ELSEVIER

Netherlands Journal of Medicine 53 (1998) S19–S23

The Netherlands
JOURNAL OF
MEDICINE

Intestinal conditions mimicking Crohn's disease

G.N.J. Tytgat *

Academic Medical Center, Department of Gastroenterology and Hepatology, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

Keywords: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Differential diagnosis

1. Introduction

Many disorders may mimic Crohn's disease (CD). Erroneous diagnosis of CD may be responsible at least in part for the general impression that CD is being over-diagnosed. An atypical clinical course or an atypical therapeutic response should always lead to reassessment of the diagnosis in order not to overlook other medically or surgically treatable conditions. This chapter gives an overview of the conditions that may masquerade as CD, and provides clues as to how erroneous diagnosis can be prevented.

2. Idiopathic ileocolonic inflammatory bowel disease

Although both ulcerative colitis and CD may display characteristic histological features, none of the morphological changes is entirely specific. The three most characteristic features in CD, transmural inflammation, fissuring ulceration and granulomas, can be seen in many other conditions. An unknown percentage of patients with so-called CD of the colon presumably suffers from idiopathic ulcerative colitis. A more appropriate term to label those patients is 'indeterminate colitis' [1]. The well-known characteristic features of ulcerative colitis may disappear or blur after prior anti-inflammatory therapy. Not only the distal part of the colorectum may appear relatively spared after prior topical therapy but also in the more proximal colon the disease may become patchy. Not uncommonly caecal inflammation is present together with abnormalities in the distal colon suggesting CD if biopsies show an unequal degree of severity of the inflammatory infiltrate [2].

The percentage of so-called 'indeterminate colitis' varies from 10% to 20%. Out of 362 consecutive IBD patients carefully analysed in our unit, 23 (6%) were considered to suffer from indeterminate colitis. The majority of those patients ultimately do appear to suffer from ulcerative colitis [3]. Most do well after proctocolectomy and restorative ileo-anal pouch anastomosis [4], in contrast to patients with genuine CD who relapse sooner or later after such surgery.

One way to avoid confusion in IBD is to analyse precisely the inflammatory change at the very onset of the illness, both endoscopically and histologically, before any anti-inflammatory therapy has been given. Moreover, the histopathologist should refrain from applying nosological terminology instead of using the term 'indeterminate' when the spectrum of histopathological abnormalities is incomplete or lacks characteristic features [5–7].

A defunctioned rectum in patients with ulcerative colitis may show, in addition to mucosal inflammation, features which may erroneously suggest CD, such as florid lymphoid follicular hyperplasia, trans-

* Tel.: +31-20-5669111

PII: S0300-2977(98)00119-3

mural inflammation, fissures and granulomas [8]. Thus histology of the rectal stump in ulcerative colitis may lead to an erroneous diagnosis of CD, and the patient may subsequently be denied the advantage of a pelvic ileal reservoir.

Similar confusion appears to occur in patients with ileo-anal pouching. For unclear reasons pouchitis may appear patchy, and in particular such patchy ulceration may mimic CD and erroneously lead to consideration of the latter diagnosis. The cause of such patchiness is ill-understood, and may perhaps be related to the patchy distribution of lymphoid aggregates in the terminal ileum from which the pouch is constructed. Moreover, a diagnosis of CD cannot be made on pathological examination of the pelvic ileal reservoir alone [9]. The pathological hallmarks of CD, granulomas, transmural inflammation and fissures, may all be seen as a consequence of surgical manipulation and reservoir construction. Only florid characteristic Crohn lesions in the prepouch ileum allow the diagnosis of recurrent or recrudescent CD [10–12].

3. Infectious enterocolitides

A large spectrum of infectious conditions can truly mimic CD. These mimicking infections include bacterial, parasitic, viral and fungal causes [13]; tuberculosis obviously leads in this regard [14]. The classical appearance of ileocecal tuberculosis is a conical, shrunken contracted cecum with a narrow, ulcerated terminal ileum. The cecum may be pulled out from the right iliac fossa due to mesocolonic retraction. With more advanced stricturing of the ileocecal valve, dilatation of the terminal ileum occurs and excavating ulcerations, fissuring ulceration and fistulous tracts may develop. However, other conditions such as histoplasmosis [15], actinomycosis, etc., may also cause confusion. The chronic stage of amebiasis with discrete patchy, flat, whitish ulceration with normal intervening mucosa readily confuses the clinician. Also *Chlamydia* of the LVG type can mimic distal CD because of its characteristic predilection for the Houston valves in the rectum.

It may be difficult to differentiate infectious colitis, particularly in the resolving phase, from CD in colonic biopsy specimens. Well-formed granulomas are a feature of several infective colitides such as chlamydial infection, yersiniosis and tuberculosis. Yersiniosis is perhaps the most likely infectious enterocolitis to produce pathological confusion with CD. Helpful differentiating features are central necrosis within granulomas and the lack of transmural inflammation. Tuberculosis is favoured if there is florid coalescent granulomatous inflammation, extensive caseous necrosis and nodal granulomas in the absence of intramural granulomas [1]. Acid-fast bacilli are absent in half the cases.

4. Neoplastic disorders

A serious error is to confuse a malignant disorder, in particular of the ileocecal area, with CD. In particular lymphoma or carcinoma of the ileocecal area may occasionally mimic CD. Other more rare disorders are histiocytosis, carcinoid tumour, leiomyosarcoma, and diffuse peritoneal metastasis. Usually the error is based upon misinterpretation of X-ray studies. Upon reexamination it becomes apparent that the X-ray features are usually not characteristic for CD. In particular the classical triad in the terminal ileum is usually lacking, as is typical striking rigidity of the involved intestinal segment [16]. A further atypical therapeutic response should hasten radiological/endoscopic re-evaluation and/or even, although exceptionally, surgical exploration. Clinicians should realize that corticosteroids may improve symptoms in a variety of diseases including malignancy. When such improvement is short-lived, again re-evaluation is warranted.

Lymphoma of both B and T cell phenotype may cause large and fissuring ulceration which may readily mimic CD, especially when the lesions contain few neoplastic cells and innumerable eosinophils [1,17,18]. The endoscopic radiological diagnosis should be considered when large excavated ulcers are found in addition to conspicuous nodularity.

Adenocarcinoma of the ileum or colon, especially the diffusely infiltrating signet-ring cell mucinous carcinoma, may readily masquerade as CD [19].

Carcinoid tumours regularly occur in the terminal ileum and cecal area. Such tumours may result in nodular masses distorting the bowel, and sometimes resulting in sharply angulated loops as a conse-

quence of fibrotic mesenteric retraction [20]. Carcinoid tumours characteristically induce a marked desmoplastic reaction in the mesentery and bowel wall to produce inflammation and stenosis.

Images mimicking CD may also be seen in patients with diffuse abdominal metastasis involving the ileum and omentum. When due to breast cancer, such metastasis may become apparent many years after the initial disease presentation [20]. Because intraperitoneal tumour spreads along mesenteric planes along the pathways of flow of ascitic fluid, the terminal ileum is commonly involved when the tumour does spread to the small bowel.

Intestinal ganglioneuromatosis may also mimick CD [21].

Ileal carcinoid tumors may also simulate CD [22].

5. Pelvic inflammatory disease

Inflammation of adjacent pelvic organs may cause sufficient alteration of the radiological/endoscopic appearance of the small and/or large bowel as to simulate CD. Mimicking conditions are: periappendiceal inflammation [23], appendiceal abscess or mucocele, pelvic inflammatory disease due to adnexitis, ovarian cysts or tumours, ectopic pregnancy, Meckel's or cecal diverticulitis, etc.

The presence of granulomas in the appendix may readily suggest CD, but in general this condition seems to be unrelated to CD [24].

6. Endometriosis

Ileal or sigmoid endometriosis should be carefully considered in the differential diagnosis of CD in menstruating females who are nulliparous and have dysmenorrhoea, dyspareunia, dyschezia or menometrorrhagia [20,25]. The involved bowel may appear inflamed, indurated, thickened, strictured and angulated, with dense adhesions.

7. Vascular disorders — ischemic enterocolitis

Changes in the bowel secondary to vasculitis or thrombotic changes within the framework of hypercoagulation [26,27] may mimic CD, although often the terminal ileum is spared.

Ischemic damage may be confused with CD; this occurs especially during the ulcerative phase of the disease, in the case of non-resolving ischemic colitis or of late stricturing. Yet the history of abrupt onset of pain and bloody diarrhea, the unisegmental topography and the predilection for the splenic flexure area should readily point towards the correct diagnosis.

Ischemic damage superimposed on distal ulcerative colitis may cause disturbing appearances, suggesting CD because of the heterogeneity of the abnormalities. The frequency with which this occurs is unknown. We do not know how many of the patients with so-called CD developed after ulcerative proctitis/proctosigmoiditis are in fact due to superimposed ischemia instead of CD [28].

Of equal clinical importance is the development of CD in the elderly, often located in the diverticula-bearing sigmoid. One may speculate that perhaps the presence of diverticulosis predisposes to colitis by an effect on the microcirculation, ultimately leading to ischaemia [29,30]. The clinical and histological diagnosis of CD restricted to the sigmoid colon can be very difficult when diverticular disease is present. The three pathological hallmarks of CD – granulomas, transmural inflammation and fissuring ulceration – may all be seen as a result of sigmoid diverticular disease [1].

Isolated involvement of the sigmoid in CD is unusual and doubt should be cast on any such diagnosis in the presence of diverticular disease together with the absence of any other stigmata of CD.

Intestinal involvement in thrombotic thrombocytopenic purpura may mimic CD [31]. The intestinal changes are caused by microvascular occlusive disease causing irregular luminal narrowing because of edema and scattered areas of mucosal necrosis due to discrete infarction.

8. Diversion colitis

Although diversion colitis usually resembles ulcerative colitis, occasionally it may mimic CD, especially when features of aphthoid erosions, surrounded by a striking erythematous rim, predomi-

nate. Furthermore the presence of lymphoid follicular hyperplasia and mucosal granulomas may create a histological appearance reminiscent of CD [32].

9. Drug-associated colitis

Numerous medications have been associated with intestinal inflammatory disease including antibiotics, chemotherapeutic agents, colchicine, methyldopa, gold and non-steroidal anti-inflammatory drugs. Enteric coated drugs especially may cause damage to the small or large bowel, sufficiently severe to mimic CD.

Non-steroidal anti-inflammatory drugs may cause important ulcerations in the terminal ileum but also in the colon, resembling CD [33–35]. The so-called diaphragm disease may also occasionally mimic CD. The clinical picture is complicated by the fact that these drugs may exacerbate chronic inflammatory bowel disease [36]. Banarjee and Peters even tried to 'unify' the permeability changes seen in CD and in non-steroidal anti-inflammatory drug-induced enteritis [37]. Such mucosal permeability is considered to allow exposure and/or sensitization to luminal antigens with pro-inflammatory or immunogenic properties.

10. Mucosal prolapse-associated disorders

Solitary rectal ulcer syndrome is often confused with CD involving the rectum. The pathological changes are believed to arise from ischemia secondary to mucosal prolapse into the distal rectum and anal canal, which contract around the prolapsed mucosa and cause focal ischaemia.

11. Miscellaneous conditions

Various disorders have been described as occasionally simulating CD. Lipomatosis of the ileocaecal valve rarely mimics CD. Hypertrophic ileal Peyer's paches can occasionally be difficult to distinguish from early CD since both entities show mucosal coarsening and nodularity. Graft-versus-host disease may, although rarely, mimic CD.

12. Concluding remarks

Careful scrutiny in accepting the diagnosis of CD, especially when characteristic features are lacking or unclear, is mandatory. The need to adhere to the characteristic diagnostic criteria of CD is self-evident. Moreover an atypical therapeutic response should hasten endoscopic/histological or radiological re-evaluation and/or even laparoscopy/laparotomy in borderline cases. The differential diagnosis of CD is broad and must be considered at the time of the initial diagnosis. Infectious causes represent the broadest group of CD imitators. Most problematic are the conditions where macroscopic and microscopic features of ulcerative colitis and CD overlap, the so-called 'indeterminate colitis'. Such a dilemma often occurs in patients with severe disease where discriminating attributes are few and unreliable. Relative rectal sparing is an accepted feature of CD, but may be present in 5% of ulcerative colitis patients. Another misleading feature is discontinuous ulceration caused by variable inflammatory intensity in ulcerative colitis. Fissuring ulceration is an accepted feature of CD but is occasionally observed in severe ulcerative colitis. More specific for CD are submucosal widening with neuromatous hyperplasia, focal vasculitis, normal goblet cell appearance, and granulomas.

With the increasing usage of potent non-steroidal anti-inflammatory drugs the incidence of mucosal complications in the intestinal tract can be expected to rise. Omission of such drug exposure in the medication history and the lack of specific clinical endoscopic or histological features will obfuscate the correct diagnosis.

Neoplastic diseases are a less common source of confusion, but represent the most serious and potentially lethal group of ileocolonic masquerading diseases. The need for diagnostic re-evaluation should be stressed when response to treatment does not follow a predicted course.

References

[1] Shepherd NA. Pathological mimics of chronic inflammatory bowel disease. J Clin Pathol 1991;44:726–733.
[2] Moum B, Ekbom A, Vatn MH, et al. Inflammatory bowel disease: re-evaluation of the diagnosis in a prospective popu-

lation based study in south eastern Norway. Gut 1997;40:328–332.
[3] Wells AD, McMillan I, Price B, Ritchie JK, Nicholls RJ. Natural history of indeterminate colitis. Br J Surg 1991;78:179–181.
[4] Pezim ME, Pemberton JH, Beart RW Jr., et al. Outcome of 'indeterminant' colitis following ileal pouch-anal anastomosis. Dis Colon Rectum 1989;32:653–658.
[5] Theodossi A, Spiegelhalter DJ, Jass J, et al. Observer variation and discriminatory value of biopsy features in inflammatory bowel disease. Gut 1994;35:961–968.
[6] Bernstein CN. On making the diagnosis of ulcerative colitis. AJG 1997;92:1247–1252.
[7] Vasiliauskas EA, Plevy SE, Landers CJ, et al. Perinuclear antineutrophil cytoplasmic antibodies in patients with Crohn's disease define a clinical subgroup. Gastroenterology 1996;110:1810–1819.
[8] Warren BF, Shepherd NA, Bartolo DCC, Bradford JWB. Pathology of the defunctioned rectum in ulcerative colitis. Gut 1993;34:514–516.
[9] Snepherd NA. The pelvic ileal reservoir: pathology and pouchitis. Neth J Med 1990;37:S57–S64.
[10] Ilnyckyj A, Greenberg H, Bernstein CN. Eschericia coli 0157: H7 infection mimicking Crohn's disease. Gastroenterology 1997;112:995–999.
[11] Pasha TM, Leighton JA, Smilack JD, Heppell J, Colby TV, Kaufman L. Basidiobolomycosis: an unusual fungal infection mimicking inflammatory bowel disease. Gastroenterology 1997;112:250–254.
[12] Taniwaki S, Kataoka M, Tanaka H, Mizuno Y, Hirose M. Multiple ulcers of the ileum due to Cytomegalovirus infection in a patient who showed no evidence of an immunocompromised state. J Gastroenterol 1997;32:548–552.
[13] Lavy A, Militianu D, Eidelman S. Diseases of the intestine mimicking Crohn's disease. J Clin Gastroenterol 1992;15:17–23.
[14] Shah S, Thomas V, Mathan M, et al. Colonoscopic study of 50 patients with colonic tuberculosis. Gut 1992;33:347–351.
[15] Gonzalez Keelan C, Imbert M. Histoplasmosis of the colon simulating Crohn's disease in a patient with AIDS. Bol Assoc Med Puerto Rico (Spa) 1988;80:248–250.
[16] Tytgat GNJ, Reeders JWAJ. Crohn's disease. In: Gitnick G, editor. Inflammatory bowel disease: diagnosis and treatment. New York: Igaku Shoin, 1991: 159–190.
[17] Lebrun GP. Pitfalls in the radiological diagnosis of inflammatory bowel disease. Can J Gastroenterol 1990;4:317–323.
[18] McCullough JE, Kim CH, Banks PM. Mantle zone lymphoma of the colon simulating diffuse inflammatory bowel disease. Dig Dis Sci (Eng) 1992;37:934–938.
[19] Badley AD, MacCormick RE, Lebrun GP. Neoplastic imitators of small bowel Crohn's disease. Can J Gastroenterol 1992;6:77–83.
[20] Chang SF, Burrell MI, Belleza NA, Spiro HM. Borderlands in the diagnosis of regional enteritis. Trends in overdiagnosis and value of therapeutic trial. Gastrointest Radiol 1978;3:67–72.
[21] Webster GJM, Greenfield SM, Lock MR, Talbot IC, Vicary FR. Intestinal ganglioneuromatosis mimicking Crohn's disease of the small bowel. Gastroenterology 1996;3:121–126.
[22] Hsu EY, Feldman JM, Lichtenstein GR. Ileal carcinoid tumors simulating Crohn's disease: incidence among 176 consecutive cases of ileal carcinoid. AJG 1997;92:2062–2065.
[23] Huang JC, Appelman HD. Another look at chronic appendicitis resembling Crohn's disease. Modern Pathology 1996;9:975–981.
[24] Wettergren A, Munkholm P, Grupe Larsen L, et al. Granulomas of the appendix: is it Crohn's disease?. Scand J Gastroenterol 1991;26:961–964.
[25] Cappell MS, Friedman D, Mikhail N. Endometriosis of the terminal ileum simulating the clinical, roentgenographic, and surgical findings in Crohn's disease. Am J Gastroenterol 1991;86:1057–1062.
[26] Alving BM. The hypercoagulable states. Hospital Practice, February 15, 1993; 109–121.
[27] Sandler RS, Wurzelmann JI, Lyles CM. Oral contraceptive use and the risk of inflammatory bowel disease. Epidemiology 1992;3:374–378.
[28] Langevin S, Menard DB, Haddad H, Beaudry R, Poisson J, Devroede G. Idiopathic ulcerative proctitis may be the initial manifestation of Crohn's disease. J Clin Gastroenterol 1992;15:199–204.
[29] Peppercorn MA. Drug-responsive chronic segmental colitis associated with diverticula: a clinical syndrome in the elderly. Am J Gastroenterol 1992;87:609–612.
[30] Shepherd NA. Diverticular disease and chronic idiopathic inflammatory bowel disease: associations and masquerades. Gut 1996;38:801–802.
[31] Winwood PJ, Iredale JP, Williamson PJ, Lesna M, Leohry CA. Thrombotic thrombocytopenic purpura mimicking acute small bowel Crohn's disease. Gut 1992;33:857–859.
[32] Ma CK, Gottlieb C, Haas PA. Diversion colitis: a clinicopathological study of 21 cases. Hum Pathol 1990;21:429–436.
[33] Gibson GR, Whitacre EB, Ricotti CA. Colitis induced by nonsteroidal anti-inflammatory drugs. Report of four cases and review of the literature. Arch Intern Med 1992;152:625–632.
[34] Schönberger B, Nickl S, Schweiger F. Colonic ulcerations associated with diclofenac treatment. Can J Gastroenterol 1992;6:15–20.
[35] Hudson N, Wilkinson MJ, Swannel AJ, Steele RJ, Hawkey CJ. Ileo-caecal ulceration associated with the use of diclofenac slow release. Aliment Pharmacol Ther 1993;7:197–200.
[36] Bjarnason I, Hayllar J, MacPherson J, Russell AS. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. Gastroenterology 1993;104:1832–1847.
[37] Banerjee AK, Peters TJ. Crohn's disease and NSAID enteropathy a unifying model. Gastroenterology 1990;99:1190–1192.