Thieme

Additional information obtained from mucosal biopsies is limited after pan-enteric capsule endoscopy in patients with suspected Crohn's disease

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ABSTRACT

Background and study aims Pan-enteric capsule endoscopy (CE) is an emerging alternative to ileo-colonoscopy for diagnosing Crohn's disease (CD). However, CE does not offer the opportunity to take biopsies to support the diagnosis. This study examined the additional information obtained with mucosal biopsies and the feasibility of CE as a single diagnostic procedure.

Patients and methods This retrospective study was based on a prospective, blind multicenter trial in which patients with suspected CD were examined with ileo-colonoscopy plus segmental biopsies and CE. Histopathological findings were compared to the result of CE.

Results A total of 107 patients with a complete CE were included in the analysis. CE was consistent with CD in 44 patients (41.1%) and ulcerative colitis in 10 patients (9.3%). Histopathology confirmed the result of CE in 39.3% of patients and added new diagnostic information in 6.5% of patients. A CE consistent with CD was histologically confirmed in 20.5% of patients. Biopsies most often showed non-specific inflammation (61.4%). Only one patient with a normal CE had a specific histological diagnosis (microscopic colitis). Biopsies altered the diagnosis of ulcerative colitis to CD in two patients, and in two patients with a normal CE, biopsies showed CD or ulcerative colitis. In one patient with lymphoma in the terminal ileum and cecum, CE was misinterpreted as CD.

Conclusions In patients with suspected CD and an evident result of CE, the additional information obtained from biopsies is limited, and CE as a single diagnostic procedure might be feasible in selected patients. Biopsies are warranted, however, in patients with an atypical endoscopic appearance or suspected malignancy.

Introduction

Crohn's disease (CD) is a syndrome diagnosis based on a combination of clinical, biochemical, stool, endoscopic, cross-sectional imaging, and histopathological investigations [1]. No single modality or finding is exclusively diagnostic. In patients with a clinical suspicion of CD, ileocolonoscopy (IC) with segmental biopsies is the preferred modality for the initial diagnosis [1, 2].

Cardinal endoscopic lesions are mucosal ulcerations ranging from small aphthous ulcerations to large ulcers and fissures. However, the examination is invasive, associated with patient discomfort and a small risk of colonic perforation (< 1 per 1,000 colonoscopies), and conscious sedation is often required [3, 4].

A universally accepted criterion for the diagnosis of CD with histopathology does not exist [1]. For an optimal assessment, biopsy samples should be accompanied by the patient's demographic data, clinical history, symptoms, comorbidities, microbiological and serological data, and endoscopic findings [5, 6]. The histological evaluation considers multiple findings, e. g. crypt architecture, ulcerations, the density and distribution of inflammatory cells in the lamina propria, cryptitis, crypt abscesses and granulomas [5]. Non-necrotizing epithelioid granulomas are a hallmark of CD, but they are only seen in a minority of biopsy specimens [7, 8].

Since its US Food and Drug Administration approval in 2001, capsule endoscopy (CE) has revolutionized gastrointestinal imaging. CE is highly sensitive, patient-friendly, and less invasive. Compared to cross-sectional imaging, CE allows a direct and detailed evaluation of the gastrointestinal mucosa with detection of the earliest lesions of CD [1]. Pan-enteric CE is now available, allowing a detailed evaluation of the entire gastrointestinal tract in one procedure, and there is an increasing amount of evidence to support the utility of CE for the diagnosis and follow-up of CD [9, 10, 11, 12]. In a recent work by our group, pan-enteric CE had a high sensitivity and specificity for the detection of lesions consistent with CD [9]. The patient-experienced discomfort is significantly less with CE compared to IC, and pan-enteric CE could be a patient–friendly alternative to IC in selected patients with suspected CD. However, pan-enteric CE does not offer the opportunity to take biopsies. If biopsies are mandatory to confirm CD or for differential diagnosis, a minimally invasive diagnostic strategy will not be feasible.

The aim of this study was to examine the additional information obtained with mucosal biopsies and the feasibility of pan-enteric CE as a single diagnostic procedure in a group of patients undergoing their first diagnostic work-up for CD.

Patients and methods

This retrospective cohort study is based on data from a prospective blinded multicenter trial by Brodersen et al. [9]. Patients with suspected CD were recruited from three centers in the Region of Southern Denmark managing adult patients with inflammatory bowel diseases. All patients were prospectively enrolled in a clinical trial examining non-invasive modalities for diagnosing suspected CD.

CD was clinically suspected in patients with diarrhea and/or abdominal pain for more than one month (or repeated episodes of diarrhea and/or abdominal pain) associated with a fecal calprotectin above 50 mg/kg and at least one additional finding suggesting CD: elevated inflammatory markers, anemia, fever, weight loss, perianal abscess or fistula, a family history of inflammatory bowel disease, or suspicion of CD after sigmoidoscopy. Use of nonsteroidal anti-inflammatory drugs (NSAIDS) was an exclusion criterion. All patients had a standardized work-up including medical history, physical examination, blood and stool samples, bowel ultrasound, magnetic resonance imaging (MRI) enterocolonography, pan-enteric CE and IC within 2 weeks (in that order). Patients with a high-grade stenosis detected with MRI were excluded from CE, and CE was performed before IC to avoid misinterpretation from biopsies. Endoscopies and imaging procedures were interpreted by specialists blinded to the results of the other imaging modalities, and findings were reported in a standardized fashion. None of the patients received medical treatment between examinations.

Capsule endoscopy

CE was performed with the PillCam Colon–2 capsule (n = 43), and once commercially available, the PillCam Crohn's capsule (n = 90) (Medtronic, Dublin, Ireland) after overnight fasting and bowel preparation with 2 + 2 L of Polyethylene glycol plus ascorbate (Moviprep, Norgine, Amsterdam, Netherlands) and Sodium Phosphate booster as previously described by European Society of Gastrointestinal Endoscopy [13]. Images were reviewed with PillCam software v9. CE was not performed in all patients; the reasons are described elsewhere [9]. Only patients with a complete CE were included in this analysis to ensure an endoscopic assessment of all bowel segments from which biopsies were obtained. A capsule expelled from the rectum within the recording period defined a complete procedure. Examinations were interpreted by four gastroenterologists with expertise in chronic inflammatory bowel diseases and CE. All observers were trained in pan-enteric CE before the study was conducted.

Colon cleansing

The colon cleansing was graded on a 4-point scale: Poor: Large amount of fecal residue precludes a complete examination. Fair: Enough feces or turbid fluid to prevent a reliable examination. Good: Small amount of feces or turbid fluid not interfering with examination. Excellent: No more than small bits of adherent feces.

Diagnostic criteria and endoscopic classification

The same diagnostic criterion was used with IC and CE. Immediately after CE, the gastroenterologist made a diagnosis without knowing the result of histopathology. CD was diagnosed by the presence of more than three aphthous ulcerations, irregular ulcers/fissures, or luminal narrowing caused by fibrosis or inflammation. A diagnosis of ulcerative colitis (UC) was based on European Crohn's and Colitis Organisation recommendations, and endoscopic lesions were not explicitly defined in this study [1]. Inflammatory lesions restricted to the colon consistent with inflammatory bowel disease (IBD) but not diagnostic for CD or UC were categorized as IBD unclassified (IBD-U). Erythema and edema not diagnostic for IBD or any other gastrointestinal disorder was classified as non-specific inflammation.

Histopathology

IC was performed according to standard clinical practice, and segmental biopsies were obtained from the terminal ileum, colon and rectum following current recommendations [5]. The medical history and IC findings accompanied biopsy samples. After fixation in formalin and embedment in paraffin, biopsies were cut into three pieces, stained with hematoxylin and eosin and examined under a standard light microscope. The subsequent pathology report contained a detailed description of histological findings and a conclusion following common clinical practice.

A critical review of pathology reports was performed retrospectively by first author S.H.T. The following data were recorded: The number and location of mucosal biopsies, histopathological findings and the pathologist's conclusion. Histopathological findings included: 1) architecture and surface: ulceration, crypt irregularity, atrophy and mucin depletion; 2) chronic inflammation: plasmacytosis and lymphocytosis, basal plasmacytosis, eosinophilia, and granuloma; and 3) acute inflammation: neutrophilia, cryptitis, and crypt abscess. Histological findings and their locations were recorded including whether lesions were segmental or continuously distributed.

The pathologist's diagnosis was categorized into normal mucosa, CD, UC, IBD-U, or other pathology including neoplasia. Inflammatory changes which could not be classified as CD, UC, IBD-U or any other gastrointestinal disorder were categorized as non-specific inflammation.

Statistics

Demographic data, endoscopy results, and histopathology were analyzed using descriptive statistics. No tests for statistical significance were performed in this retrospective study.

Ethics

The study was approved by the Local Ethics Committee of Southern Denmark (S-20150189) and the Danish Data Protection Agency (journal number 16/10457) and conducted in accordance with the principles of the Helsinki Declaration [9]. All patients gave informed consent before participation.

Results

A total of 153 patients were enrolled in the study of non-invasive modalities for diagnosing suspected CD. A complete CE and mucosal biopsies were available in 107 patients, and these patients entered the present analysis. Patient characteristics are shown in ▶ **Table 1**. The bowel preparation quality with CE was rated excellent, good, fair, and poor in 44 (41.1%), 41 (38.3%), 22 (20.6%), and 0 (0%) patients, respectively.

▶ **Table 1** Characteristics of 107 patients with suspected Crohn's disease examined with pan-enteric capsule endoscopy.

Patient characteristics			
Gender (n)	Male	31	(29%)
	Female	76	(71%)
Age (years)	Median	28	
	Range	17–72	
Genetic predisposition for IBD (n)	No	71	(66%)
	Yes	36	(34%)
BMI (kg/m^2)	Median	25.2	
	Range	18.9–57.2	
Smoking status (n)	Never	61	(57%)
	Former	18	(17%)
	Current	28	(26%)
Duration of symptoms (months)	Median	6	
	Range	1–48	
Symptoms (n)	Abdominal pain	104	(97%)
	Chronic diarrhea	52	(49%)
	Weight loss > 3 kg	38	(36%)
	Fever	10	(9%)
	Blood in stool	21	(20%)
C-reactive protein (mg/L)	Median	11	
	Range	0.6–122	
Fecal calprotectin (mg/g)	Median	428	
	Range	51–6000	
No. of bowel movements	Median	4	
	Range	every 3rd day-17	
Non-steroidal anti-inflammatory drug use (n)		0	(0%)

CE was consistent with CD in 44 patients (41.1%): small bowel 18, colon seven, small bowel and colon 19. In 47 patients with a normal CE, a subsequent IBD diagnosis was made in three patients after a median follow-up of 4.8 years (range 2.6–6.8). Two patients were diagnosed with mild CD in the small bowel 1 and 2 years after the initial diagnostic work-up, and one patient was diagnosed with ulcerative proctitis 3 years later.

Histopathological findings

In 44 patients with a CE consistent with CD, the most common histopathological finding was chronic inflammation in the lamina propria with plasma cells and lymphocytes (59.1%, ▶ **Table 2**). Architectural alterations were less common with crypt irregularity and ulcerations described in 38.6%. Approximately half of the patients had signs of acute inflammation (neutrophilia 47.7% and cryptitis 38.6%). Granulomas were present in 11 patients (25.0%).

A total of 47 patients had an endoscopically normal mucosa. However, mild inflammation was described in a number of patients: Plasmacytosis and lymphocytosis in 11 (23.4%), crypt irregularity in seven (14.9%), and cryptitis in eight (17.0%). None of the patients had granulomas. Only one patient with plasmacytosis and lymphocytosis and crypt irregularity was subse-

▶ **Table 2** Histopathological findings in 106 patients with a normal pan-enteric capsule endoscopy, non-specific endoscopic inflammation or endoscopic lesions consistent with Crohn's disease or ulcerative colitis.*

		Result of pan-enteric capsule endoscopy			
Histopathological findings		Normal (n = 47)	Crohn's disease (n = 44)†	Ulcerative colitis (n = 10)	Non-specific inflammation (n = 5)
Architecture and surface	Ulceration	2 (4.3%)	17 (38.6%)	1 (10.0%)	0 (0.0%)
	Crypt irregularity	7 (14.9%)	17 (38.6%)	5 (50.0%)	1 (20.0%)
	Atrophy	3 (6.4%)	6 (13.6%)	3 (30.0%)	0 (0.0%)
	Mucin depletion	4 (8.5%)	3 (6.8%)	2 (20.0%)	1 (20.0%)
Chronic inflammation	Plasmacytosis and lymphocytosis	11 (23.4%)	26 (59.1%)	9 (90.0%)	1 (20.0%)
	Basal plasmacytosis	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)
	Eosinophilia	7 (14.9%)	10 (22.7%)	3 (30.0%)	2 (40.0%)
	Granuloma	0 (0.0%)	11 (25.0%)	2 (20.0%)	1 (20.0%)
Acute inflammation	Neutrophilia	7 (14.9%)	21 (47.7%)	5 (50.0%)	2 (40.0%)
	Cryptitis	8 (17.0%)	17 (38.6%)	9 (90.0%)	1 (20.0%)
	Crypt abscess	3 (6.4%)	12 (27.3%)	7 (70.0%)	1 (20.0%)

*Data for one patient with a tumor in the rectum detected with capsule endoscopy are not shown. †In one patient, CE was interpreted as ileocecal Crohn's disease. Biopsies diagnosed a B-cell lymphoma.

quently diagnosed with IBD (ulcerative proctitis three years later).

Acute and chronic inflammation was the most frequent histological finding in 10 patients with endoscopic lesions consistent with UC: Cryptitis in nine (90.0%), crypt abscesses in seven (70.0%), and plasmacytosis and lymphocytosis in nine (90.0%). Crypt irregularity was detected in five patients (50.0%).

In two of 10 patients (20.0%) with endoscopic lesions consistent with UC, the histopathological assessment revealed granulomas suggesting a diagnosis of CD. Granulomas were detected in one additional patient with non-specific endoscopic inflammation. Biopsies showed inflammatory changes including eosinophilia, neutrophilia, cryptitis and micro-granulomas. A toxic etiology or infection were alternative causes, and a diagnosis of CD was not clear-cut. However, a firm diagnosis of colonic CD was made during follow-up including a repeat IC with biopsies.

Consensus between pan-enteric capsule endoscopy and histopathology

The histopathological assessment and CE reached the same conclusion in 42 patients (39.3%) (▶ **Table 3**). CE was consistent with CD in 44 patients, which was histologically confirmed in nine (20.5%). Biopsies showed non-specific inflammation in 27 patients (61.4%) and a normal result in six (13.6%).

In 47 patients with a normal CE, this was confirmed histologically in 24 (51.1%). Twenty patients (42.6%) had non-specific inflammation. A total of three patients (6.4%) had an unambiguous histological diagnosis: One patient was diagnosed with microscopic colitis. In two patients, histology was consistent with CD or UC. These patients also had macroscopic lesions located in the colon confirmed by IC. CE was classified false negative.

CE was consistent with UC in 10 patients, which was histologically confirmed in five (50.0%). In two patients (20.0%), histopathology suggested a diagnosis of CD.

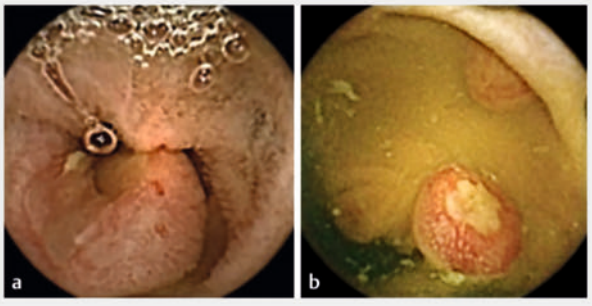
Neoplasia was detected with CE in one patient with a juvenile polyp in the rectum. In one patient, CE was interpreted as ileocecal CD. However, biopsies diagnosed a B-cell lymphoma. In retrospect, the macroscopic appearance was not typical for CD, and lesions should warrant additional diagnostic work-up including histopathology (▶ **Fig. 1**).

In total, histopathology contributed to significant diagnostic information in seven (6.5%) of 107 patients with clinically suspected CD and a complete pan-enteric CE.

▶ **Table 3** Histopathological diagnosis compared to the result of pan-enteric capsule endoscopy in 107 patients with clinically suspected Crohn's disease and a complete capsule endoscopy.

	Result of pan-enteric capsule endoscopy				
Histopathological diagnosis	Normal (n = 47)	Crohn's disease (n = 44)	Ulcerative colitis (n = 10)	Non-specific inflammation (n = 5)	Neoplasia (n = 1)
Normal	24 (51.1%)	6 (13.6%)	0 (0.0%)	1 (20.0%)	0 (0.0%)
Crohn's disease	1 (2.1%)	9 (20.5%)	2 (20.0%)	0 (0.0%)	0 (0.0%)
Ulcerative colitis	1 (2.1%)	0 (0.0%)	5 (50.0%)	0 (0.0%)	0 (0.0%)
Non-specific inflammation	20 (42.6%)	27 (61.4%)	3 (30.0%)	3 (60.0%)	0 (0.0%)
Neoplasia	0 (0.0%)	1* (2.3%)	0 (0.0%)	0 (0.0%)	1† (100.0%)
Other pathology	1‡ (2.1%)	1§ (2.3%)	0 (0.0%)	1¶ (20.0%)	0 (0.0%)

*CE was interpreted as Crohn's disease in the terminal ileum. Biopsies diagnosed a lymphoma.
†Juvenile polyp located in the rectum.
‡Microscopic colitis.
§Histopathology concluded inflammatory bowel disease unclassified.
¶Biopsies suggested post-infectious inflammation.



▶ **Fig. 1** A B-cell lymphoma in the terminal ileum and cecum misinterpreted as Crohn's disease with pan-enteric capsule endoscopy. In retrospect, an ulcerated tumor in the **a** terminal ileum and **b** adjacent ulcerated polyps is not consistent with Crohn's disease.

Clinical presentation in patients with a significant histological finding

Microscopic colitis

A 32-year-old woman presented with non-bloody diarrhea and lower abdominal pain for five weeks. Fecal calprotectin was significantly elevated (> 6000 mg/kg) with a CRP 13 mg/L. Stool samples for pathogenic bacteria were negative. IC and CE were macroscopically normal, but biopsies showed lymphocytic colitis. Symptoms resolved spontaneously.

Crohn's disease

A 20-year-old woman was referred with non-bloody diarrhea for 8 weeks, a fecal calprotectin 307 mg/kg, and CRP 21 mg/L. IC showed a mild terminal ileitis, and biopsies from the cecum were highly suggestive of CD although granulomas were not present. CE was false negative. The bowel preparation quality was rated fair.

A 36-year-old man was referred with non-bloody diarrhea and a 3 kg weight loss. Fecal calprotectin was 827 mg/kg and CRP 11 mg/L. Stool samples for pathogenic bacteria were negative. IC and CE were suggestive of an extensive UC (diffuse superficial inflammation), but biopsies revealed granulomas suggesting a diagnosis of CD.

A 25-year-old man was referred with non-bloody diarrhea and abdominal pain for six months. Laboratory tests showed a fecal calprotectin 1075 mg/kg, CRP 7 mg/L and iron deficiency anemia. Stool samples for pathogenic bacteria were negative. IC showed a left sided UC, and CE was suggestive of extensive UC. Biopsies revealed granulomas in all colonic segments consistent with a diagnosis of CD.

Ulcerative colitis

A 30-year-old woman with a familial disposition to IBD presented with recurrent episodes of diarrhea. Blood tests were normal, but fecal calprotectin was elevated (775 mg/kg). Although the patient reported intermittent rectal bleeding, a diagnosis of CD was suspected. IC and biopsies were consistent with ulcerative proctitis. CE was false negative. The bowel preparation quality was rated good.

Polyp

A 21-year-old woman was referred with abdominal pain, altered bowel habits and intermittent rectal bleeding. Fecal calprotectin 428 mg/kg and CRP 11 mg/L. IC and CE showed a polyp in the rectum. Histopathology revealed a juvenile polyp.

Lymphoma

A 68-year-old woman was referred to colonoscopy because of a positive fecal occult blood test. The patient experienced mild abdominal pain but not diarrhea or rectal bleeding. A colonoscopy in the Surgical Department revealed edema, ulcerations and multiple polypous lesions in the cecum. Pathology showed chronic inflammation, and the patient was referred to the Gastroenterology Department with a clinical suspicion of CD. Laboratory tests showed a fecal calprotectin 610 mg/kg and CRP 14 mg/L. A repeat IC showed polypous lesions in the cecum and terminal ileum. Biopsies revealed a B-cell lymphoma. CE was misinterpreted as CD.

Discussion

The present study aimed to evaluate the additional information obtained with mucosal biopsies in patients with a high clinical suspicion of CD and to examine the feasibility of minimally invasive diagnosis with CE. Histological findings varied considerably with a significant overlap between CD and UC, although few patients were diagnosed with the latter. Important information obtained from mucosal biopsies compared to CE alone was restricted to a minority of patients. The benefit of histopathology was limited in patients with a firm endoscopic diagnosis of CD or normal mucosa. On the contrary, in patients with an atypical endoscopic presentation, suspicion of neoplasia or other types of IBD, biopsies contributed significantly to the final diagnosis.

Although CD is a syndrome diagnosis based on multiple findings, current guidelines recommend IC with segmental biopsies for the initial diagnosis [1, 6, 14]. Mucosal biopsies can show signs of microscopic inflammation suggesting CD or help distinguish CD from UC or other types of segmental colitis, e. g. segmental colitis associated with diverticulosis or ischemic colitis [15, 16, 17, 18, 19]. Furthermore, a preserved crypt architecture and predominance of acute inflammation can suggest infectious colitis over IBD. In a prospective analysis of 152 consecutive patients with suspected or established colitis who underwent colonoscopy, segmental biopsies changed the diagnosis in 26% [20]. Hence, mucosal biopsies are considered pivotal for the differential diagnosis of various types of colitis.

The focus of this study was not differentiating distinct types of enterocolitis. Instead, we included a group of patients with a high suspicion of CD based on symptoms for more than 1 month, clinical findings, familial disposition, biochemistry and an elevated fecal calprotectin. Most patients were young with a median age of 28 years, and use of NSAIDs was an exclusion criterion. The diagnostic work-up before endoscopy included stool samples for pathogenic bacteria (plus parasites if clinically suspected) and serology for celiac disease. Hence, the probability of differential diagnoses such as infection, malignancy, ischemia, or diverticulosis was expected to be low. Intestinal tuberculosis is rare in Denmark; especially among ethnic Danes [21]. On the contrary, irritable bowel syndrome is a very common differential diagnosis in a young population, and the primary task was to exclude or diagnose early CD.

In patients with an established diagnosis of IBD, histological remission has been associated with a better clinical outcome than endoscopic remission alone, and multiple scoring systems exist for assessing the histological disease activity [22, 23]. However, histopathological scores are not routinely used in clinical practice, and they are not applicable in the diagnostic setting. A universally accepted criterion for the initial diagnosis of CD does not exist, and there are no data available on how many features must be present in an endoscopically derived biopsy before a diagnosis can be made [1]. The diagnosis relies on a combined assessment of multiple findings, e. g. disturbed crypt architecture, ulcerations, acute and chronic inflammation in the lamina propria and the presence of granulomas [5]. The most distinct feature of CD is the presence of granulomas, although they are not an obligate finding [8]. In a registry study including mucosal biopsies from 10,456 patients with CD, granulomas were found in 9% [7]. Despite being a hallmark of CD, the absence of granulomas does not exclude this diagnosis. For surgical specimens, it has been suggested that CD is diagnosed when three features are present in the absence of granulomas, or when granulomas are present with one extra feature. Most experts agree that the same definition could be applied to endoscopic biopsies, i. e. granulomas plus crypt irregularity and/or chronic inflammation is suggestive of CD [6, 24]. The distribution of inflammatory lesions also supports a specific diagnosis – segmental inflammation in CD versus continuous inflammation in UC.

CE is highly sensitive for mucosal ulcerations seen in CD, and small bowel CE is currently recommended in patients with suspected CD and a negative IC as the initial diagnostic modality for investigating the small bowel [1, 2]. Hence, CE is already considered a diagnostic procedure for the small bowel without biopsies. Recent studies have examined pan-enteric CE as an alternative to IC and found it feasible in patients with suspected or known CD [9, 10, 11, 12]. Although the role of pan-enteric CE in CD is not yet established, it could replace IC for diagnosing CD in selected patients without obstructive symptoms. A diagnostic algorithm with pan-enteric CE as a first-line examination in patients with clinically suspected CD was recently suggested [25]: A normal CE should prompt clinical follow-up but no additional diagnostic work-up. A CE consistent with CD should trigger an IC with biopsies. In the present study, however, histopathology contributed with significant new information in only 6.5% of patients with a complete pan-enteric CE. Most of these patients had an atypical endoscopic presentation that would require additional examinations. One (0.9%) patient with a normal CE had an unsuspected diagnosis of microscopic colitis, and an endoscopic diagnosis of CD was histologically confirmed in only 20% of patients. These data call into question the need for a routine IC with biopsies in patients with CD diagnosed with pan-enteric CE. Instead, patients with an atypical endoscopic appearance, suspicion of IBD other than CD including micro-

scopic colitis or suspected malignancy should be referred for an IC with biopsies.

A major concern with minimally invasive diagnosis is the risk of misinterpreting malignancy as a benign condition. In the present study including patients with a complete CE, there was one case of malignancy and one patient with a benign polyp. In one patient, a lymphoma in the terminal ileum and cecum was misinterpreted as CD. However, lesions were polypous and not typical for CD (▶ **Fig. 1**) and should prompt additional investigations. In one additional patient with a stricturing tumor in the colon, CE was not complete but the tumor was visualized [9]. This emphasizes the need for a meticulous assessment of lesions in the absence of biopsies, which also applies to small bowel CE with lesions located outside the reach of the colonoscope. Restricting pan-enteric CE to young patients with suspected CD (e. g. below 40 years of age) would minimize the prevalence of malignancy.

Strengths and limitations

This study was based on a prospective, blind, multicenter trial including an appropriate population with clinically suspected CD. Patients were carefully selected, and CE detected CD in 41%. Experienced gastroenterologists interpreted CEs in a blind fashion, and a diagnosis of CD was based on a predefined criterion without knowing the histopathology result.

There are several limitations to this study. First, the study was a retrospective analysis of pathology reports generated in a prospective diagnostic trial. Hence, biopsies were not systematically analyzed, and lesions may have been present but not reported. Second, although the pathologists were specialized in gastrointestinal pathology, they were appointed to three IBD centers in the Region of Southern Denmark, and there might have been heterogeneity between centers in terms of interpretation and diagnostic criteria. No predefined histopathological criterion for CD was included, and the inter-observer agreement was not accounted for in this study. Third, although the study population consisted of patients with suspected CD, 9% were diagnosed with UC, and histological findings in these patients may not represent UC in general. Fourth, pathologists were not blinded to the clinical history or findings at IC, which could have biased the histopathological conclusion. However, we intended to examine the benefit of mucosal biopsies in a clinical setting by applying the recommended procedure for histopathological diagnosis. Even with these optimal conditions, the value of mucosal biopsies was limited compared to endoscopy alone. Fifth, biopsy protocols were not standardized, i. e. whether biopsies were taken from ulcerations or the surrounding mucosa. This could lead to sampling bias and a normal result of biopsies in patients with mild CD.

Conclusions

The benefit of mucosal biopsies is limited in patients with a high clinical suspicion of CD and an evident result of CE. Hence, CE as a single diagnostic procedure might be feasible in selected patients with suspected CD and no obstructive symptoms. A routine IC with biopsies to confirm a positive or negative result of CE adds no significant information in the majority of patients. However, IC with biopsies is warranted in patients with an atypical endoscopic appearance, suspected malignancy or an incomplete CE. Prospective studies confirming these results are warranted.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Clinical trial

Trial registry: ClinicalTrials.gov (http://www.clinicaltrials.gov/)
Registration number (trial ID): NCT03134586
Type of Study: Prospective, multicenter study

References

[1] Maaser C, Sturm A, Vavricka SR et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. J Crohn Colitis 2019; 13: 144–164 doi:10.1093/ecco-jcc/jjy113

[2] Pennazio M, Rondonotti E, Despott EJ et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2022. Endoscopy 2023; 55: 58–95 doi:10.1055/a-1973-3796

[3] ASGE Standards of Practice Committee. Early DS, Lightdale JR et al. Guidelines for sedation and anesthesia in GI endoscopy. Gastrointest Endosc 2018; 87: 327–337

[4] Kothari ST, Huang RJ, Shaukat A et al. ASGE review of adverse events in colonoscopy. Gastrointest Endosc 2019; 90: 863–876 e833 doi:10.1016/j.gie.2019.07.033

[5] Magro F, Sabino J, Rosini F et al. ECCO Position on Harmonisation of Crohn's Disease Mucosal Histopathology. J Crohn Colitis 2022; 16: 876–883 doi:10.1093/ecco-jcc/jjac006

[6] Magro F, Langner C, Driessen A et al. European consensus on the histopathology of inflammatory bowel disease. J Crohn Colitis 2013; 7: 827–851 doi:10.1016/j.crohns.2013.06.001

[7] Turner K, Genta RM, Lujan G et al. Significance of the epithelioid granuloma in biopsies of Crohn's colitis. Inflam Bowel Dis 2014; 20: 2271–2275 doi:10.1097/MIB.0000000000000196

[8] Hong SW, Yoon H, Shin CM et al. Clinical significance of granulomas in Crohn's disease: A systematic review and meta-analysis. J Gastroenterol Hepatol 2020; 35: 364–373 doi:10.1111/jgh.14849

[9] Brodersen JB, Knudsen T, Kjeldsen J et al. Diagnostic accuracy of panenteric capsule endoscopy and magnetic resonance enterocolono-

graphy in suspected Crohn's disease United Euro Gastroenterol J 2022; 10: 973–982 doi:10.1002/ueg2.12307

[10] D'Haens G, Lowenberg M, Samaan MA et al. Safety and feasibility of using the second-generation pillcam colon capsule to assess active colonic Crohn's disease. Clin Gastroenterol Hepatol 2015; 13: 1480–1486 e1483 doi:10.1016/j.cgh.2015.01.031

[11] Leighton JA, Helper DJ, Gralnek IM et al. Comparing diagnostic yield of a novel pan-enteric video capsule endoscope with ileocolonoscopy in patients with active Crohn's disease: a feasibility study. Gastrointest Endosc 2017; 85: 196–205 e191

[12] Bruining DH, Oliva S, Fleisher MR et al. Panenteric capsule endoscopy versus ileocolonoscopy plus magnetic resonance enterography in Crohn's disease: a multicentre, prospective study. BMJ Open Gastroenterol 2020; 7: e000365 doi:10.1136/bmjgast-2019-000365

[13] Spada C, Hassan C, Galmiche JP et al. Colon capsule endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2012; 44: 527–536 doi:10.1055/s-0031-1291717

[14] Pouw RE, Bisschops R, Gecse KB et al. Endoscopic tissue sampling - Part 2: Lower gastrointestinal tract. European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2021; 53: 1261–1273 doi:10.1055/a-1671-6336

[15] Lamps LW, Knapple WL. Diverticular disease-associated segmental colitis. Clin Gastroenterol Hepatol 2007; 5: 27–31 doi:10.1016/j.cgh.2006.10.024

[16] Brandt LJ, Boley SJ. AGA technical review on intestinal ischemia. American Gastrointestinal Association. Gastroenterology 2000; 118: 954–968 doi:10.1016/s0016-5085(00)70183-1

[17] FitzGerald JF, Hernandez Iii LO. Ischemic colitis. Clin Colon Rectal Surg 2015; 28: 93–98 doi:10.1055/s-0035-1549099

[18] Tanaka M, Riddell RH, Saito H et al. Morphologic criteria applicable to biopsy specimens for effective distinction of inflammatory bowel disease from other forms of colitis and of Crohn's disease from ulcerative colitis. Scand J Gastroenterol 1999; 34: 55–67

[19] Tanaka M, Saito H, Fukuda S et al. Simple mucosal biopsy criteria differentiating among Crohn disease, ulcerative colitis, and other forms of colitis: measurement of validity. Scand J Gastroenterol 2000; 35: 281–286

[20] Dejaco C, Oesterreicher C, Angelberger S et al. Diagnosing colitis: a prospective study on essential parameters for reaching a diagnosis. Endoscopy 2003; 35: 1004–1008 doi:10.1055/s-2003-44593

[21] Holden IK, Lillebaek T, Andersen PH et al. Extrapulmonary tuberculosis in denmark from 2009 to 2014; characteristics and predictors for treatment outcome. Open Forum Infect Dis 2019; 6: ofz388

[22] Neri B, Mossa M, Scucchi L et al. Histological scores in inflammatory bowel disease. J Dig Dis 2021; 22: 9–22 doi:10.1111/1751-2980.12937

[23] Gupta A, Yu A, Peyrin-Biroulet L et al. Treat to target: the role of histologic healing in inflammatory bowel diseases: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2021; 19: 1800–1813 e1804 doi:10.1016/j.cgh.2020.09.046

[24] Langner C, Magro F, Driessen A et al. The histopathological approach to inflammatory bowel disease: a practice guide. Virchows Arch 2014; 464: 511–527 doi:10.1007/s00428-014-1543-4

[25] Ungar B, Eliakim R. Does pan-enteric capsule endoscopy obviate magnetic resonance entero-colonography in suspected Crohn's disease? United European Gastroenterol J 2022; 10: 917–918 doi:10.1002/ueg2.12315