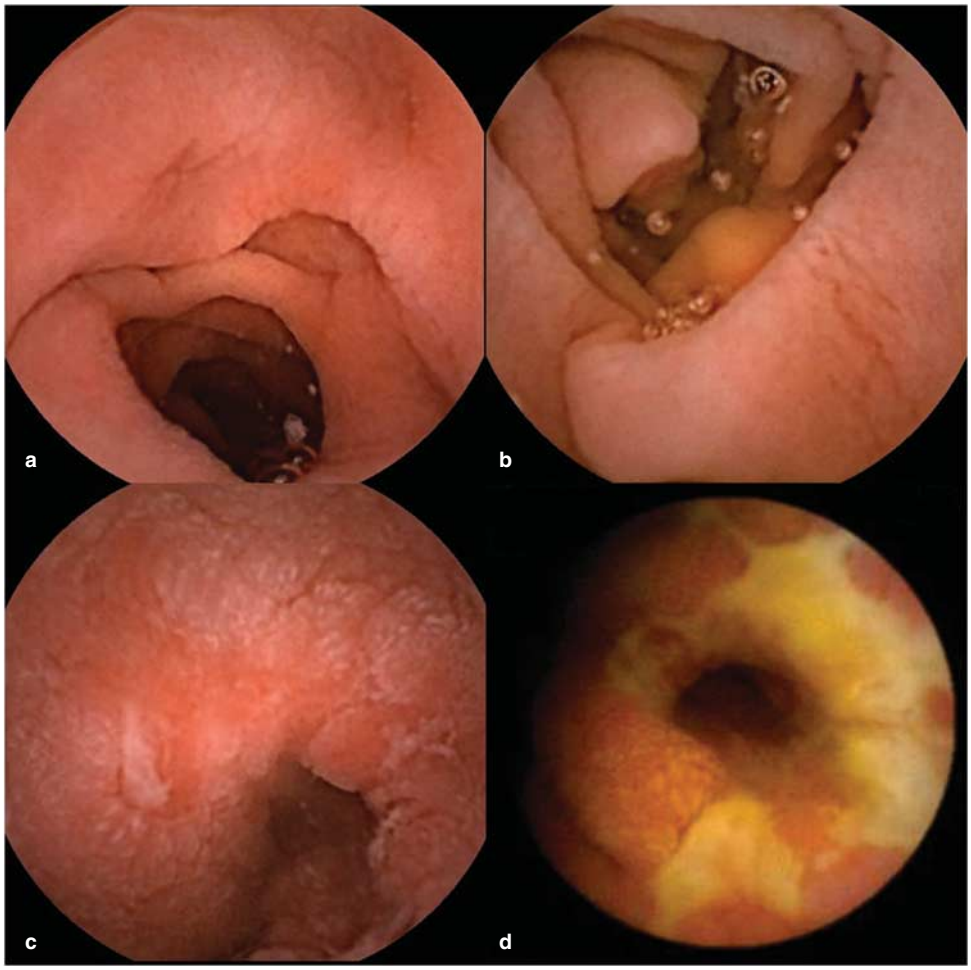

Figure 1. Capsule endoscopy view of study patients: severe villous atrophy in symptomatic celiac disease (**a**) and in type I refractory celiac disease (**b**); mucosal ulceration and severe villous atrophy (**c**) in type II refractory celiac disease; circumferential ulceration on an intestinal stricture in type II refractory celiac disease (**d**).

Table 5. ANOVA of the extent of CE mucosal damage and clinical parameters

Extent of CE mucosal damage[a]	1 (*n*=7)	2 (*n*=20)	3 (*n*=17)	F(2, 41)	*P* value
BMI (kg/m^2)	23.9±4.0	20.8±5.4	21.3±4.3	1.09	0.34
Serum albumin (g/l)	37.6±4.0	37.2±7.6	29.2±7.6	6.7	0.003
Hemoglobin (g/dl)	13.1±1.2	12.7±1.3	12.4±1.8	0.61	0.54

ANOVA, analysis of variance; BMI, body mass index; CE, capsule endoscopy.
[a]1: Enteropathy limited to the duodenum; 2: jejunal enteropathy; 3: extensive enteropathy.

Taken together, our data show how intestinal mucosal lesion assessment by CE in nonresponsive CD (i) can predict the type of RCD, (ii) is associated with the patient's nutritional status, and (iii) is useful to detect EATL. These characteristics position CE among the first-line investigations for the characterization and follow-up of nonresponsive CD.

CONFLICT OF INTEREST

Guarantor of the article: Christophe Cellier, MD, PhD.
Specific author contributions: Collected the data, conducted the study, and drafted the manuscript: Maximilien Barret and Georgia Malamut; performed the endoscopic examinations: Gabriel Rahmi, Elia Samaha, and Joël Edery; analyzed the histological samples:

Virginie Verkarre; performed multiplex polymerase chain reaction: Elizabeth Macintyre; performed the statistical analyses: Emilie Lenain and Gilles Chatellier; performed lymphocyte phenotyping: Nadine Cerf-Bensussan; planned and conducted the study: Christophe Cellier. All authors reviewed the manuscript and approved the final draft submitted.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Capsule endoscopy may provide complete evaluation of the intestinal mucosa.
- ✓ Capsule endoscopy is able to diagnose villous atrophy in celiac disease and complications such as ulcerative jejunitis and features of enteropathy-associated T-cell lymphoma.
- ✓ The correlations between the severity of mucosal intestinal damage and the clinical features of celiac disease remain controversial.

WHAT IS NEW HERE

- ✓ Capsule endoscopy has a high diagnostic yield in refractory celiac disease.
- ✓ Capsule endoscopy correlates more accurately with histology than does endoscopy in the diagnosis of villous atrophy.
- ✓ The extent of intestinal lesions observed by capsule endoscopy is associated with the nutritional status in celiac disease and may predict the type of refractory celiac disease.

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