

Small bowel Crohn's disease: comparison of enteroclysis, bowel sonography and Tc-99m-HMPAO leukocyte scintigraphy

A. RISPO, M. IMBRIACO*, L. CELENTANO**, A. COZZOLINO, P.P. MAINENTI*, L. CAMERA*, E. DI GIROLAMO, T. DE FALCO, F. CASTIGLIONE

Gastroenterology; Radiology*; Nuclear Medicine**; "Federico II" University of Naples (Italy)

Abstract. – **Background:** Crohn's disease (CD) frequently involves the small bowel. Actually, the diagnosis of CD is made by ileo-colonoscopy (IC) and small bowel enteroclysis (SBE), while trans-abdominal bowel sonography (BS) and Tc-99m-HMPAO leukocyte scintigraphy (LS) are only partially used in spite of their minimal invasiveness.

Aim: to compare the diagnostic accuracy of these procedures for the diagnosis of small bowel CD.

Patients and methods: in about two years a series of consecutive subjects underwent IC, SBE, BS and LS for either suspected or known small bowel CD.

Results: Sensitivity, specificity, positive and negative predictive value for CD diagnosis of the studied procedures were respectively: 98%, 97%, 98% and 97% for SBE; 92%, 97%, 98%, and 88% for BS; 90%, 93%, 96% and 85% for LS. In addition, the parallel combined use of BS and LS led to overall sensitivity, specificity, positive and negative predictive value of 100%, 93%, 96%, 100%, respectively.

Conclusion: SBE, BS and LS are accurate procedures for the diagnosis of small bowel Crohn's disease. The use of BS and LS, particularly in combination, can be proposed as early diagnostic approach to subjects with a suspicion of disease.

Key Words:

Crohn, Bowel sonography, Enteroclysis, Leukocyte scintigraphy.

are performed by ileo-colonoscopy (IC) and small bowel enteroclysis (SBE), in view of their high sensitivity, specificity, and diagnostic accuracy^{3,4,5}. Unfortunately, ileo-colonoscopy is an invasive and expensive procedure and often requires an expert operator⁶. In effect, ileal intubation is successfully performed only in 75-90% of endoscopies^{7,8}; besides, a further limiting factor is represented by the need for adequate bowel cleaning, which is obtained in 85% of patients undergoing IC at the most⁹. Similarly, small bowel enteroclysis is expensive and invasive, it causes X-ray exposure and requires conversion to follow-through examination in about 19% of cases due to intolerance or refusal of naso-jejunal or oro-jejunal intubation¹⁰.

Trans-abdominal bowel sonography (BS) and Tc-99m-HMPAO leukocyte scintigraphy (LS) are two procedures that are increasingly used for the diagnosis of Crohn's disease due to their minimal invasiveness, their reproducibility and acceptable costs. BS can visualize and locate trans-mural bowel inflammation showing the alteration of the echo-architecture of the bowel wall in CD¹¹. It has been reported that the technique is accurate in identifying CD in the differential diagnosis of ulcerative colitis¹², and in assessing the extent of the disease, with the exception of the stomach and of the deep pelvic tract of the sigmoid colon¹³. Many authors have found that BS is an accurate method for the detection of intestinal complications in CD and that it compares favorably with enteroclysis in the detection of obstruction, being able to correctly identify 90% of strictures documented by small bowel enema and confirmed at surgery¹⁴. Furthermore, BS has proven effective for the diagnosis of post-

Introduction

Crohn's disease (CD) is frequently localized in the small bowel, with or without colonic involvement^{1,2}. Currently, the diagnosis of small bowel CD and the assessment of its extension

surgical recurrence¹⁵. Tc-99m-HMPAO leukocyte scintigraphy has been used for many years in the investigation of pediatric inflammatory bowel disease because of its minimal invasiveness^{16,17}. The procedure is based on the ability of Tc-99m-HMPAO labeled leukocytes to accumulate into the inflamed tissues (i.e., gut and joints). LS has previously shown a sensitivity of 76%, a specificity of 91% and a diagnostic accuracy of 82% for ileo-colonic CD¹⁸; the diagnostic accuracy of LS seems to increase in presence of CD involving the terminal ileum¹⁹. In addition, LS has demonstrated a good correspondence with the spiral computed tomography findings¹⁸ and a high sensitivity for the diagnosis of post-surgical recurrence of CD²⁰.

However, comparative data about the diagnostic accuracy of all these procedures in patients with Crohn's disease are scanty. Aim of this study is the evaluation of the diagnostic accuracy of SBE, BS and LS in the diagnosis of small bowel Crohn's disease.

Materials and Methods

Eighty-four patients were considered in the study. Twenty out of these patients had received a previous diagnosis of CD and were being followed up at our IBD Unit; ten of them had undergone previous surgery with ileo-colic anastomosis. The remaining 64 patients were studied for suspected small bowel CD. All 84 patients underwent IC with biopsy, SBE, BS and LS within ten days. The procedures were performed with the operators blinded about the result of the previous examinations. The investigators were not privy to the results of the biochemistry and were aware of any surgical resection previously performed.

The diagnosis of small bowel CD was made according to the ileoscopy and histological findings^{21,22}; the diagnosis was also confirmed at surgery when indicated.

The patients with a diagnosis of Crohn's disease were stratified according to the Vienna Classification²³ and had their biochemical and clinical disease activity parameters recorded (Erythrocyte Sedimentation Rate – ESR; C Reactive Protein – CRP; Crohn's disease activity index – CDAI).

All patients were followed up for at least 12 months.

Ileo-Colonoscopy

IC was performed by an expert operator with a conventional colonoscope (Fujinon EC-410MP; 150 cm) after a liquid dietary regime of 48 hours and an oral bowel cleaning with 90 mL of oral sodium phosphate the day before the examination. The intubation of the ileo-cecal valve was performed according to a previous report⁶. All patients underwent ileal biopsies. Endoscopic and histological diagnosis of CD was made according to the literature^{2,21,22}.

Small Bowel Enteroclysis

SBE was performed by oral intubation without sedation after an overnight fast. A pre-selected amount of barium and methylcellulose was infused through a catheter positioned at the duodenojejunal flexure as described by Herlinger²⁴. Compression views were obtained in all patients for the evaluation of the terminal ileum. Three categories of lesion were defined according to Engelhom²⁵. In brief, fold thickening, aphthous ulcerations, and granular appearance of the villi were considered to be early lesions. The nodular pattern and the presence of ulcerations on the mesenteric border characterized intermediate lesions, whereas "cobblestoning" appearance, fixed mechanical obstructions and fistulae were considered to be advanced lesions. In case of diagnosis of CD the radiologist would also describe the exact location and extension of the disease.

Trans-Abdominal Bowel Sonography

BS was performed in the morning hours following an overnight fast using an Aloka SSD-1700 with linear and convex probes (5-7.5 MHz). No special preparation was prescribed. The procedure was performed by a gastroenterologist with experience in bowel sonography. In every patient the entire abdomen was systematically scanned starting from the right iliac fossa. The bowel wall thickness was measured both in longitudinal and transverse sections and was considered normal for values up to 3 mm²⁶. In accordance with Maconi¹⁴, stricture was considered present at BS examination when there was coexistence of thickened (more than 4 mm) and stiff intestinal wall, narrowed intestinal lumen along with fluid-distended or echogenic content-filled loops just above the thickened in-

testinal tract. Entero-cutaneous, entero-enteric and entero-mesenteric fistulas were considered present when hypoechoic duct-like structures with fluid or air content were seen between skin and intestinal loops, between two intestinal loops or between intestinal loop and mesentery, respectively²⁷. The presence of abscesses was evaluated according to the current literature²⁸. In case of diagnosis of CD the gastroenterologist would describe the exact location and extension of the disease.

Tc-99m-HMPAO Leukocyte Scintigraphy

Fresh venous blood (20-50 mL) was drawn from each patient into a 50-mL plastic sterile syringe containing 5 to 10 mL of acid-citrate-dextrose (ACD). Five milliliters of hydroxyethyl starch were added and mixed gently. Sedimentation at room temperature was then allowed. The supernatant was collected and centrifuged for 5 minutes (900 g). The cell pellet was collected, re-suspended in 5 mL of plasma, and carefully layered onto the upper part of the double Hystopaque gradient (Fycoll/Hypaque) (density = 1.14), which was centrifuged at 700 g for 20 minutes. The layer of granulocytes was collected with a sterile disposable 2 mL pipette and resuspended in 5 mL of the cell-poor plasma. The autologous leukocytes were prepared according to a previously published method²⁹. The labeling efficiency (mean and SD) was $77.4\% \pm 13.5$; WBC count median (range) = $6.9 (4-10.1) \times 10^9 L^{-1}$. The final mean dose administered was 185 ± 74 MBq, depending on the labeling efficiency. Scintigraphy was performed using a GE Starport 400 AT gamma camera (General Electric) equipped with a low-energy medium-resolution collimator. Anterior and posterior images of the abdomen were obtained at the time of injection by means of dynamic framing acquisition (1 frame/1 min/30 min). Following static acquisitions were done – spot view of abdomen – at 30, 60, 120 and 180 minutes (in preset time mode: 600 sec/frame) and whole body study, were performed in anterior and posterior projections. The scintigraphy was considered positive for inflammatory bowel disease only when uptake, of labeled autologous granulocytes, was seen – along development of the bowel – within 1 hour from the injection of labeled cells. The activity scoring method, previously described³⁰ was applied to grading

uptake. Only in case of the faint uptake or, though, in case of ambiguous results, the imaging was repeated later, in the same mode as described. However, the activity detected in the gut beyond 3 hours, from the cells re-injection, was considered doubtful meaning inflammatory bowel disease. To analyze the scintigraphy, all bowel was then divided into 9 segments (jejunum, ileum, terminal ileum, cecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum).

Statistical Analysis

The statistical analyses were performed using the SPSS software package for Windows (release 12.0.1. – 11 Nov 2003; SPSS Inc., Chicago, IL, USA). Sensitivity, specificity, positive predictive value, and negative predictive value of the single procedure were calculated using StatsDirect statistical software (release 2.3.8 – 17 Apr 2004). With the same software we also calculated the aforesaid statistics for the parallel combined use of BS and LS (BS + LS), defined as a positive result on at least one of the two procedures.

Results

CD diagnosis was made in 54 out of the 84 patients. Fifty patients presented a small bowel CD with the involvement of the terminal ileum (Table I). The remaining 4 patients had an isolated colonic CD and were excluded from the study. The last 30 subjects received a different diagnosis.

The sensitivity, specificity, positive and negative predictive value of SBE, BS and LS are reported in Table II. All procedures showed high diagnostic accuracy (i.e., Figure 1, 2 and 3). Furthermore, the parallel combined use of BS and LS led to an overall sensitivity, specificity, positive and negative predictive value of 100%, 93%, 96% and 100%, respectively.

With regard to sensitivity, SBE showed signs of disease in 49 out of 50 patients. The only CD patient with negative SBE had mild aphthoid inflammation at ileoscopy. Forty-six out of 50 patients with CD were positive at BS. The 4 patients with negative BS had mild inflammatory ileitis; 2 of them also presented involvement of the deep pelvic ileum. LS

Table I. Characteristics of the 50 patients with small bowel CD.

Characteristics	#
Sex (M/F)	27/23
Mean age (range)	31.8 years (15-57)
Mean follow-up (range)	36 months (6-72)
Location	
Terminal ileum	39
Jejuno-ileal	3
Ileo-colic anastomosis	8
Behaviour	
Non stricturing-non penetrating	26
Stricturing	21
Penetrating	3
CDAI	
> 150	34
< 150	16

CDAI = Crohn's Disease Activity Index.

showed a significant uptake of leukocytes in 45 of 50 patients with CD; three of the 5 false negative patients had extensive jejuno-ileal CD, in 1 patient the labeling of leukocytes had been unsatisfactory and in one patient LS described as sigma the inflamed pelvic ileum. Thirteen out of the 50 patients with CD (26%) underwent surgery within 6 months; in all these cases the diagnosis was confirmed at surgery.

In terms of specificity, SBE gave one false positive finding amongst the 30 patients with-

out CD; this case was diagnosed as jejunal lymphoma by spiral computed tomography and the diagnosis was then confirmed at surgery. With BS, one false positive result was found in a case of sclerosing mesenteritis. LS showed 2 false positive outcomes, one in a case of bleeding jejunal lymphoma and the other in a case of ulcerative colitis (data not shown).

As for the intestinal complications of Crohn's disease, BS detected 12 out of the 14 strictures identified by SBE (85%), 4 out of the 5 fistulas highlighted at radiology (80%) and 3 abdominal abscesses not shown at enteroclysis (7%).

Discussion

The invasiveness of procedures utilised in CD diagnosis is a very relevant topic. In fact, such invasiveness can make the clinician reluctant to recommend these investigations at an early stage of the diagnostic approach to a case of suspected CD, especially in the presence of mild symptoms or only slight biochemical alterations, thus causing a delay in the diagnosis³¹.

Trans-abdominal bowel sonography and leukocyte scintigraphy are two techniques that are increasingly used for the diagnosis of CD due to their minimal invasiveness, their

Table II. Diagnostic results of SBE, BS and LS for the diagnosis of small bowel CD.

Procedure	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
SBE	98 (83-100)	97 (89-100)	98 (89-100)	97 (83-100)
BS	92 (80-97)	97 (83-100)	98 (89-100)	88 (72-97)
LS	90 (77-96)	93 (78-99)	96 (85-99)	85 (68-95)
BS + LS	100 (93-100)	93 (78-99)	96 (87-100)	100 (88-100)

SBE = small bowel enteroclysis; BS = Trans-abdominal bowel sonography; LS = Tc-99m-HMPAO leukocyte scintigraphy.



Figure 1. Enteroclysis. Crohn's ileitis: the inflammatory involvement of the terminal ileum (and right colon) is evident.

reproducibility and acceptable costs^{12,16} and could be very useful in the diagnostic approach to a suspected CD.

Our work has confirmed the high diagnostic accuracy of SBE for the diagnosis of small bowel CD^{4,5} when compared to ileocolonoscopy. Similarly, BS and LS demonstrated high diagnostic accuracy for CD, with a reduction in information in case of extensive jejuno-ileal disease for LS and of involvement of the pelvic ileum for BS. In comparison with enteroclysis, BS revealed a good correlation with regard to intestinal compli-



Figure 2. Bowel sonography. Crohn's ileitis: the thickened wall of the ileum with narrowed lumen is evident.

cations such as strictures and fistulas, additionally showing the presence of abscesses.

As regards specificity, both SBE and LS gave one false positive finding in a case of jejunal lymphoma (data not shown); therefore, this differential diagnosis appears to be the most relevant issue in a case of suspected isolated jejunal CD.

Interestingly, in our experience, the parallel combined use (with positivity of at least one of the two performed procedures) of bowel sonography and leukocyte scintigraphy led to an overall sensitivity of 100% with the same diagnostic accuracy of SBE (97%), with the disease being diagnosed in all cases. The combined approach showed a sensitivity of 100% also for the diagnosis of post-surgical recurrence.

Also, the combined use of BS and LS showed a negative predictive value of 100%; as a result, the patients with negative BS and LS would not require further investigations to exclude the diagnosis of small bowel Crohn's disease.

In conclusion, SBE, BS and LS are accurate procedures for the diagnosis of small bowel Crohn's disease. The combined use of BS and LS can be proposed as early diagnostic approach to subjects with a suspicion of CD.



Figure 3. Tc-99m-HMPAO leukocyte scintigraphy. Crohn's ileitis: the uptake of the labeled leukocytes into the ileum is evident.

References

- 1) CROHN BB, GINZBURG L, OPPENHEIMER GD. Regional ileitis. A pathological and clinical entity. *JAMA* 1932; 99: 1323-1329.
- 2) MEKHJIAN HS, SWITZ DM, MELNYK CS, et al. Clinical features and natural history of Crohn's disease. *Gastroenterology* 1979; 77: 898-906.
- 3) COREMANS G, RUTGEERTS P, GEBOES K, et al. The value of ileoscopy in the diagnosis of intestinal Crohn's disease. *Gastrointest Endosc* 1984; 30: 167-72.
- 4) MAGLINTE DDT, CHERNISH SM, KELVIN FM, et al. Crohn's disease of the small bowel: accuracy and relevance of enteroclysis. *Radiology* 1992; 184: 541-545.
- 5) CIRILLO LC, CAMERA L, DELLA NOCE M, et al. Accuracy of enteroclysis in Crohn's disease of the small bowel: a retrospective study. *Eur Radiol* 2000; 10: 1894-1898.
- 6) CHEN M, KHANDUJA KS. Intubation of ileocecal valve made easy. *Dis Colon Rectum* 1997; 40: 494-496.
- 7) KUNDROTAS LW, CLEMENT DJ, KUBIK CM, et al. A prospective evaluation of successful terminal ileal intubation during routine colonoscopy. *Gastrointest Endosc* 1994; 40: 544-546.
- 8) ZWAS FR, BONHEIM NA, BERKEN CA, et al. Diagnostic yield of routine ileoscopy. *Am J Gastroenterol* 1995; 90: 1441-1443.
- 9) LAZZARONI M, BIANCHI PORRO G. Preparation, pre-medication and surveillance. *Endoscopy* 2003; 35: 103-111.
- 10) TOMS AP, BARLTROP A, FREEMAN AH. A prospective randomised study comparing enteroclysis with small bowel follow-through examinations in 244 patients. *Eur Radiol* 2001; 11: 1155-1160.
- 11) HATA J, HARUMA K, YAMANAKA H, et al. Ultrasonographic evaluation of the bowel wall in inflammatory bowel disease: comparison of in vivo and in vitro study. *Abdom Imaging* 1994; 19: 395-399.
- 12) LIM JH, KO YT, LEE DH, et al. Sonography of inflammatory bowel disease: findings and value in differential diagnosis. *Am J Roentgenol* 1994; 163: 343-347.
- 13) HOLLERBACH S, GEISSLER A, SCHIEGL H, et al. The accuracy of abdominal ultrasound in the assessment of bowel disorders. *Scan J Gastroenterol* 1998; 33: 1201-1208.
- 14) MACONI G, BOLLANI S, BIANCHI PORRO G. Ultrasonographic detection of intestinal complications in Crohn's disease. *Dig Dis Sci* 1996; 41: 1643-1648.
- 15) ANDREOLI A, CERRO P, FALASCO G, et al. Role of ultrasonography in the diagnosis of post-surgical recurrence of Crohn's disease. *Am J Gastroenterol* 1998; 93: 1117-1121.
- 16) GRAHNQUIST L, CHAPMAN SC, HDVISTEN S, et al. Evaluation of 99mTc-HMPO leukocyte scintigraphy in the investigation of pediatric inflammatory bowel disease. *J Pediatr* 2003; 143: 48-53.
- 17) CUCCHIARA S, CELENTANO L, DE MAGISTRIS TM, et al. Colonoscopy and technetium-99 white cell scan in children with suspected inflammatory bowel disease. *J Pediatr* 1999; 135: 727-732.
- 18) MOLNAR T, PAPOS M, GYULAI C, et al. Clinical value of technetium 99-m-HMPAO-labeled leukocyte scintigraphy and spiral computed tomography in active Crohn's disease. *Am J Gastroenterol* 2001; 96: 1517-1521.
- 19) ALBERINI JL, BADRAN A, FRENEAUX E, et al. Technetium-99m HMPAO-labeled leukocyte imaging compared with endoscopy, ultrasonography, and contrast radiology in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2001; 32: 278-286.
- 20) BIANCONE L, SCOPINARO F, IERARDI M, et al. 99mTc-HMPAO granulocyte scintigraphy in the early detection of postoperative asymptomatic recurrence in Crohn's disease. *Dig Dis Sci* 1997; 42: 1549-1556.
- 21) JENKINS D, BALSITIS M, GALLIVAN S, et al. Guidelines for the initial biopsy diagnosis of suspected chronic idiopathic inflammatory bowel disease. The British Society of Gastroenterology Initiative. *J Clin Pathol* 1997; 50: 93-105.
- 22) LENNARD JONES JE. Classification of inflammatory bowel disease. *Scan J Gastroenterol* 1989; 170: 2-6.
- 23) GASCHÉ C, SCHOLMERICH J, BRYNSKOV J, et al. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis* 2000; 6: 8-15.
- 24) HERLINGER H. A modified technique for the double contrast small bowel enema. *Gastrointest Radiol* 1978; 3: 201-207.
- 25) ENGELHOM L, DE TOEUFF C, HERLINGER H, et al. Crohn's disease of the small bowel. In: Herlinger H, Maglinte D. *Clinical radiology of the small intestine*. Saunders, 1998, Philadelphia, 295-334.
- 26) SOLVIG J, EKBERG O, LINDGREN S, et al. Ultrasound examination of the small bowel: comparison with enteroclysis in patients with Crohn's disease. *Abdomin Imaging* 1995; 20: 323-326.
- 27) OBERHUBER G, STANGL PC, VOGELANG H, et al. Significant association of strictures and internal fistula formation in Crohn's disease. *Virchows Arch* 2000; 437: 293-297.
- 28) JOSEPH AEA, MACVICAR D. Ultrasound in the diagnosis of abdominal abscesses. *Clin Radiol* 1990; 42: 154-156.
- 29) FERRANTE A, THONG YA. Optimal condition for simultaneous purification of mononuclear and polymorphonuclear leukocytes from human peripheral blood by the Hypaque-Ficoll method. *J Immunol Methods* 1980; 36: 109-117.
- 30) SCIARRETTA G, FURNO A, MAZZONI M, et al. Technetium-99m hexamethyl propylene amine oxime granulocyte scintigraphy in Crohn's disease: diagnostic and clinical relevance. *Gut* 1993; 34: 1364-1369.
- 31) ADMANS H, WHORWELL PJ, WRIGHT R. Diagnosis of Crohn's disease. *Dig Dis Sci* 1980; 25: 911-915.