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Review

Indeterminate colitis - definition, diagnosis, characteristics and management

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SUMMARY

The distinction between ulcerative colitis (UC) and Crohn's disease (CD) affecting the colon is of paramount importance in inflammatory bowel disease (IBD) patients. However, this differentiation cannot always be definitively made, and these cases are usually characterized as cases of "indeterminate colitis". The Working Party of the World Congress of Gastroenterology in Montreal recommended the term IBD-type unclassified (IBDU) for IBD cases when characteristic features of UC and CD are absent, and the term indeterminate colitis (IC) only when colectomy is performed and a definitive diagnosis cannot be reached. Most cases of IC eventually evolve into definite CD or UC, but a percentage of patients remain with a diagnosis of IC for many years without ever showing typical features of either disease, suggesting that IC might represent a separate subgroup of IBD. There are no widely accepted histological criteria or findings for the diagnosis of IC; therefore it remains a diagnosis of exclusion. The use of ancillary tests, like serological markers and wireless capsule endoscopy, as an aid in the diagnosis of IC is still under investigation. Medical treatment of IC is similar to UC and CD. Ileal pouch-anal anastomosis surgery can be performed in IC patients with rates of pouch failure and functional outcome similar to UC patients, but with an increased risk of postoperative complications.

Key words: Indeterminate colitis, Crohn's disease, Ulcerative colitis, Ileal pouch-anal anastomosis

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INTRODUCTION

The distinction between ulcerative and Crohn's colitis is based on clinical, radiological, endoscopic and pathological findings. Unfortunately, in a subgroup of inflammatory bowel disease patients, despite an extensive diagnostic work-up, this distinction cannot be definitively made because of the presence of overlapping features between the two diseases. These cases are usually characterized as cases of indeterminate colitis, although no strictly defined criteria have been established. Despite the fact that three decades have already passed since the introduction of this term into medical practice, there is still considerable confusion regarding the definition, diagnosis, evolution and management of indeterminate colitis.

DEFINITION

Price introduced the term indeterminate colitis in 1978 in order to describe cases of severe or fulminant colitis after colectomy was performed and thorough pathological examination of the surgical specimen failed to make a distinction between UC and Crohn's colitis.[1] The extensive use of colonoscopy with endoscopic mucosal biopsies in the following years led to a broader use of the

Abbreviations:

UC=Ulcerative colitis
CD=Crohn's disease
IBD=Inflammatory bowel disease
IC=Indeterminate colitis
IBDU=Inflammatory bowel disease-type unclassified
ESPGHAN=European Society for Paediatric Gastroenterology, Hepatology and Nutrition
GI=gastrointestinal
FEG=focally enhanced gastritis
WCE=wireless capsule endoscopy
pANCA=perinuclear antineutrophilic cytoplasmic antibodies
ASCA=anti-Saccharomyces Cerevisiae antibodies
IPAA=Ileal pouch-anal anastomosis

term by gastroenterologists, pathologists and surgeons in IBD patients whenever the differentiation between UC and CD was not possible. As a consequence, IC expanded from a purely histological diagnosis made after colectomy, into a clinicopathological entity creating considerable confusion as the same term was used to describe a variety of conditions.

In 2005, the Working Party of the World Congress of Gastroenterology in Montreal in an attempt to put an end to the existing confusion reintroduced the original definition by Price and recommended that[2]:

- the term "Indeterminate colitis" should be used only when colectomy has been performed and the pathologists are unable to make a definite diagnosis of either UC or CD after careful examination of the surgical specimen
- the term "IBD-type unclassified or IBDU" should be used in all other IBD cases when no colectomy is performed and a distinction between UC and CD cannot be made despite an extensive diagnostic work-up (Table 1).

In contrast, the IBD Working Group for the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in the Porto Criteria recommended the use of the term IC for children and adolescences with IBD, when a full endoscopic examination including biopsies of the upper GI, colon and terminal ileum, in addition to a small bowel follow-through or enteroclysis, cannot establish a diagnosis of either UC or CD with certainty.[3]

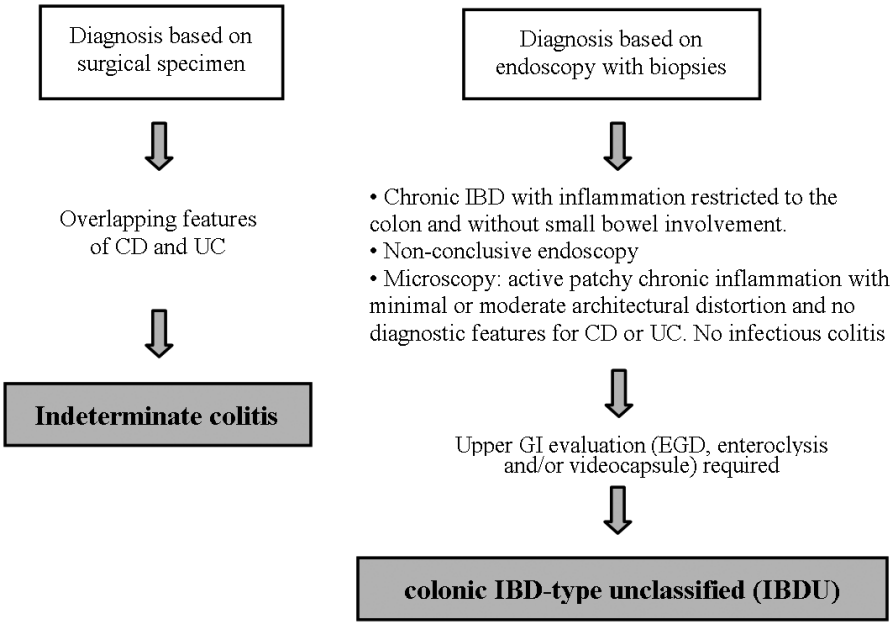
Recently, an International Organization of Inflammatory Bowel Diseases (IOIBD) working party proposed another classification for IBD patients with an unclear diagnosis. They recommended the term IBD-unclassified (IBDU), as suggested by the Montreal Working Party, for patients that clearly have IBD colitis but definitive features of UC or CD are absent and proposed the term "colitis of uncertain type or etiology" for colectomy specimens, thus abandoning the term IC.[4]

DIAGNOSIS

Macroscopic and microscopic findings in IC

Macroscopically, the large intestine in IC cases diagnosed after colectomy, according to the original definition by Price, demonstrates an extensive severe colitis which can take two main patterns; either a severe continuous disease throughout the colon often with relative rectal sparing or a discontinuous involvement of the colon with extensive intermittent ulceration. More than 50% of the mucosal surface is affected and the lesions are more severe at the right and transverse colon.[5]Microscopically, there is severe and extensive ulceration with non specific transmural inflammation, but also intervening mucosal islands with normal epithelium and a well preserved population of gob-

Table 1. Montreal 2005 Working Party recommendations for the definition of IC[2]



let cells. The presence of multiple V shaped fissures in areas of severe inflammation, which are covered by inflammatory cells and accompanied by loss of smooth muscle cells (myocytolysis) and vascular congestion in surrounding tissue is a common finding. Some authors have also described "knife like" fissures in IC colectomy specimens. Both aforementioned types of fissures differ from the fissures typically found in CD patients, which are serpiginous and covered by granulomatous tissue but no type can be considered specific or pathognomonic for either CD or IC. In IC well defined transmural epithelioid granulomas and transmural lymphoid aggregates are absent and their presence is strongly suggestive of CD. In contrast, mucosal microgranulomas, especially those adjacent to inflamed and distorted crypts, and the presence of scattered monocytes in the muscularis propia can be seen in IC cases.[5,6]

In summary, there are no widely accepted histological criteria or findings for the diagnosis of IC. It is a diagnosis of exclusion and is mainly based on the absence of characteristic features of UC or CD.

Confounding factors leading to a false diagnosis of IC

Several factors regarding either the macro- or microscopic findings in IBD patients may be confusing, leading to a false diagnosis of IC.

UC patients with left sided colitis may show patchy, mild, isolated inflammation near the appendiceal orifice or at the cecum (cecal patch) giving the false impression of a "skip lesion", a characteristic of CD.[7-9] Rarely, in UC the transition area from the inflamed to normal mucosa may be irregular and patchy creating also a similar confusion. Local treatment with enemas or suppositories may change the macroscopic appearance of UC giving the misleading impression of rectal sparing. In addition, medical treatment may also alter the microscopic features of UC, thus leading to the characterization of colitis as indeterminate.[5]

In fulminant UC, the proximal and particularly the transverse colon is more severely affected creating an impression of discontinuous colonic involvement or rectal sparing, characteristic features of Crohn's colitis. In the quiescent, inactive phase of IBD only minimal histological changes can be found making an accurate differential diagnosis difficult and most pathologists refrain from offering a specific diagnosis of either UC or CD.[6] Characteristic histological findings useful in the differentiation between the two diseases may also be absent in their very early stages, especially in children. Pediatric UC patients frequently show relative rectal sparing or microscopically patchy disease at their initial presentation.[10]

Interobserver variability in the pathological diagnosis is another confounding factor as shown by studies that demonstrated significant disagreement between participating pathologists[11]. In a study by Theodossi et al.[12] there was agreement on the final diagnosis between 10 GI specialized pathologists in only 65-76% of the cases presented to them.

Finally, various other conditions such as diverticular colitis, NSAID induced colitis, radiation, ischemic or infectious colitis especially in its fulminant form can be misdiagnosed as IC.[6]

The role of upper GI endoscopy

Upper GI endoscopy as part of the evaluation of patients with IBD colitis is recommended by both the Montreal Working Party and the ESPGHAN.[2,3] Macroscopic findings such as aphthoid erosions, atypical or linear ulcers, Kerckring's folds notching, stenosis and fistulas in the upper GI track point towards a diagnosis of CD. The presence of granulomas in upper GI biopsies varies in different studies between 9-30%, and is consistent with a diagnosis of CD after the exclusion of H.pylori infection and granulomatous disorders like tuberculosis, foreign body reactions, sarcoidosis, vasculitis or malignancy (lymphoma).[13]

Although upper GI involvement in UC is extremely rare in adults, cases of diffuse duodenitis have been reported.[14] In contrast, upper GI inflammation seems to be relatively common in pediatric UC patients.[15,16] Focally enhanced gastritis (FEG) is defined as foci of small collections of inflammatory cells, predominately lymphocytes and histiocytes, surrounding a small group of gastric glands or foveolae and separated by intervening normal mucosa. Focally enhanced gastritis with or without granulomas has been demonstrated in up to 76% of H.pylori-negative CD patients and was initially considered to be highly specific of CD with a positive predictive value of 94%.[17] However, subsequent studies questioned its clinical significance as a diagnostic marker of CD or IBD in general[18]. Although FEG is relatively common in CD, it can also be found in 20% of pediatric UC patients and case-controlled studies showed a prevalence of up to 19% in non-IBD patients.[19,20] In conclusion, FEG is more frequently observed in CD but does not reliably distinguish between CD and UC and its role in the reclassification of IC cases remains to be determined.

The role of wireless capsule endoscopy

Wireless capsule endoscopy (WCE) is being increasingly used in the evaluation of patients with IBD. WCE

can identify small bowel mucosal lesions that cannot be detected with conventional imagining modalities and may allow the reclassification of some IC cases as Crohn's disease. In a recent study of Maunoury et al,[21] 30 IBDU patients underwent WCE and in 5 of them multiple mucosal ulcerations or erosions were found in the small bowel, thus leading to their reclassification as CD cases. However, the absence of small bowel mucosal lesions did not definitively exclude a diagnosis of CD, as 5 of the remaining 25 patients with no visible lesions in WCE were diagnosed as definite CD cases during follow up. In another report of 13 IC cases, WCE led to the reclassification of 5 (38%) as CD due to the presence of small bowel lesions.[22]

It is worth mentioning though, that mild lesions in the small intestine (mucosal erosions) have been observed in a small percentage (15%) of healthy volunteers[23] and currently there are no established criteria for the diagnosis of Crohn's disease based on WCE findings. Nevertheless, it seems that WCE will be proved a valuable tool in the evaluation of patients with IC and will allow the reclassification of a percentage of them as CD cases.

The role of serological markers

The measurement of serological markers has been used as a method of differentiating between UC and CD. Two kinds of antibodies have been extensively studied for this purpose: perinuclear antineutrophil cytoplasmic antibodies (pANCA) and antibodies against the cell wall of Saccharomyces Cerevisiae (ASCA). pANCA are found in 60-80% of patients with UC while ASCA are found in 40-60% of CD patients.[24-26] The value of these serological markers is limited by the fact that some UC patients will also test positive for ASCA and likewise a percentage of CD patients may be pANCA positive.

Joosens et al,[27] in a large multicenter prospective study of six years duration, studied the value of these antibodies in the classification of 97 IC patients, diagnosed on the basis of colonic mucosal biopsies. 80% of the ASCA (+) and pANCA (-) patients eventually developed definite CD while 63.6% of ASCA (-) and pANCA (+) patients developed UC. It is interesting that almost half of the patients (47/97) were negative for both markers and the vast majority of them (40/47) remained with a diagnosis of IC until the end of the study, a finding that the authors concluded, supports the hypothesis that IC may be a separate subgroup of IBD (Table 2). In a follow up study, 87 serum samples of the 97 original patients were examined for the presence of two novel serological markers, anti-I2 (antibodies against Pseudomonas Fluorescens) and anti-Ompc IgA antibodies (antibodies against E.Coli's outer membrane porin C) reported to be found in almost 50% of CD patients.[28,29] 23 of the 87 patients (26.4%) tested negative for all four serological markers and 74% of them (17/23) remained with a diagnosis of IC until the end of the study.[30] A sensitivity and specificity of 72% and 63% respectively for the pANCA(-)/ASCA(-) pattern in the diagnosis of IC has been reported in a recent but relatively small study.[31] In the population based "IBSEN" study, however, no substantial number of IC patients with the pattern of pANCA(-)/ASCA(-) was found.[32]

At present, no immunogenetic markers have been significantly correlated to IC. According to Vermeire et al,[33] NOD2/CARD15 mutations are as common in IC patients as in control patients.

These data suggest that for the time being the serological diagnosis of IC is not feasible as no marker has been positively associated with it. The combined use of the current serological markers may be of value in the exclusion diagnosis of IC but more data from larger studies are needed before any firm conclusion is reached.

EPIDEMIOLOGY, EVOLUTION AND CHARACTERISTICS OF IC

Prospective population-based studies from Scandinavia have demonstrated that the average annual incidence of IC ranges from 1.6 to 2.4/100.000.[32,34] Indeterminate colitis is diagnosed in 9-20% of IBD patients after colectomy.[1,35-38] In pediatric patients an initial diagnosis of IC is reported in 4%-24% of IBD cases.[39-41] Initially, IC was considered a temporary diagnosis or a provisional descriptive term because the majority of these cases eventually evolved into typical cases of UC or CD. In fact, epidemiological studies report that 50-80% of adult IC patients and

Table 2. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of the pANCA(-)/ASCA(-) combination in IC patients

Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
40/66 (60.6%)	24/31 (77.4%)	40/47 (85.1%)	24/50 (58%)

Data from reference 27

64% of pediatric IC patients are reclassified as definite UC (33%-72.5%) or CD (17-27.5%) during follow-up.[32,42,43] Overall, most cases turn out to be diagnosed as UC over time. Nevertheless, it is obvious that a substantial number of patients remain with a diagnosis of IC for many years without ever showing typical features of either disease and may represent a separate subgroup of IBD.

The clinical characteristics of IC are usually examined in comparison to those of UC. IC patients tend to have more extensive disease and a more severe clinical course, in terms of frequency of exacerbations, use of immunosuppressives, severity of initial attack and rates of urgent colectomy due to fulminant disease, compared to UC patients. In the original study by Price, 90% of patients diagnosed as IC had undergone urgent colectomy due to fulminant disease, in contrast to about 30% of patients in whom UC or CD was confidently diagnosed. IC shows an equal sex distribution -in contrast to UC where there is a male predominance- and the mean age at onset is 36-39 years.[35,37,44-46]

According to Rudolph et al[38] the extraintestinal manifestations in IC are almost equally common as in UC and CD. Approximately one-third (31%) of the IC patients in their study exhibited extraintestinal manifestations, although no data on the exact type were reported. Similarly, a recent study in a large cohort of paediatric IBD patients demonstrated that the incidence of extraintestinal manifestations is independent of the type of IBD, including IC.[47]

Based on the fact that longstanding UC and Crohn's colitis carry an increased risk of large bowel cancer it is logical to assume that IC patients are also at increased risk of carcinogenesis. Unfortunately, the currently published data are insufficient to draw any firm conclusions since most studies have excluded IC patients and included only those with established UC. In a nationwide retrospective study in the Netherlands, in 149 patients with a confirmed diagnosis of IBD associated colorectal cancer, only 1 case of IC was identified.[48] Stewenius et al[49] reported a higher incidence of colorectal cancer in IC compared to UC patients (IC: 2.4 vs UC: 1.4 per 1000 person-years).

MANAGEMENT

Medical Therapy

Medical treatment commonly used in UC and CD is also being used in IC, but up to now no prospective studies regarding medical therapy in IC have been published. In a retrospective study which included 20 patients with severe, active, medically refractory IC who received 1 to 16 infusions of infliximab, 16 patients responded to infliximab but 8 of them were later on diagnosed as CD. However, those patients who remained with a diagnosis of IC had similar long term response as those with a subsequent diagnosis of CD.[50] Other studies on the use of infliximab, tacrolimus and 6-thioguanines have either included a very small number of IC cases or both IC and UC patients making difficult the determination of the efficacy in the IC group only.[51-54]

Surgical management

Total proctocolectomy and ileal pouch-anal anastomosis (IPAA) has become the surgical treatment of choice for a large number of patients with UC. It offers complete relief of symptoms in patients not responding to medical treatment or experiencing serious side effects and eliminates the danger of carcinogenesis, while preserving normal sphincter function and defecation. It is however a major operation with possible significant complications, requiring careful patient selection and preoperative counseling. IPAA is generally not recommended in CD due to high rates of pouch failure (30-50%), leading to the excision of the pouch with significant loss of small intestinal length and serious postoperative complications like pelvic infections and fistula formation.

Controversial data exist regarding the role of IPAA in patients with IC. Earlier studies reported increased rates of pouch failure in IC patients in comparison to UC patients,[55-58] while more recent studies show more favorable results with rates similar between the two groups.[38,45,59-61] In a study from Mayo Clinic, in 82 patients with IC followed up for 10 years, pouch failure and other complication rates were significantly higher in IC compared to UC.[62] However, during follow up a significant percentage (15%) of IC patients were diagnosed as CD and if these cases are excluded from the original cohort then failure rates are similar. In a recent study of Hahnloser et al,[63] IPAA was a reliable surgical procedure for 76 IC patients, with excellent clinical and functional outcomes and pouch failure, pouchitis and fistula rates almost similar to UC patients, in 20 years of follow up. Abscess rates, however, were substantially increased in IC patients. In the largest published study up to date by Delaney et al,[61] pouch failure rates were similar in IC and UC but complications like pelvic abscesses and fistulas were increased in IC patients. Increased rates of postoperative complications in IC patients after IPAA were reported and in several other studies, reinforcing the view that these patients are at increased risk of complications like pelvic sepsis and fistula formation[38,55-57,59,60] (Table 3). Interestingly, in a retrospective study by Hui et al,[64] in 28 IC patients who underwent IPAA those positive for at least one serologic

Table 3. Pouch failure and complication rates in IC after IPAA.

	I.C patients (n)	Pouch failure (IC vs UC)	Complications	
Delaney et al[61]	115	3.4% vs 3.5%	Pelvic abscess Perianal fistula Fistula	8.7% IC vs 2.2% UC 7% IC vs 2.6% UC 3.5% IC vs 1.7% UC
Dayton et al45	79	2.5% vs 1.2%	Pouch fistula Pouchitis	2.5% IC vs 1.6% UC 34.2% IC vs 25% UC
Rudolph et al[38]	35	0% vs 6%	Pouch fistula All complications	11.4% IC vs 0% UC 26% IC vs 10% UC
Yu et al[62]	82	27% vs 11%	Pelvic sepsis Pouch fistula	17% IC vs 7% UC 31% IC vs 9% UC
Marcello et al57	53	12.5% vs 2.3%	Pouchitis Perianal complications	25% IC vs 21% UC 44% IC vs 23% UC
McIntyre et al[58]	71	19% vs 8%	Pouchitis similar in both IC and UC (33%)	
Hansloser et al[63]	76	12% vs 6%	Pouchitis Abscess	78% IC vs 70% UC 29% IC vs 16% UC

marker (ASCA, pANCA, Ompc, or I2) had significantly higher risk of pouchitis compared to those negative for any marker (63% vs 17%). Increased serum levels of TNF-alpha in IC patients with perianal complications after IPAA have been reported and this finding may support the use of anti-TNF alpha antibodies in such patients.[65] Despite the high risk of postoperative complications, the functional outcome of IPAA, in terms of number of daily bowel movements and episodes of incontinence, does not seem to differ between UC and IC.[45,58,61]

In conclusion, the current opinion is that IPAA is not contraindicated in IC, as it seems that pouch failure rates and functional outcome are similar to UC patients. In contrast, postoperative complications like serious pelvic infections and fistulas are more commonly observed in IC patients after IPAA. It is important to ensure that every patient with IC scheduled to undergo this operation must be fully informed for the high risk of complications and that every possible effort is made preoperatively to exclude the possibility of a missed diagnosis of CD.

CONCLUSIONS

Although most cases of indeterminate colitis eventually "evolve" into definite UC or CD, a substantial number of patients remain with a diagnosis of IC. Thus, while initially IC was considered a temporary diagnosis or a provisional descriptive term, it may actually represent a separate subgroup of IBD, although the lack of a specific diagnostic test or marker makes it a diagnosis of exclusion. The distinction of IC from Crohn's colitis is of great importance, because IC patients can be submitted to IPAA with success rates similar to UC patients and only a slightly increased risk of postoperative complications. IPAA on the other hand, is generally contraindicated in CD due to high rates of pouch failure and possible dangerous complications. The strict and precise use of the terms "indeterminate colitis" and "IBD-type unclassified (IBDU)" according to the Montreal Working Party recommendations, by physicians and pathologists may stop the confusion regarding the definition of IC and will permit the undertaking of standardized prospective studies with well defined inclusion criteria which should shed more light on the clinical characteristics, course, prognosis and management of the disease.

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