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ORIGINAL ARTICLE

## Retrospective Study

# Essential role of small bowel capsule endoscopy in reclassification of colonic inflammatory bowel disease type unclassified

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## Abstract

### AIM

To evaluate the role of small bowel capsule endoscopy (SBCE) on the reclassification of colonic inflammatory bowel disease type unclassified (IBDU).

## METHODS

We performed a multicenter, retrospective study including patients with IBDU undergoing SBCE, between 2002 and 2014. SBCE studies were reviewed and the inflammatory activity was evaluated by determining the Lewis score (LS). Inflammatory activity was considered significant and consistent with Crohn's disease (CD) when the  $LS \geq 135$ . The definitive diagnosis during follow-up (minimum 12 mo following SBCE) was based on the combination of clinical, analytical, imaging, endoscopic and histological elements.

## RESULTS

Thirty-six patients were included, 21 females (58%) with mean age at diagnosis of  $33 \pm 13$  (15-64) years. The mean follow-up time after the SBCE was  $52 \pm 41$  (12-156) mo. The SBCE revealed findings consistent with significant inflammatory activity in the small bowel ( $LS \geq 135$ ) in 9 patients (25%); in all of them the diagnosis of CD was confirmed during follow-up. In 27 patients (75%), the SBCE revealed no significant inflammatory activity ( $LS < 135$ ); among these patients, the diagnosis of Ulcerative Colitis (UC) was established in 16 cases (59.3%), CD in 1 case (3.7%) and 10 patients (37%) maintained a diagnosis of IBDU during follow-up. A  $LS \geq 135$  at SBCE had a sensitivity = 90%, specificity = 100%, positive predictive value = 100% and negative predictive value = 94% for the diagnosis of CD.

## CONCLUSION

SBCE proved to be fundamental in the reclassification of patients with IBDU. Absence of significant inflammatory activity in the small intestine allowed exclusion of CD in 94% of cases.

**Key words:** Inflammatory bowel disease; Inflammatory bowel disease type unclassified; Capsule endoscopy; Crohn's disease; Lewis score; Reclassification

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**Core tip:** This is a retrospective study to evaluate the role of small bowel capsule endoscopy (SBCE) on the reclassification of colonic inflammatory bowel disease type unclassified (IBDU). The SBCE revealed findings consistent with significant inflammatory activity in the small bowel, Lewis score ( $LS \geq 135$ ), in 9 patients (25%); in all of them the diagnosis of Crohn's disease (CD) was confirmed during follow-up. In 27 patients (75%) without significant inflammatory activity ( $LS < 135$ ), the diagnosis of ulcerative colitis was established in 16 cases (59.3%), CD in 1 case (3.7%) and 10 patients (37%) maintained a diagnosis of IBDU during follow-up.

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## INTRODUCTION

The differential diagnosis of Crohn's disease (CD) and ulcerative colitis (UC) relies on a combination of clinical, analytical, imaging, endoscopic and histologic data<sup>[1,2]</sup>. In 5% of patients with inflammatory bowel disease limited to the colon is not possible to establish a definitive diagnosis into CD or UC<sup>[3]</sup>. In 1978, Price introduced the concept of indeterminate colitis to describe cases in which colonic resections had been undertaken for chronic inflammatory bowel disease but a definitive diagnosis of either of UC and CD was not possible<sup>[4]</sup>. In 2005, the Montreal Working Party proposed that the term "indeterminate colitis" should be reserved for patients in whom surgical specimen is available and the term "colonic IBD type unclassified" (IBDU) for patients with no surgical specimen available and for whom the endoscopy is inconclusive and histology reveals chronic inflammation with absence of definite diagnostic features of either CD or UC<sup>[5]</sup>. Actually, for most patients, IBDU represents a temporary diagnosis, as it has been estimated that 80% of them will be reclassified to either CD or UC within 8 years<sup>[6]</sup>.

The correct diagnosis of inflammatory bowel disease is extremely important to define prognosis, therapeutic orientation and surgical intervention<sup>[7,8]</sup>. Since Small Bowel Capsule Endoscopy (SBCE) enables a direct endoscopic visualization of throughout the small intestine with higher diagnostic yield compared to conventional endoscopy or imaging studies<sup>[9,10]</sup>, it may be expected to contribute for the reclassification of IBDU. We report a multicenter study that aimed to evaluate the role of SBCE to reclassify patients with IBDU.

## MATERIALS AND METHODS

We performed a multicenter study including consecutive patients undergoing SBCE between 2002 and 2014 for IBDU, ASCA negative/pANCA negative.

All patients had undergone an ileocolonoscopy prior to SBCE. Inclusion criteria were as follows: Patients with clinical features of chronic IBD, without previously known small bowel involvement, in whom endoscopic type and/or distribution of lesions did not allow a definite diagnosis of CD or UC, microscopy indicating active and patchy transmucosal chronic inflammation with minimal or moderate architectural distortion and absence of unequivocal diagnostic features for either CD or UC, after exclusion of infectious colitis<sup>[5]</sup>. Subjects were excluded from entering the study if they had nonsteroidal anti-inflammatory drugs intake within 4 wk prior to capsule endoscopy<sup>[11]</sup>, clinical or imaging evidence of bowel stenosis or occlusion, or a follow-up of less than 12 mo.

Patients underwent SBCE with PillCam® SB1/SB2/

**Table 1 Demographics and clinical characteristics of the inflammatory bowel disease type unclassified patients**

No. of patients, <i>n</i> (%)	36 (100)
Gender	
Female	21 (58.3)
Male	15 (41.7)
Age (yr) (mean ± SD) at diagnosis	33.2 ± 13.1 (15-64)
Age (yr) (mean ± SD) at SBCE	35.9 ± 13.3 (18-64)
Device (no. patients), <i>n</i> (%)	
PillCam® SB1	13 (36.1)
PillCam® SB2	16 (44.4)
PillCam® SB3	1 (2.8)
Mirocam®	5 (13.9)
Endocapsule®	1 (2.8)
Gastric transit time (min)	38.6 ± 44.7 (2-257)
Small bowel transit time (min)	290.4 ± 101.5 (52-480)
Incomplete SBCE	1 (2.8)
Capsule retention	0
Follow-up (mo) before SBCE	30.2 ± 29.9 (1-108)
Follow-up (mo) after SBCE	51.9 ± 40.5 (12-156)

IBDU: Inflammatory bowel disease type unclassified; SB: Small bowel; SBCE: Small bowel capsule endoscopy.

SB3 (Given® Imaging, Yoqneam, Israel), Endocapsule® (Olympus Medical Systems Corporation, Tokyo, Japan) or Mirocam® (Intromedic Co., Ltd., Seoul, South Korea) receiving a clear liquid diet the day before capsule ingestion and an overnight 12 h fast. No bowel purge was administered prior to capsule ingestion.

SBCE videos were reviewed by two experienced gastroenterologists in each center. In case of disagreement, the findings were reviewed by investigators until a consensus was reached. Inflammatory activity was objectively assessed by determining the Lewis score (LS)<sup>[12]</sup>. Inflammatory activity was considered significant and consistent with CD when the LS ≥ 135<sup>[13]</sup>.

The mean, SD, and range were calculated for continuous data. Categorical data analysis was conducted using the Fisher exact test. Data analysis was performed using SPSS version 20.0 (IBM, Armonk, New York, United States). Test characteristics were determined using a 2 × 2 table and calculating the sensitivity, specificity, positive predictive value and negative predictive value.

Statistical significance was considered when the *P* value was less than 0.05.

## RESULTS

A total of 36 consecutive patients with IBDU underwent SBCE procedures between October 2002 and August 2014, with a mean follow-up before the exam of 30 mo (1-108 mo).

The mean age of patients at the time of diagnosis of IBDU and at time of SBCE was 33 years and 36 years, respectively, with 58% being of female gender.

Table 1 summarizes the demographic and clinical characteristics of the study population. The capsule was ingested without difficulty by all of the 36 subjects. There were no cases of capsule retention or reported adverse

events in any of the subjects included in this study.

A complete small-bowel examination was achieved in 97.2% of studies. The mean follow-up after SBCE was 52 mo (12-156 mo).

At the moment of SBCE thirty four patients had clinically active disease and received anti-inflammatory treatment, as summarized in Tables 2 and 3. SBCE revealed small bowel lesions in 13 of patients (36.1%) and 23 (63.9%) patients had no lesions detected on SBCE. The distribution of the lesions in the small intestine were as follows: Two patients had multiple ulcerations (*n* ≥ 8) throughout the entire small bowel, 1 patients had ulcerations in first and second tertiles, 1 patient had ulcerations only in the second tertile, 5 patients had multiples ulcerations in the third tertile. In 4 patients the capsule revealed subtle findings of focal edema in a single short segment of the small bowel (Table 2).

Nine patients (25%) had inflammatory lesions considered significant (LS ≥ 135) and consistent with a diagnosis of CD (Table 2). In 4 of those patients (44.4%) a subsequent ileocolonoscopy showed, by this occasion, lesions compatible with CD in the terminal ileum and histology of colonic lesions was unspecific. In the remaining 5 patients (55.6%), the histology of colonic lesions was unspecific and ileoscopy detected no lesions.

In 27 patients (75%), the SBCE revealed no significant inflammatory activity (LS < 135). Among these patients, no lesion was detected in 23 patients and subtle lesions were found in 4 cases (Tables 2 and 3).

One patient (4.3%) with no lesions at SBCE had on follow-up a subsequent ileoscopy which revealed lesions compatible with CD (Table 3).

In 12 of 23 patients (52.2%) with no lesions at SBCE, a diagnosis of UC was established on follow-up, on average 38.3 mo after SBCE (Table 3). Four patients (25%) with a final diagnosis of UC had subtle lesions (focal edema) on SBCE (Table 2). In all of these patients the endoscopic and histological findings were consistent with the diagnosis of UC, which remained in clinical and analytical remission on follow-up.

Ten patients (27.8%) remained with a diagnosis of IBDU after a mean follow-up of 42 mo (Table 3). Considering the endoscopic criterion of significant inflammatory activity to predict a diagnosis of CD, using a cut-off for LS ≥ 135<sup>[13]</sup>, it would result in no false positive and only one false negative examinations, corresponding to a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 90%, 100%, 100% and 94%, respectively.

In 6 of 9 patients (66.7%) with significant inflammatory activity detected in SBCE, the treatment during the follow-up was escalated to immunosuppressive drugs or biological therapy (Table 2). In 3 of 16 (18.8%) patients with a definitive diagnosis of UC and in 4 of 10 (40%) patients who remained with a diagnosis of IBDU on follow-up, a new IBD medication was introduced during the follow-up.

The start of treatment with thiopurines and/or biologics in patients who were previously naïve to those medications

**Table 2 Clinical characteristics and outcome of the patients with positive small bowel capsule**

Case	Sex	Age	SBCE Findings	LS	Treatment pre-SBCE	Treatment post-SBCE	Diagnostic at follow-up
1	F	38	Multiple jejuno-ileal ulcerations	1404	5ASA	5 ASA + AZT	CD
2	F	18	Ulcer (n = 1) and edema of 3° tertile	143	AZT	Anti-TNF	CD
3	M	23	Ulcer (n = 1) and edema of 3° tertile	143	5ASA	5ASA	CD
4	F	20	Ulcerations (n = 2) and edema of 3° tertile	233	5ASA	5ASA	CD
5	F	33	Ulcer (n = 3) of 2° tertile	225	5ASA	5ASA	CD
6	F	19	Multiple ulcerations and edema of 3° tertile	908	5ASA	AZT	CD
7	M	60	Focal edema of 1° tertile	8	No treatment	5ASA	UC
8	M	22	Multiple jejuno-ileal ulcerations	2080	5ASA	5ASA + AZT	CD
9	F	32	Multiple ulcerations and edema of 3° tertile	908	5ASA	AZT	CD
10	F	27	Focal edema of 3° tertile	8	Prednisolone	anti-TNF	UC
11	F	47	Focal edema of 2° tertile	8	5ASA	5ASA	UC
12	F	31	Ulceration and edema of 1° (n = 5) and 2° tertile (n = 6)	879	5ASA+Prednisolone	AZT	CD
13	M	44	Focal edema of 3° tertile	8	5ASA	5ASA	UC

5ASA: Mesalamine; anti-TNF: Anti-tumor necrosis factor drug; AZT: Azathioprine; CD: Crohn’s disease; SBCE: Small bowel capsule endoscopy; LS: Lewis score; UC: Ulcerative colitis.

**Table 3 Clinical characteristics and outcome of the patients with negative small bowel capsule**

Case	Sex	Age	Treatment pre-SBCE	Treatment post-SBCE	Diagnostic at follow-up
1	M	45	5ASA	5ASA	IBDU
2	F	15	Prednisolone, 5ASA	5ASA	UC
3	F	27	AZT, 5ASA	AZT	UC
4	F	26	5ASA	5ASA	UC
5	M	31	5ASA	5ASA	IBDU
6	F	34	5ASA	5ASA	IBDU
7	M	21	5ASA	5ASA	IBDU
8	F	22	5ASA	5ASA, AZT	IBDU
9	F	56	5ASA	5ASA	UC
10	F	27	AZT, anti-TNF	AZT, anti-TNF	UC
11	F	30	5ASA	5ASA	UC
12	M	24	5ASA	5ASA	CD
13	M	49	5ASA	5ASA	UC
14	M	43	5ASA	5ASA	UC
15	F	30	5ASA + AZT	Anti-TNF	IBDU
16	M	24	5ASA	5ASA	UC
17	F	20	5ASA	5ASA	UC
18	M	55	5ASA	5ASA	IBDU
19	F	31	5ASA	5ASA, AZT, Anti-TNF	UC
20	F	48	5ASA	5ASA, AZT	IBDU
21	M	64	5ASA	5ASA	UC
22	M	44	No treatment	5ASA	IBDU
23	M	53	5ASA	5ASA	IBDU

5ASA: Mesalamine; anti-TNF: Anti-tumor necrosis factor drug; AZT: Azathioprine; CD: Crohn’s disease; IBDU: Colonic inflammatory bowel disease type unclassified; SBCE: Small bowel capsule endoscopy; UC: Ulcerative colitis.

occurred in 6/9 (66.7%) vs 5/27 (18.5%) patients with or without significant inflammatory activity detected at the SBCE, respectively ( $P = 0.012$ ).

## DISCUSSION

Ileocolonoscopy remains the first line exam to achieve the diagnosis in patients with suspected IBD<sup>[14]</sup>. Nonetheless, ileocolonoscopy can miss CD and result in false negative results due to skip lesions throughout the terminal ileum<sup>[15]</sup>.

Upper endoscopy, SBCE, computed tomography enterography (CTE) and magnetic resonance entero-

graphy (MRE) can provide important information and may be useful to establish a definitive diagnosis<sup>[14]</sup>.

In patients with suspected CD and negative ileocolonoscopy findings, recent European guidelines recommends SBCE as the next diagnostic exam for small bowel investigation, in the absence of obstructive symptoms or known stenosis<sup>[11]</sup>.

SBCE has proven its superiority in identifying inflammatory lesions consistent with the diagnosis of CD in the small intestine when compared to CTE<sup>[9,16]</sup> or MRE<sup>[10]</sup>, thus it has assumed an important role on the evaluation of patients with suspected CD<sup>[13,17-19]</sup>, having a high negative predictive value for the absence of significant



inflammatory activity<sup>[13]</sup>. However, there is still limited evidence for the role of SBCE in patients with IBDU<sup>[11]</sup>.

Most studies<sup>[20-22]</sup> used the non-validated diagnostic criteria for small-bowel CD proposed by Mow *et al*<sup>[23]</sup> (presence of more than three ulcerations).

Meanwhile, two scoring systems have been developed to standardize the quantification of inflammatory activity in the small bowel. The Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) is based on evaluation of the following parameters: Inflammation, extent of disease and presence of a stricture, while the LS evaluates villous appearance, ulcers and strictures<sup>[12]</sup>. The LS has shown a better performance than the CECDAI at describing small-bowel inflammation<sup>[24]</sup>.

Indeed, LS has been shown a strong interobserver agreement for the determination of the inflammatory activity, and it is validated for the reporting small-bowel inflammatory activity<sup>[25,26]</sup>.

In our study, the findings revealed by SBCE were consistent with a diagnosis of CD, based upon LS  $\geq$  135, in 9 of 36 (25%) of the subjects with IBDU, which is in line with the 16%-50% range described in other previous series<sup>[20-22,27-29]</sup>. An even higher percentage has been reported in pediatric patients<sup>[14]</sup>.

In the present study, 4 patients (25%) with final diagnosis of UC had subtle small bowel lesions, such as focal edema, without a significant inflammatory activity, LS < 135, and with clinical and analytical remission during follow-up. Indeed, previous studies already reported a significantly higher frequency of small-bowel lesions in UC patients as compared with that in the control healthy volunteers<sup>[30]</sup>. The significance of the presence of these lesions and the possible risk of misdiagnosis is still indeterminate<sup>[31]</sup>.

Although a negative SBCE study did not allow to definitely exclude a future diagnosis of small bowel CD, as further investigation and biopsies on follow-up led to a diagnosis of CD in one patient, the absence of significant inflammatory activity (LS < 135) in the small intestine actually allowed exclusion of CD in 94% of cases.

Based on our findings, SBCE may lead to reclassification of disease from suspected IBDU to definitive CD in 25% of cases. Furthermore, treatment with thiopurines and/or biologics was initiated more often in patients with significant inflammatory activity detected on SBCE (66.7% vs 18.5%,  $P = 0.012$ ). This association suggests that capsule findings may be helpful in the clinical management of these patients, as already been proven in other series<sup>[28,32-34]</sup>.

There are some limitations of this study, including its retrospective design, a limited number of subjects, and no direct comparison of SBCE with alternative small bowel diagnostic imaging, however, the last was not an aim of this study.

Nevertheless, to our knowledge this is one of the studies with larger number of patients included to evaluate this particular issue<sup>[20-22,27-29]</sup>.

There are no definite diagnostic criteria for IBDU, as it must be considered a provisional diagnosis until more

information (clinical, endoscopic, radiologic or pathologic) or data on follow-up enable a definitive reclassification<sup>[35]</sup>. Mucosal biopsy samples before treatment can be useful to distinguish UC from CD, but this distinction is based primarily on the pattern, type and location (distribution) of the disease, rather than specific histological features, for which there is much overlap between the two diseases<sup>[36]</sup>. Therefore, SBCE has a valuable role in the reclassification of patients with IBDU, may also contribute to establish the strategy for clinical management, and should be performed in the undefined diagnosis, which IBDU represents, in order to contribute to a definite diagnosis.

## COMMENTS

### Background

Colonic inflammatory bowel disease type unclassified (IBDU) is defined as a chronic idiopathic inflammatory bowel disease limited to the colon, whose combination of clinical, analytical, imaging, endoscopic and histological elements does not allow a differential diagnosis between Crohn's disease (CD) and ulcerative colitis.

### Research frontiers

In patients with suspected CD and negative ileocolonoscopy findings, small bowel capsule endoscopy (SBCE) is the next diagnostic exam for small bowel investigation, in the absence of obstructive symptoms or known stenosis. Since SBCE enables a direct endoscopic visualization of throughout the small intestine, it may be expected to contribute for the reclassification of IBDU. However, the role of SBCE in IBDU has not been clearly established. In this study, the authors evaluate the role of SBCE on the reclassification of IBDU.

### Innovations and breakthroughs

In this study, inflammatory activity on SBCE was objectively assessed by determining the Lewis score (LS). SBCE lead to reclassification of disease from IBDU to definitive CD in 25% of cases. Although a negative SBCE study did not allow to definitely exclude a future diagnosis of small bowel CD, as further investigation and biopsies on follow-up led to a diagnosis of CD in one patient, the absence of significant inflammatory activity (LS < 135) in the small intestine actually allowed exclusion of CD in 94% of cases.

### Applications

This study suggests that SBCE is useful in the reclassification of patients with IBDU. Facing a patient with IBDU, a SBCE should be performed in order to diagnosis or exclude a CD.

### Peer-review

This manuscript "Essential role of small bowel capsule endoscopy in reclassification of colonic inflammatory bowel disease type unclassified" is well written.

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