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But how many misunderstood Crohn's disease are revealed "*by chance*" using Capsule Endoscopy in Chronic Recurrent OGIB? Experience of a Single Italian Center and long term follow-up

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Abstract. – OBJECTIVE: The role of capsule endoscopy (CE) in Crohn's disease (CD) has expanded with greater understanding of the technology. The ability of CE to differentiate CD from other causes of inflammation has been questioned. Longitudinal studies are required to assess the long-term impact and significance of CE findings in suspected CD. The aim of this work is to verify in how many misunderstood cases of suspected Crohn's Disease CE was able to identify precociously and "by chance" when it is performed for recurrent obscure GI bleeding (OGIB), to evaluate how many of them were later confirmed during a median 24 months follow-up. Moreover, we observed the role of the early diagnosis in changing the clinical management of these patients.

PATIENTS AND METHODS: A retrospective review was carried out on CE procedures performed for suspected OGIB. 1008 consecutive patients was enrolled and 492 included in the study. Previous investigations such as ileocolonoscopy and/or previous small bowel imaging were documented. Only patients with at least 6 months of documented follow-up were included. A chart review was undertaken to record CE findings/correlate with subsequent diagnosis and outcome.

RESULTS: 94/492 (19.1%) patients positive for suspected CD were identified. Follow-up data were available 64/94 (68%). The mean follow-up was 24 months. There was a strong positive correlation between results of CE and subsequent clinical diagnosis. The suspected CD was confirmed in 100% (94/94) of follow-up patients.

CONCLUSIONS: CE appears able to identify lesions compatible with suspected Crohn's disease otherwise unacknowledged with consequently change in treatment options for the patients.

Key Words:
Capsule endoscopy, Negative predictive value, Suspected Crohn's disease.

Introduction

The superiority of capsule endoscopy (CE), when compared with traditional endoscopic or radiological procedures, has been demonstrated in several cases, most notably in obscure gastrointestinal bleeding (OGIB)[1] and both suspected and established Crohn's Disease (CD)[2]. CE is now an established and integral part of the investigation pathway for suspected CD[3].

Crohn's Disease (CD) is a chronic inflammatory disorder associated with mucosal and transmural inflammation of the bowel wall. It is well known that CD can affect the entire gastrointestinal tract from the mouth to the anus although the ileum-colon is involved in 50% of the cases[4]. However, the small bowel involvement has been observed up to 30% of the patients have only[5,6]. Jejunal lesions are also detected in more than half of the patients affected by CD and this condition is associated with an increased risk of further clinical relapse[7]. Although there is no gold standard test for the diagnosis of small bowel Crohn's Disease[8], diagnosis should be made using a combination of clinical, endoscopic, radiological, histological, and biochemical tests. The radiological procedures such as barium radiography, abdominal computed tomography (CT) and

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Magnetic Resonance Enterography (MRE), and endoscopic analyses are routinely used to evaluate the small bowel, but they have several recognized limitations[9].

The development of CE modified our approach to the diagnosis of gastrointestinal disease and, moreover, it led to change the management of gastrointestinal disease[10].

Despite these advances, the potential interval time between symptoms occurrence and diagnosis, which can be as long as 7 years[11,12], remains a major issue in suspected CD, because any delay in commencement of treatment should be detrimental[13]. Therefore, the use of CE in the suspected CD cohort could be favorable in terms of of diagnosis and treatment in these patients.

The primary end-point of this report is to evaluate the role of CE to identify the *misunderstood* cases of suspected Crohn's Disease *precociously* and *"by chance"* when it is performed for OGIB according to Criteria for suspected Crohn's disease of ICCE 2005 that include iron deficiency anemia[14]; the secondary end-point is to establish how many of them were later confirmed during a median 24 months follow-up and the role of the early diagnosis in changing the clinical management of these patients.

Patients and Methods

We reported a retrospective, tertiary care center study involving a consecutive series of patients referred to the Digestive Endoscopy Unit of the Catholic University of the Sacred Heart in Rome to undergo a CE analysis between December 1st, 2002 and January 30th, 2014 for several indications (Over GI bleeding, obscure GI bleeding, suspected Crohn's, malabsorption syndrome, polyposis, suspected neoplasm) after an initial negative complete endoscopic and radiological evaluation [17]. Exclusion criteria included intestinal obstruction, stricture or fistula, paralysis or impaired mobility, pregnancy, neurological diseases, or any treatment affecting GI motility, any documentation of nonsteroidal anti-inflammatory drug (NSAID) use in the 3 months prior to CE and any patient without a previous ileocolonoscopy. Patients with a known diagnosis of CD were also excluded from the study.

Thousand and eight patients were enrolled in the study: 527 male and 481 female with a median age of 50.5 years. The clinical data considered were patient demographics, past medical history, and presenting symptoms. Previous investigations such as ileo-colonoscopy and/or previous small bowel imaging were included.

All patients, opportunely consented, underwent a CE with the PillCam capsule endoscopy system (Given Imaging, Yoqneam, Israel), according to the standard protocols endorsed by the American Society for Gastrointestinal Endoscopy[18]. Some procedures were performed in an outpatient setting, others in inpatient setting. All procedures were performed after fasting for 8 h with bowel preparation (Polietilenglicol plus Simethicone 2 L). The PillCam small bowel (Given Imaging) was then administered. The patients had a light breakfast 2 h after and a light meal 4 h after the administration of the PillCam as recommended in the standard protocol. After 8 h, they returned to the Endoscopy Unit, data recorder was removed and images were downloaded on the computer. The recordings of CE were reviewed by 2 experienced endoscopists/gastroenterologists independently at 8-10 frames per second using the Rapid® Reader. The interobserver differences in interpretation about any findings were less than 5% and resolved by reexamination.

We defined as suspected Crohn's disease and included in the statistical analysis all patients who underwent exam for OGIB with the following CE findings: mucosal fissure, linear ulcers, round ulcers, irregular ulcers, cobblestoning mucosa (composed of multiple longitudinal ulcers running parallel and hill-like elevations due to submucosal swelling), aphthous lesions, strictured and ulcerated areas of mucosa scarring, erythema, edema, loss of villi (when celiac disease serology was negative), denudated area.

The following data were recorded in each patient: possible cecum visualization; clinically significant findings, such as angiodysplasia, tumors, erosions/ulcers, any kind of mucosal abnormalities; presence of adverse events; small bowel preparation bowel preparation was arbitrarily defined as adequate or inadequate (adequate: clear secretion; inadequate: the presence of bubbles or residues).

Statistical Analysis

The statistical analysis was performed using the SPSS 13.0 software package (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

Results

An amount of 1008 CE procedures were consecutively performed for various indications. Therefore, all subjects underwent CE to not recurrence of OGIB (210/1008), those in chronic therapy with NSAIDs (42), the cases cannot be assessed for inadequate preparation/small bowel cleaning (25), were excluded.

All patients with a negative CE investigations (239) were excluded.

Four hundred ninety-two out of 1008 (48.8%) patients were enrolled; in 94 out of 492 patients (19.1%) CE findings were suggestive for suspected Crohn's disease. Table I summarizes the demographic characteristics of these patients and CE findings.

In 60 out of 94 (63.9%) patients, the findings were located in the distal small bowel only. A further 31 (33%) had findings in the mid-small bowel with only three studies demonstrating changes in the proximal small bowel mucosa. A histological diagnosis was obtained in 15/94 patients (16%) by single balloon enteroscopy biopsies. In one case an intestinal lymphoma was diagnosed and left in the follow-up study. In the remaining cases, any histological confirmation was obtained due to factors including previous imaging suggestive of CD.

29 out of 93 patients with a positive CE investigation enrolled were lost at follow-up (30.8%). In the others 64 patients with a positive CE, all with at least 2-years follow-up, 60 (93.7%) had a confirmed clinical and histological diagnosis of CD, while, the other four (6.3%) patients had a confirmed clinical but not histological diagnosis. All confirmed cases had an alteration in their management as a result of the CE findings. One patient underwent surgery for a distal ileal stricture, identified by CE examination (though the capsule passed the identified stricture spontaneously). In the other patients, a medical therapy was started. The univariate analysis showed a strongly positive correlation between the results of CE and subsequent clinical diagnosis (r = 0.828, $p < 0.01$). CE showed also a diagnostic yield of 19.1%, considering the totality of patients with recurrent OGIB enrolled in the study (94/492). In fact, it was able to identify lesions compatible with suspected Crohn's disease. The sensibility, specificity, predictive positive value (PPV) and negative predictive value (NPV) were 100%, 56.4%, 19.1% and 100%, respectively.

In addition, observing the 64 patients during follow-up, the number of subjects hospitalized more than once for recurrence of obscure bleeding was significantly decreased. All patients were hospitalized at least once in a year before diagnosis; during follow-up, after diagnosis and early treatment, only 19/64 (29.6%; $p < 0.05$) patients were readmitted for a recurrence of anemia.

Table I. Demographic characteristics and mucosal finding in positive CE patients.

No.	94
M/F	56/38
Median age (years)	54.6
Type of findings:	
	No. of patients
Mucosal fissure/> 3 erosions	45
Single or multiple round ulcers	28
Aphthous lesions	19
Diffuse erythema and/or edema	2

Discussion

The aim of our study was to establish the accuracy of CE in identifying probable and misunderstood cases of Crohn's Disease when it is performed for obscure GI bleeding (OGIB) and to evaluate the role of the early diagnosis in changing the clinical manegment of these patients during a median 24 months follow-up.

The major focus of modern CD medical therapy is disease modification, with a lower rate of surgery and hospitalization[15]. The potential 'treatment lag' due to delayed diagnosis of CD is an important issue, particularly in the era of biological therapy[16]. This potential 'treatment lag' between symptoms occurrence and diagnosis has been largely investigated in studies assessing cross-sectional imaging. The potential ability of CE to accurately assess mucosal disease is unknown. The results of our study, even with the limitations related to the sample size, would suggest that CE is capable of fulfilling this role. Even though many studies and meta-analysis have reported the CE in suspected CD with previous negative ileo-colonoscopy should be be superior to many forms of cross-sectional imaging, magnetic resonance imaging/computed tomography (MRI/CT) are still a useful tool in the diagnostic paradigm of this patient cohort.

Herrerías et al[17] studied 21 patients who underwent CE because of abdominal pain, diarrhea,

weight loss, fever, anemia, and elevated C-reactive protein with previous negative endoscopic e radiological examinations. CE found lesions compatible with CD in nine patients (43%). Other studies, reported similar results with a diagnostic yield of CE in suspicious Crohn's disease of 26%[18], 59%[19], or 52.4%[20]. Fireman et al[21] reported the presence of CE findings compatible with CD in 12/17 (71%) patients with normal radiological and endoscopic studies but with a high clinical suspicion of CD. CT Enterography (CTE) and Magnetic Resonance Enterography (MRE) achieved better results than the conventional radiology. In a recent study Jensen et al[21] compared CE, CTE, and MRE in patients with negative ileocolonoscopy reported a significantly superior detection of CD in the proximal small bowel by CE. In suspected or newly diagnosed CD, in patients without endoscopic or clinical suspicion of stenosis, CE should be the first-line modality for detection of small bowel Crohn's disease beyond the reach of the colonoscope.

In the meta-analysis of Triester et al[22], including nine studies with 250 patients comparing CE with other imaging techniques of the small bowel, CE resulted be superior to all other modalities for diagnosing nonstricturing CD, with a number needed to test (NNT) of 3 to yield one additional diagnosis of CD over small bowel barium radiography and NNT = 7 over colonoscopy with ileoscopy. More recently the meta-analysis of Dionisio et al[2] comparing 12 trials (8 of them compared CE with ileo-colonoscopy, 4 CE with CT-Enteroclysis, 2 CE with Push enteroscopy, and 4 CE with MRE) confirmed the superiority of CE compared to conventional endoscopy and radiological techniques in the evaluation of suspected CD patients.

Furthermore, the yield of the CE has been compared with assisted balloon enteroscopy concluding that CE and Double Balloon Enteroscopy have comparable diagnostic yield in small bowel diseases[24,25].

It should be considered that many lesions described in studies of suspected CD are not specific and this could explain the variability of the "diagnostic yield" of CE.

The study by Tukey et al [26] showed data of efficacy of CE, with the overall sensitivity for the diagnosis of CD of 85%, specificity of 73%, PPV of 31%, and negative predictive value of 97%, but when the test characteristics were determined according to CE findings alone, those patients with >3 small bowel ulcers had a PPV of 50% for CD and, if assessed only in patients under 30 years, the sensitivity of CE is 100%, specificity 78%, and PPV 67%. In our selected cohort of OGIB patients with findings compatible with suspected disease, the diagnostic yield was 19.1%. The established diagnosis of CD was made in 94/492 of suspected patients; the sensibility, specificity, predictive positive value (PPV) and negative predictive value (NPV) were 100%, 56.4%, 19.1% and 100%, respectively. During long-term (24 months) follow-up CD was confirmed in all 94 patients (100%).

Conclusions

The retrospective nature of our study is a limitation, in that referral of patients for CE may be biased. Furthermore, the unvalidated criteria of three or more ulcers with concomitant ulceration/oedema for detecting Crohn's disease on CE employed in our study may have had an influence on diagnostic yield. However, our data confirm the role of CE in the early diagnosis of CD in the subgroup of patients with recurrent OGIB and that CE is a good method to evaluate the small bowel resulting in better outcomes of diagnosis, classification, therapeutic management, and prognosis of CD patients.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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