Colonoscopy and technetium-99m white cell scan in children with suspected inflammatory bowel disease

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Objectives: To determine the utility of the technetium-labeled autologous white cell scintigraphy (Tc-WCS) for detecting intestinal inflammation in children with suspected inflammatory bowel disease (IBD). Tc-WCS was compared with colonoscopy and histologic examination.

Study design: Forty-eight children (26 boys; median age, 10 years; range, 2-17 years) with symptoms and signs suggesting IBD had colonoscopy with exploration of terminal ileum and mucosal biopsies. The scans were judged to be abnormal if activity was seen in the gut within the first hour.

Results: Twenty-one patients had a diagnosis of IBD (Crohn's disease, 13; ulcerative colitis, 5; indeterminate colitis, 3); results of scintigraphy were positive in 16 and negative in 5 (sensitivity, 76.2%); the latter had a moderate degree of intestinal inflammation. In 27 patients, IBD was ruled out. Results of scintigraphy were negative in children with non-specific colitis and in those with lymphoid hyperplasia of the terminal ileum, whereas results were positive in 6 of 12 patients with spondyloarthropathy. In children with IBD, there was a significant correlation between results of scintigraphy and endoscopy for the intensity of inflammation ($r = 0.70$); however, there was a poor correlation regarding the number of involved segments ($r = 0.30$) because in 16 patients, endoscopy revealed additional diseased segments as compared with scintigraphy.

Conclusions: A positive Tc-WCS result indicates the presence of an inflammatory process of the gut, whereas a negative test result does not rule out intestinal inflammation, especially when the latter is of moderate degree. Colonoscopy and biopsy are the investigations of choice to establish the diagnosis of IBD and are superior to Tc-WCS in assessing topographic extension of IBD. (J Pediatr 1999;135:727-32)

The diagnosis of children with inflammatory bowel disease requires interventional tools such as contrast radiology and endoscopy, which may be invasive and produce discomfort.[1] Furthermore, definition of the nature and extent of the underlying inflammatory disorder is essential for determining disease severity and appropriate treatment.[2] Because IBD in children may present with systemic non-gastrointestinal features, the least invasive techniques in the initial approach have also been advocated.[3]

Scintigraphic scanning of the abdomen, with the use of autologous granulocytes labeled with technetium hexamethyl-propyleneamine-oxime, has been proposed as a useful tool for detecting areas of inflamed bowel and for selecting patients with suspected IBD for further investigations.[4-7] Technetium white cell scintigraphy can be useful in children with IBD and narrowed bowel segments to discriminate between inactive strictures and narrowing caused by active inflammation.[8] Nevertheless, no studies have systematically examined the diagnostic value of this method in children with different types of gut inflammation.

CD	Crohn's disease
IBD	Inflammatory bowel disease
Tc-WCS	Technetium white cell scintigraphy
UC	Ulcerative colitis

We aimed to assess the role of Tc-WCS in children with suspected IBD. Intensity and distribution of intestinal inflammation as detected by scintigraphy were compared with findings on endoscopy and biopsy, the gold standard investigations.[9]

SUBJECTS AND METHODS

The study included 48 consecutive patients (26 boys; median age, 10 years; range, 2-17 years) referred because of suspected IBD from 1996 to

Table. Summary of endoscopic and scintigraphic assessment in the patient population

Patient No.	Sex	Age (y)	Involved areas at endoscopy	Tc-WCS uptake
1	M	3	DC, S, R, no vascular pattern, granularity, friability	Negative
2	F	9	S, patchy erosions, small ulcers	S
3	F	5	DC, S, R, hyperemia, friability, granularity	Negative
4	M	5	DC, S, R, hyperemia, friability, granularity	Negative
5	M	14	C, AC, TC, DC, S, R, hyperemia, granularity, friability	Negative
6	M	14	TI, C, DC, S, R, apthous erosions, serpiginous ulcerations	TI, C
7	M	15	TI, C, AC, TC, DC, apthous erosions, serpiginous ulcerations	TI, C, AC
8	F	16	R, S, DC, hyperemia, post-bioptic friability	Negative
9	F	11	TI, C, DC, S, R, hyperemia, apthous erosions, friability	DC
10	M	12	TC, DC, S, R, hyperemia, friability, granularity	Negative
11	M	4	TI, C, AC, TC, serpiginous ulcers, cobblestoning	TI, C, AC
12	F	9	TI, C, AC, TC, DC, S, R, ulcers, cobblestoning, pseudo-polyps	AC, TC, DC, S, R
13	F	8	TC, hyperemia, friability, small erosions	TC
14	F	10	TC, DC, S, R, hyperemia and granularity, friability	TC, DC
15	M	9	C, AC, TC, DC, S, R, no vascular pattern, ulcerations	C, AC, DC
16	M	8	DC, S, R, hyperemia, friability, granularity	Negative
17	M	5	DC, S, R, isolated erosions, hyperemia, edema	Negative
18	M	8	C, AC, R, serpiginous ulcers, aphthoid erosions	C
19	F	6	TC, DC, S, R, hyperemia, granularity	Negative
20	F	10	TI, lymphoid hyperplasia	Negative
21	M	10	R, TI, TC, DC, S, aphthous erosions, hyperemia, friability	DC
22	M	11	TI, lymphoid hyperplasia	Negative
23	F	15	TC, DC, S, R, ulcers, erosions, no vascular pattern	TC, DC, S, R
24	M	4	DC, S, R, hyperemia, friability, no vascular pattern	Negative
25	M	10	TI, lymphoid hyperplasia	Negative
26	F	8	DC, S, R, hyperemia, friability, no vascular pattern	DC
27	M	5	DC, S, R, no vascular pattern, ulcerations	S
28	F	14	TI, C, AC, TC, DC, S, R, ulcers, cobblestoning, pseudo-polyps	C, AC, TC
29	F	9	TI, AC, DC, small erosions, friability, no vascular pattern	Negative
30	F	10	TI, lymphoid hyperplasia	Negative
31	F	9	TI, lymphoid hyperplasia	Negative
32	M	7	TI, C, AC, TC, serpiginous ulcers, aphthoid erosions, cobblestoning	C, AC
33	M	13	TI, C, AC, TC, serpiginous ulcers, aphthoid erosions, cobblestoning	C, AC
34	M	16	C, AC, TC, DC, S, R, vascular pattern, large ulcers	C, AC, TC, DC, S, R
35	M	9	C, AC, TC, DC, S, R, hyperemia, friability	Negative
36	F	8	TI, lymphoid hyperplasia	Negative
37	M	4	DC, S, R, no vascular pattern, friability, granularity	Negative
38	M	10	DC, S, R, no vascular pattern, friability, granularity	Negative
39	F	13	TI, C, AC, TC, serpiginous ulcers, aphthoid erosions, cobblestoning	C, DC
40	M	13	C, AC, TC, DC, S, R, no vascular pattern, large ulcers	C, AC, TC, DC, S, R
41	F	10	AC, TC, DC, hyperemia, no vascular pattern, granularity	Negative
42	M	9	TI, AC, TC, DC, areas of intense hyperemia, friability	AC, TC, DC
43	M	17	TI, C, serpiginous ulcers, cobblestoning, aphthoid erosions	TI, C
44	F	15	TI, erosions	Negative
45	F	8	C, AC, TC, DC, S, R, small isolated erosions, no vascular pattern	Negative
46	F	12	TI, AC, S, R, hyperemia, aphthoid ulcers	Negative
47	F	11	TI, C, hyperemia, erosions, apthous ulcers	Negative
48	F	17	TI, C, AC, R, hyperemia, edema, microerosions	Negative

DC, Descending colon; *S,* sigmoid; *R,* rectum; *C,* cecum, *AC,* ascending colon; *TC,* transverse colon; *SpA,* spondyloarthropathy; *TI,* Terminal ileum.

Diagnosis
UC
Indeterminate colitis
Non-specific colitis
Non-specific colitis
SpA
CD
CD
Non-specific colitis
SpA
Non-specific colitis
CD
CD
SpA
SpA
UC
Non-specific colitis
Non-specific colitis
CD
SpA
TI lymphoid hyperplasia
SpA
TI lymphoid hyperplasia
Indeterminate colitis
Non-specific colitis
TI lymphoid hyperplasia
SpA
UC
CD
SpA
TI lymphoid hyperplasia
TI lymphoid hyperplasia
CD
CD
UC
SpA
TI lymphoid hyperplasia
Non-specific colitis
Non-specific colitis
CD
UC
SpA
SpA
CD
CD
Indeterminate colitis
CD
CD
SpA

the beginning of 1998. The main presenting symptoms and signs were incapacitating abdominal pain in 45, rectal bleeding in 42, mucus in the stools in 31, tenesmus and urgency in 30, diarrhea in 28, arthralgia and/or arthritis and/or enthesopathy in 25, fever in 14, growth delay in 7, and erythema nodosum in 3. The diagnostic approach included biochemical profile for nutrition and disease activity and exclusion of systemic disorders. Stools were examined for bacteria and parasites. All patients had total colonoscopy; at least 25 to 30 cm of the distal ileum was explored with the use of a pediatric videocolonoscope (Olympus, Torino, Italy) after intravenous sedation had been achieved with pethidine (1-2 mg/kg) and diazepam (0.3-0.5 mg/kg).

Ileo-colonic mucosal specimens obtained from all patients were assessed by a pathologist who was unaware of the clinical and endoscopic data. Endoscopic variables suggesting ulcerative colitis were loss of vascular pattern with hyperemia and edema, mucosal granularity and friability, diffuse contiguous and symmetric involvement, left-sided colitis, normal ileum, blunting of haustral pattern, and small ulcerations. Mixed acute and chronic inflammation in the lamina propria, crypt branching, and atrophy were histologic features indicating UC. Endoscopic features suggesting Crohn's disease were involved areas interspaced with normal zones ("skip areas"), aphthoid ulcers with normal intervening mucosa, large stellate or linear ulcers, cobblestone-like areas of non-ulcerated mucosa, villous atrophy, aphthoid ulcers over lymphoid aggregates, and macroscopic involvement of ileum. Although crypt atrophy, branching, and neutrophil infiltrate suggest UC, only the presence of granuloma discriminated CD from UC; the absence of granuloma, however, was not helpful. The final diagnosis of CD rested on a combination of clinical, endoscopic, and pathologic features. Indeterminate colitis was diagnosed whenever the above-mentioned endo-

scopic and histologic criteria did not clearly discriminate between CD and UC.[10] When a diagnosis of CD or indeterminate colitis was suggested, an upper gastrointestinal endoscopy and a small bowel barium enema were performed.

Scanning Technique

Briefly, 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 Five milliliters of hydroxyethyl starch was added and mixed gently. Sedimentation at room temperature was then allowed. The supernatant was collected and centrifuged for 5 minutes ($900g$). The cell pellet was collected, re-suspended in 5 mL of plasma, and carefully layered onto the upper part of the double Histopaque gradient (Ficoll-Hypaque) (density = 1.14), which was centrifuged at $700g$ for 20 minutes. The layer of granulocytes was collected with a sterile disposable 2-mL pipette and re-suspended in 5 mL of the cell-poor plasma. These autologous leukocytes were prepared according to a method published previously.[11] The labeling efficiency (mean and SD) was 56% ± 13%. The final mean dose administered was 185 ± 74 MBq, depending on the labeling efficiency. Scintigraphy was performed by using a GE Starport 400 AT gamma camera (Siemens) equipped with a low-energy medium-resolution collimator. Anterior and posterior images of the abdomen were obtained at the time of the injection by means of dynamic framing acquisition (1 frame/1 min/30 min) and successively in static preset time framing mode at 30, 60, 120, and 180 minutes. Only uptakes seen within 1 hour of the injection of labeled cells were judged as positive for inflammation; activity seen in the gut only after 2 or 3 hours was taken to be normal. Images were evaluated by one of the authors who was unaware of diagnosis and endoscopic data. The bowel was divided into 9 segments (jejunum, ileum, terminal ileum, cecum, ascending colon, transverse colon, descending
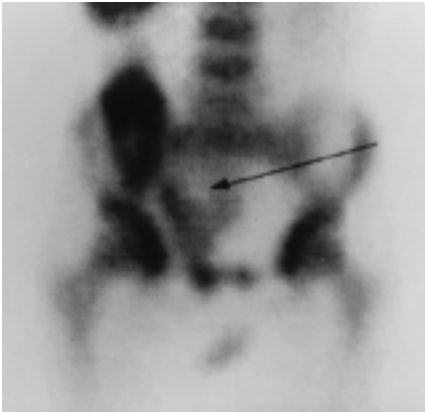
Fig 1. Scintigraphic spot view of lower abdomen 30 minutes after injection of autologous granulocytes labeled with HMPAO-Tc99m (total activity administered = 296 MBq). Uptake of medium grade (score = 2) in the distal ileum *(arrow)* and high grade (score = 3) in cecum and ascending colon. Pattern of distribution of labeled granulocytes suggests the diagnosis of CD, confirmed by ileo-colonoscopy and histologic examination.

Fig 2. Scintigraphic spot view of lower abdomen 30 minutes after injection of autologous granulocytes labeled with HMPAO-Tc99m (total activity administered = 240 MBq). Uptake of medium grade (score = 2) in transverse colon, descending colon, and rectum; uptake of elevated grade (score = 3) in sigmoid. Lumen reduction in involved colonic segments. Pattern of distribution of labeled granulocytes suggests the diagnosis of UC, confirmed by ileo-colonoscopy and histologic examination.

Fig 3. Scintigraphic spot view of lower abdomen 30 minutes and 4 hours after injection of autologous granulocytes labeled with HMPAO-Tc99m (total activity administered = 333 MBq). Early scan shows granulocyte uptake (score = 3) in left descending colon. Delayed scan in the same patient reveals atypical shifting of activity in right colon (cecum and ascending colon). This case illustrates a typical mismatch pattern of imaging, probably related to non-specific and elevated transit of hydrophilic HMPAO-Tc99m through the intestinal wall.

defined by endoscopy was graded as follows: 0 = no lesions; 1 = granularity, loss of vascular pattern, erythematous plaques; 2 = friability or small ulcers; and 3 = large or serpiginous ulcers, spontaneous bleeding. Parents gave informed written consent for performing diagnostic procedures. The latter had been approved by the ethical committee of the faculty.

RESULTS

A diagnosis of IBD was made in 21 patients (CD in 13, UC in 5, indeterminate colitis in 3): the Tc-WCS scan was positive in 16 and negative in 5 (Figs 1 and 2) (sensitivity, 76.2%). The 5 patients with IBD and negative Tc-WCS results had moderate intestinal inflammation: one had left-sided UC, one had pan-colonic indeterminate colitis, and 3 had CD (1 with distal ileitis, 1 with involvement of the right colon and rectosigmoid region, and 1 with involvement of the distal ileum and cecum). There was a significant correlation ($r = 0.70$, $P < .01$) between endoscopy and scintigraphy regarding the grading of intestinal inflammation; however, there was a poor correlation ($r = 0.36$, $P = NS$) between the 2 techniques regarding the number of involved segments: 16 patients with IBD showed additional diseased segments on endoscopy as compared with Tc-WCS (Table).

In 27 patients, IBD was ruled out. Nine patients with negative scintigraphy results had a diagnosis of non-specific colitis; endoscopy showed areas of hyperemia, granularity, and/or friability, whereas histologic examination revealed mild inflammatory changes in the lamina propria with lymphocytes and neutrophils. Findings of IBD (crypt abscesses or distortion, basal plasmacytosis, or lymphoid aggregates) were absent. In 6 cases lymphoid hyperplasia of the terminal ileum with post-bioptic friability was the only finding: no areas of inflammation were de-
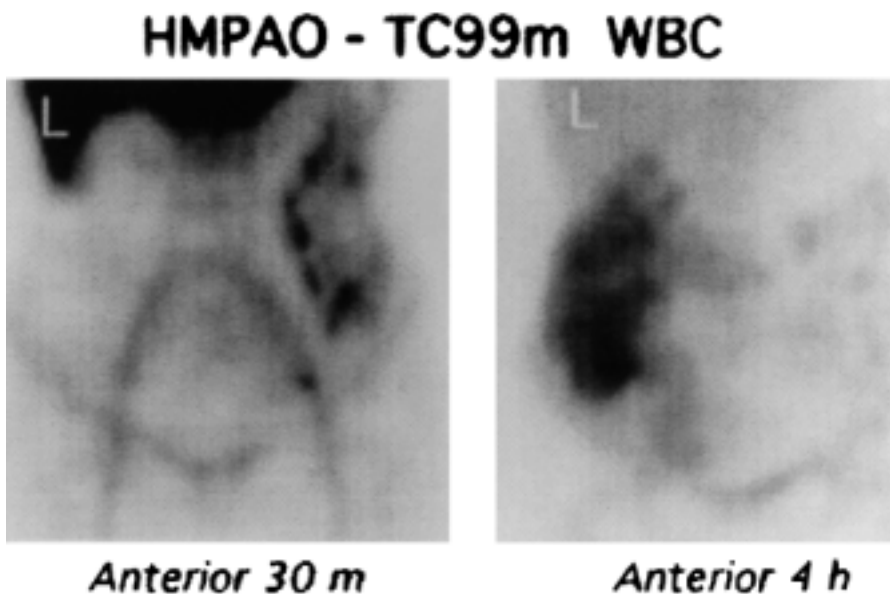
colon, sigmoid, and rectum), and the number of involved segments detected with endoscopy was compared with that evidenced by scintigraphy through linear regression analysis. Disease ac-

tivity assessed by Tc-WCS was graded as follows: 0 = no labeling; 1 = less than bone marrow; 2 = greater than bone marrow, less than liver; and 3 = greater than or equal to liver. Disease activity

tected by scintigraphy. Twelve patients were affected by spondyloarthropathy and colitis of mild-to-moderate degree: Tc-WCS results were positive in 6 of them. Diagnosis of spondyloarthropathy was based on the criteria defined by the European Spondyloarthropathy Study Group.[12] These patients are currently undergoing endoscopic follow-up to evaluate the evolution of intestinal inflammatory changes.

DISCUSSION

Our results indicate that endoscopy and histologic examination remain the gold standard procedures for detecting gut inflammation and discriminating among different inflammatory conditions in patients with suspected IBD. Previous studies have reported a concordance rate of 59% to 100% between Tc-WCS and endoscopy in patients with IBD.[11,13-15] Differences in patient populations studied and in completeness of gut investigation may explain the variation in the reported sensitivity of scintigraphy. The degree of disease activity can also affect accuracy of the Tc-WCS in detecting areas of gut inflammation: indeed, scintigraphy results tend to be negative in patients with mildly to moderately active disease.[16] Interestingly, an endoscopic score ranging from 1 to 2 was found in 5 patients with IBD and negative scintigraphy results, whereas an excellent correlation between activity of disease defined by scintigraphy and by endoscopy was detected in the patients with IBD who had the most active inflammatory changes.

A high rate of false-positive scans occurs if activity within the gut appearing on late images is considered positive (Fig 3). It has been suggested that by judging as positive only uptakes within 1 hour of re-injection, the rate of false-positive scans is significantly reduced, because late positive scans seem to be due to endoluminal appearance of labeled leukocytes via a transmucosal pathway.[17]

Our study also shows that Tc-WCS may not identify the exact number of inflamed segments of the gut, because endoscopy and histologic examination revealed additional involved segments in 16 of the patients with IBD. This can be due to several factors: mild disease in some segments of the gut, absence of landmarks on bowel images, or movements of the bowel during imaging.[18]

Results of scintigraphy were negative in 9 patients with non-specific colitis in whom endoscopy and histologic examination showed only moderate changes of the colonic mucosa: it is conceivable that these subjects had an episode of acute self-limited colitis from which they were recovering at the time of investigation.[19]

Interestingly, results of scintigraphy were positive in 6 of 12 patients with colitis and spondyloarthropathy; the latter is a clustering of diseases with axial involvement and/or peripheral inflammatory arthritis in which dactylitis and enthesopathy are also reported.[20] Previous studies in adults have revealed acute and/or chronic ileo-colonic inflammation in a high proportion of these subjects.[21] In our patients with spondyloarthropathy, endoscopy revealed patchy areas of hyperemia and/or granularity, as well as isolated erosions or small ulcerations. Histologic examination showed chronic inflammation with increased mixed lamina propria cellularity, basal lymphoid aggregates, and, less frequently, branching and/or atrophy of the crypts. The lower sensitivity of scintigraphy in patients with spondyloarthropathy than in those with IBD is likely due to a less severe degree of inflammation in the former subjects.[17]

In conclusion, although a positive labeled granulocyte scintigraphy result indicates the presence of an inflammatory condition of the gut, a negative result does not rule out an intestinal inflammation, particularly when the inflammatory lesions are mild or moderate. Future studies should be focused on other aspects of the clinical application of Tc-WCS, such as its usefulness to show remission or relapse of IBD and to influence treatment.

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50 Years Ago in The Journal of Pediatrics

CIRRHOSIS OF THE LIVER IN CHILDREN: A CLINICAL AND PATHOLOGICAL STUDY OF FORTY CASES

Keller PD, Nute WL. J Pediatr 1949;35:588-615

   Before this retrospective case study, childhood cirrhosis was thought only to exist as a rarity of nature and without much discussion as to its pathophysiology. Keller and Nute disagreed and demonstrated that childhood cirrhosis occurred commonly. They attempted to categorize this disease into more specific entities by doing a retrospective review of 40 cases of childhood cirrhosis, demonstrated by microscopic examination over a 26-year period at St Louis Children's Hospital. Seven types of childhood cirrhosis were categorized. "Obstructive biliary cirrhosis" was noted most often to occur with "congenital atresia of bile passages" (biliary atresia), inspissated bile (presumably cystic fibrosis), as well as other causes. "Diffuse nodular cirrhosis" was commonly associated with an infectious agent (eg, *Mycobacterium tuberculosis*, group A streptococci), although this form often had no discernible cause, which would lead us to consider possible metabolic or infectious diseases not yet known about 50 years ago. Other categories included cirrhosis secondary to erythroblastosis fetalis, prolonged circulatory congestion from congenital or rheumatic heart disease, toxin ingestion, and "hepatolenticular degeneration" characteristic of Wilson's disease.

   A seventh category was odd and was labeled as "unclassified juvenile cirrhosis." Seven patients with cirrhosis of an unknown cause were grouped together to represent a potpourri of diseases. Two patients had a "congenital anomaly of the bile ducts" but had normal extrahepatic trees. One wonders whether this entity represented intrahepatic sclerosing cholangitis or Alagille syndrome, although no other features consistent with these diseases were noted. Two patients with jaundice and *Bacillus coli (Escherichia coli?)* sepsis died in early infancy. Although the cirrhosis could be due to sepsis, one must consider galactosemia in light of the jaundice and Gram-negative sepsis. Two other patients had cirrhosis and unusual or recurrent infections, which could have been due to an underlying immunodeficiency, such as severe combined immunodeficiency syndrome. Finally, a young male patient developed hepatomegaly and died; his brother had died of a similar unknown disorder, which raises the specter of a storage or mitochondrial disease.

   This article is a sober reminder of our progress in the understanding of pediatric liver disease as we enter a new century. Although 50 years later we are able to diagnose causes of childhood cirrhosis more accurately (intrahepatic cholestasis syndrome, α_1-antitrypsin deficiency or other metabolic disease, cystic fibrosis, etc), our ability to administer effective treatment, outside of liver transplantation, has not advanced that much more than during the time of Keller and Nute. Perhaps in another 50 years, treatment with techniques such as gene therapy will help to alleviate the dire consequences of childhood cirrhosis that still exist today.

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