# Crohn's disease, ulcerative colitis or indeterminate colitis - how important is it to differentiate ?

K. Geboes

Department of Pathology, University Hospital Leuven, Belgium.

## Abstract

**In most patients coming to the general practitioner or specialist with a history of bloody diarrhoea, bacteria or drugs are the most likely causative agents and it will be possible to make a diagnosis fairly easily. Because of differences in treatment, ulcerative colitis (UC) and Crohn's disease (CD) must however seriously be considered especially in younger patients, with severe symptoms and whenever the history is prolonged. A variety of colitides may indeed be clinically confused with UC and CD. Pathological mimics that should not be missed include infectious diseases such as Campylobacter colitis, yersiniosis, amoebiasis and others ; drug-induced diseases (due to nonsteroidal antiinflammatory drugs...) ; diverticular disease-associated colitis ; intestinal endometriosis ; intestinal vasculitis and Behçet's disease and iatrogenic conditions such as graft-versus-host-disease and radiation colitis. In most situations a precise diagnosis of these conditions should be possible when all data are available. The term "indeterminate colitis" is used, when a diagnosis of chronic idiopathic inflammatory bowel disease (IBD) is suggested, but the differential diagnosis between UC and CD can not be solved. This occurs in approximately 5% of all patients with IBD. Diagnostic problems can occur in acute fulminant colitis, acute prolonged colitis, chronic relapsing disease and pouchitis. Indeterminate colitis is essentially a temporary diagnosis. Surgical and medical treatment of these patients can be difficult. When surgical treatment is indicated, the type of surgery must be seriously considered. The clinical course of patients with indeterminate colitis is usually more severe when compared with classical UC and these patients require often more severe medical treatment. Diagnostic problems can also arise in longstanding IBD, either UC and CD. Relapse of symptoms can be due to intercurrent infection (CMV is one of the candidates). Medical treatment can influence the microscopic features and induce a discontinuous inflammation in UC, reminiscent of CD. In cases of doubt, the original biopsies should be reviewed to ascertain the diagnosis, and orient treatment.** (Acta gastroenterol. belg., **2001**, 64, **197-200**).

## Introduction

A variety of colitides may be clinically confused with either ulcerative colitis (UC) or Crohn's disease (CD) and furthermore the differential diagnosis between UC and CD is not always clear. Differential diagnostic problems can arise in different clinical situations. These include 1) acute (prolonged) colitis ; 2) acute fulminant colitis ; 3) chronic relapsing disease and 4) relapse of established chronic inflammatory bowel disease (IBD).

When it is impossible to solve the differential diagnostic problem, a diagnosis of "indeterminate colitis" can be proposed. Originally, the term "colitis indeterminate" was proposed for the small group of unclassified cases in which there was difficulty in distinguishing CD from UC in the excised specimen (1). Most of the cases were in fulminant disease and the classification was essentially temporary before a final diagnosis was established. Later "indeterminate colitis" has also been applied as a temporary classification to cases where a definite diagnosis was not possible with endoscopic samples. In these cases it was not only a problem of distinguishing between CD and UC but also of discrimination between infective type colitis and IBD. It might however have been more appropriate to use the term "indeterminate colitis" only for surgical specimens and the term "unclassifiable" for endoscopical samples, especially for those obtained early after onset.

For the solution of the differential diagnostic problem, a proper knowledge of the clinical history is essential. It is for instance important to know if the colitis occurs in an immunocompetent or an immunocompromised patient and it is essential to know if the patient is or has been taking drugs.

The present review is divided into two parts. The first part discusses acute or acute prolonged conditions which can mimic IBD but for which a definite diagnosis should be possible on the basis of clinical data, routine investigations and microscopy. In the second part we discuss situations where the differential diagnosis between Crohn's disease and ulcerative colitis can not be solved easily.

## Pathological mimics of IBD

*Infectious diseases*

The differential diagnosis with infectious or drug-related diseases is important both in fulminant colitis and in acute colitis because treatment and outcome are entirely different and proper treatment is essential. In these clinical circumstances the differential diagnosis includes diffuse forms of colitis similar to ulcerative colitis which can occur as fulminant diseases due to C. difficile or antibiotic-associated colitis and a variety of infectious diseases such as salmonellosis, shigellosis, Escherichia coli colitis, Campylobacter colitis, amoebiasis and Schistosomiasis and toxic colitis due to potent antineoplastic agents (2,3). Histopathology can help to solve many diagnostic problems, especially in the non-

Corresponding author : Geboes K., Department of Pathology, University Hospital St. Rafaël, Minderbroedersstraat 12, 3000 Leuven, Belgium.

fulminant cases. The microscopic features which can be used for the diagnosis of IBD are however often not present in the early stage of these diseases (4).

Some infectious or drug-related diseases have a more indolent course and may mimic CD or UC. In some of these cases histopathology may even lead to confusion. Entamoeba histolytica may present as an indolent illness with apparent relapses and remissions over the course of weeks or months. It is thus essential to distinguish rapidly these conditions since inappropriate use of corticosteroids or other drugs or delay in administering an antibiotic is highly undesirable. Misdiagnosis of amoebiasis or tuberculosis with inappropriate use of corticosteroids can lead to serious complications.

*Drug-related diseases*

A medication history is indispensable in the investigation of patients with diarrhoea. A variety of drugs given either topically or systematically can cause colitis, ileocolitis or proctitis.

Some of these drugs may mimic IBD more than others.

Non steroidal antiinflammatory drug (NSAID)-induced colitis is a significant clinical problem. Usually the patients are elderly. Symptoms can develop after 2 months to 5 years. They include abdominal complaints or blood in the stool. Night sweats and weight loss are not uncommon. Anemia and elevated ESR can be present. NSAIDs can induce small bowel and colonic lesions. In the small bowel discrete ulcers, perforation and diaphragm-like strictures have been reported (5). In the colon, ulcers, perforation, or fistulas related to diverticulosis and exacerbations of colitis can appear.

The proposed mechanism for the small bowel is direct topical irritation facilitated by enterohepatic circulation of active NSAID metabolites. For the colon, the mechanism relates probably to decreased mucosal prostaglandins and a decreased production of COX-2 in underlying colitis (6).

Diclofenac, mefenamic acid and indomethacin are frequent offenders, especially the sustained release preparations. Patients present with abdominal cramps, diarrhea or constipation and laboratory tests reveal iron deficiency and positive fecal occult blood test. Colitis induced by NSAIDs can present as :

- nonspecific colitis.
- de novo colitis.
- reactivation of quiescent inflammatory bowel disease.
- hypersensitivity reaction : allergic colitis (with eosinophils) (7).
- constipation with perforation (stercoral ulcer) (8, 9).
- non-specific ulceration : caecal or ileocaecal ulceration has been described following the administration of oxyphenbutazone, slow-release diclofenac and ibuprofen while more distal ulcers have been ascribed to naproxen in association with acetyl salicylic acid.

The differential diagnosis may be difficult, especially because rheumatic diseases may be associated with genuine IBD or with a Crohn-like nonspecific form of chronic intestinal inflammation. Other drugs that can cause colitis are penicillamine and gold salts. Oral contraceptives and cocaine rather mimic ischemic colitis (10,11).

*Diverticular disease-associated colitis*

A clinical syndrome of chronic colitis, localized to the sigmoid colon and occurring in association with diverticular disease has been recognized repeatedly. Mucosal biopsies of this condition show features of idiopathic inflammatory bowel disease including a distorted crypt architecture and basal plasmacytosis. Colonic mucosa proximal and distal is usually normal.

Overall the inflammatory features can mimic either UC or CD. Crohn's disease-like features can include fat wrapping, fissures or sinuses and the presence of granulomas. The relation of the inflammatory reaction with genuine IBD is unclear. Diverticular disease-associated chronic colitis may precede the onset of conventional ulcerative proctitis and colitis (3 out of a series of 23) or Crohn's disease (2 out of a series of 25) in a minority of the cases (12,13).

*Endometriosis*

The prevalence of intestinal endometriosis varies between 3 and 37% of all endometrioses. The anatomic distribution within the gastrointestinal tract is as follows : rectosigmoid in 50 to 90%, rectovaginal septum in 10 to 20%, caecum in 2 to 5%, appendix in 3 to 18% and small intestine in 2 to 16%. Small intestinal involvement is nearly always confined to the terminal ileum. Most commonly, intestinal endometriosis is asymptomatic. Ileal endometriosis however may present with acute, chronic or recurrent distal small bowel obstruction, in the same way as Crohn's ileitis. These symptoms occur mostly only when the endometriosis is deep and invasive. The most common complaint is midabdominal, rather than right lower quadrant, crampy pain. Diarrhea or constipation, nausea and vomiting, fever, anorexia, weight loss and even hematochezia may be present. Sometimes a relationship with the menstrual cycles may be recognized. In patients with intestinal endometriosis presenting with obstructive complaints, the diagnostic features are mostly the same as obstruction due to Crohn's disease (14-16).

*Miscellaneous*

A variety of other conditions can mimic IBD. Lesions similar to CD have been reported in ileal and colonic biopsies from patients with reactive arthritis and ankylosing spondylitis (17). Less common pathological mimics include different forms of vasculitis, Behçet's disease, iatrogenic conditions such as graft-versus-host-disease and radiation colitis and cancer.

## Differential diagnosis Crohn's disease — ulcerative colitis : Indeterminate colitis

*Terminology*

Difficulties in diagnosis due to overlapping in the pathological features of Crohn's disease and ulcerative colitis have first been studied in surgical specimens. The term "colitis indeterminate" was proposed for the small group of unclassified cases in which there was difficulty in distinguishing Crohn's disease from ulcerative colitis (and even infectious diseases) in the excised specimen. The difficulty was due to the fact that features of both conditions were present in the same specimen. Most of the cases were in fulminant disease and the classification was essentially temporary before a final diagnosis was established. Later "indeterminate colitis" has also been applied as a temporary classification to cases where a definite diagnosis was not possible with endoscopic samples because of absence of diagnostic features discriminating between CD and UC.

The morphologic features of "indeterminate colitis" diagnosed on endoscopic samples include : 1) lesions which are suggestive or diagnostic for IBD such as (minimal) architectural distorsion ; 2) inflammatory features (usually transmucosal inflammation) which do not allow a firm distinction between ulcerative colitis and Crohn's disease because of their patchy nature ; and 3) absence of small bowel involvement.

*Diagnostic problems*

When the diagnostic possibilities discussed thus far have been ruled out as far as possible, the condition can be classified as IBD, either UC or CD. The differential diagnosis between CD and UC can be made in most cases on cumulative clinical, radiological, endoscopical, biochemical and pathological evidence. The many distinguishing histopathological features have been extensively described and their diagnostic value has been tested by cluster analysis and observer reliability studies. However, owing to the variable occurrence of even the most reliable features, diagnostic difficulties still occur. A confident diagnosis could not be made in 10-20% of cases in older series. Colonoscopy and an improved knowledge of the evolution of the histopathological features in time have increased the diagnostic yield but diagnostic difficulties have not disappeared completely. In a prospective study of IBD from 20 European centers, 5% of all patients with IBD were classified as having indeterminate colitis (18). Diagnostic difficulties will occur in different clinical situations including early onset disease, atypical clinical presentations, and following medical or surgical therapy.

In the initial period shortly after onset of the disease it may be difficult to reach a definite diagnosis because biopsies are less characteristic due to the absence of pathognomonic features. The differential diagnostic problem in this situation is firstly the distinction between infective colitis and IBD but the distinction between CD and UC can also be very difficult. The development of mucosal distorsion, one of the major features for the diagnosis of IBD, usually takes 2 months. Basal plasmacytosis, another feature with high predictive value, is found in only 38% of patients with symptoms for less than 2 weeks and had disappeared after one year in half of IBD patients who had no relapse (4). While one or more of the characteristic features are present in about 80% of the biopsies after 3 to 8 weeks, they are not present in about 20% of the cases and even in a larger group of patients in the first 3 weeks after clinical onset.

Patients with Crohn's disease may present with an ulcerative colitis-like pattern both on endoscopy and biopsy. The presence of ileal lesions can be of major importance for this differential diagnostic problem (19).

Microscopic colitis is clinically and morphologically different from IBD. Yet in some cases, collagenous or lymphocytic colitis can precede (or follow) genuine UC (or CD) (20).

Diagnostic difficulties may appear or reappear in patients with longstanding disease presenting with a relapse. Histopathological and endoscopical features may change or even disappear because of the relapsing nature of IBD and variability with time and treatment (21). Discontinuous inflammation, which has long been considered a good criterium for CD, has been shown to be common in resolving and long-standing UC. The proximal to distal gradient of inflammation which means that inflammation is more pronounced in the proximal colon and terminal ileum in CD, can also change (22). Review of previous biopsies is essential in such a situation.

Cytomegalovirus can be associated with an initial attack of IBD, usually UC but it can also be responsible for a clinical relapse of UC. It may further complicate pouchitis and immunomodulatory treatment (23, 24).

Major diagnostic problems can be observed also in operated patients presenting with severe pouchitis or perianal disease. Granulomas and transmural inflammation, which are considered to be diagnostic for CD can be observed in pouchitis, following surgery for ulcerative colitis. Review of the original surgical specimen and of any other material available is essential before considering to change a diagnosis of ulcerative colitis into Crohn's disease (25).

A diagnosis of gastrointestinal vasculitis of Behçet's disease can be impossible when only endoscopic (mucosal) biopsies are available, because the blood vessels in the mucosa are mainly capillaries.

*Evolution*

While only a minority of patients have a diagnosis of indeterminate colitis it is important to realize that such a diagnosis has certain consequences.

A diagnosis of indeterminate colitis means that the patient has a form of chronic idiopathic inflammatory bowel disease and that other conditions, especially infections are less likely or indeed excluded. Relapse of symptoms due to complications such as CMV infection are equally excluded.

A diagnosis of indeterminate colitis means that the patient needs to be followed carefully in order to reach a more definite diagnosis. This can be obtained during follow-up (development of small intestinal involvement), by examination of gastric biopsies and the identification of focal gastritis, by using serological markers such as pANCA (perinuclear anti-neutrophil cytoplasmic antibodies) and ASCA (anti-saccharomyces cerevisiae antibodies) (26). In a prospective multicenter study involving 83 patients, a final diagnosis was reached in 22 patients after a mean follow-up of 7.5 months. 13/22 patients had Crohn's disease and 9 ulcerative colitis.

The clinical course of patients with indeterminate colitis is at least as severe as that of patients with UC. Studies of clinical characteristics of indeterminate colitis, when compared with UC revealed that patients with indeterminate colitis have younger age at onset, more extensive disease and a more severe clinical course (severity of the first attack, frequency of clinical remissions and surgery). The risk of colorectal cancer is similar to that for UC or even somewhat enhanced (18).

Immunomodulatory agents are used more frequently because of steroid dependency, resistance or toxicity (27).

When surgery is needed, different options have to be considered. It might for instance be considered to postpone the construction of an ileoanal anastomosis. The course of indeterminate colitis is indeed more refractory than ulcerative colitis with regard to relapse, incidence of colectomy and pouch failure after ileal pouch-anal anastomosis.

## Conclusion

"Indeterminate colitis" is a temporary diagnosis for a patient presenting with symptoms which are suggestive of genuine IBD. The biopsy contains features which indicate IBD such as architectural distorsion but the differential diagnosis between UC and CD cannot be solved. In acute cases, infections must be ruled out. A diagnosis of indeterminate colitis must not be a substitute diagnosis for lack of knowledge or fear of decision. The clinical course of patients with indeterminate colitis is usually more severe when compared with classical UC. Medical and surgical treatment must be considered carefully because of possible complications and uncertain natural evolution, although basically, treatment is comparable with routine treatment for IBD.

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