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Inflammatory bowel disease unclassified

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Abstract: Objective: Inflammatory bowel diseases (IBDs) are idiopathic, chronic, and inflammatory intestinal disorders. The two main types, ulcerative colitis (UC) and Crohn's disease (CD), sometimes mimic each other and are not readily distinguishable. The purpose of this study was to present a series of hospitalized cases, which could not initially be classified as a subtype of IBD, and to try to note roles of the terms indeterminate colitis (IC) and inflammatory bowel disease unclassified (IBDU) when such a dilemma arises. Methods: Medical records of 477 patients hospitalized due to IBD, during the period of January 2002 to April 2009, were retrospectively studied in the present paper. All available previous biopsies from endoscopies of these patients were reanalyzed. Results: Twenty-seven of 477 IBD patients (5.7%) had been initially diagnosed as having IBDU. Of them, 23 received colonoscopy and histological examinations in our hospital. A total of 90% (9/10) and 66.7% (4/6) of patients, respectively, had a positive finding via wireless capsule endoscopy (CE) and double-balloon enteroscopy (DBE). The barium-swallow or small bowel follow-through (SBFT) was performed on 11 patients. Positive changes were observed under computer tomographic (CT) scanning in 89.5% (17/19) of patients. Reasonable treatment strategies were employed for all patients. Conclusions: Our data indicate that IBDU accounts for 5.7% of initial diagnoses of IBD. The definition of IBDU is valuable in clinical practice. For those who had no clear clinical, endoscopic, histological, or other features affording a diagnosis of either UC or CD, IBDU could be used parenthetically.

Key words: Inflammatory bowel disease unclassified, Ulcerative colitis, Crohn's disease, Subtype, Diagnosis
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1 Introduction

Disease classification is important, especially in the context of tailoring clinical therapy. Though many scanning procedures make the diagnosis of inflammatory bowel disease (IBD) earlier and easier, the variations and lack of endoscopic-histological correlation sometimes are difficult for decision-making. The terms indeterminate colitis (IC) and colonic inflammatory bowel disease unclassified (IBDU) were coined in an attempt to classify these entities more effectively (Guindi and Riddell, 2004). Moreover, it provides benefits for both the decision-making of the correct treatment and the prognosis and understanding of disease course. To date, few reports have documented this specific kind of disease in Chinese patients; therefore, we herein retrospectively examined IBDU patient admitted to our hospital.

2 Materials and methods

During the period of January 1, 2002 and April 15, 2009, 477 consecutive in-patients with clinically- and pathologically-confirmed IBD were studied. A diagnosis of IBDU was considered when the morphology included overlapping features of ulcerative colitis (UC) and Crohn's disease (CD) regarded as inconsistent with either diagnosis (Branco *et al.*, 2009), and all such cases were confirmed after discussions by pathologists, endoscopists, and clinicians. In this series, 261 cases were classified as UC, 189 cases as CD, and 27 cases as IBDU. The notes of

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these 27 patients were carefully reviewed, with 22 as potential diagnosis of UC, and five favoring diagnosis of CD.

3 Results

3.1 Clinical features

Eleven men and sixteen women with median age at onset of IBDU 40.22 years (range 13–75 years) were identified. Abdominal pain (21), diarrhea (11), fever (7), bloody stool (4), vomiting (4), abdominal distention (3), and constipation (1) were the main symptoms. During the course, three subjects also had extra-gastrointestinal manifestations (EIM), including arthralgia (3), erythema nodosun (3), mucocutaneous abscess (3), ulcer (2), and rectum-vagina fistula (1). Two subjects had a colonectomy performed and one underwent an appendectomy before diagnosis.

Among the subjects with IBDU, seven involved both large bowel and small bowel at onset. Three (11.1%) had pancolonic involvement at the time of diagnosis. Four (14.8%) had primarily left-sided and right-sided diseases, respectively. Fourteen (51.8%) had small bowel involvement including seven in ileum and seven showing a distribution from the jejunum to ileum. The remaining two (7.4%) had extensive diseases.

3.2 Modalities for diagnosis

Colonoscopy, upper gastrointestinal (GI) endoscopy, capsule endoscopy (CE), biopsies, serological findings, radiography, and other scanning procedures are the common modalities for separation of UC and CD. All 27 subjects underwent an endoscopy and surgical pathology study, including 23 cases conducted in our hospital. Segmental lesions of irregular or villous surface, pseudovillous appearance, backwash ileitis, and absence of lymphoid aggregates were observed in 22 potential UC subjects. Diffuse or pancolonic (rectal sparing) CD-like patchiness such as superficial fissuring ulceration or confluent linear ulcers, cobblestone sign, focal cryptitis, epithelioid granulomas, and crypt abscesses, with normal adjacent mucosa, was seen in five subjects. Only one specimen exhibited mild dysplasia. No crypt atrophy was microscopically observed.

Nine of ten subjects who accepted CE examination had multiple erosions and ulcerations in the small intestine, with only one having a negative finding. Three subjects showed luminal narrowing of the small bowel on CE studies. Gastroscopy was conducted in ten subjects, and superficial gastritis was found in the biopsies from seven subjects. Scattered slit-like fissures in the small bowel were found in three out of six subjects who underwent double-balloon enteroscopy (DBE). The small bowel follow-through (SBFT) indicated the presence of aphthous ulcers or liner ulcers, stricture exacerbation, chronic shortening with tubular narrowing, and loss of haustration in 72.7% (8/11) subjects. Wall-thickening, pneumocolon, inflammatory mass, extraluminal findings, etc. were mainly observed in 89.5% (17/19) of the subjects under computer tomographic (CT) examination.

In the full blood count, anemia was the common change which occurred in eighteen subjects. Seven subjects had high white blood count (WBC). Concentration of platelets was high in six subjects. The level of C-reactive protein (CRP) was elevated in ten subjects. Eight cases had hypoalbuminemia.

3.3 Therapy and short-time outcome

A total of 21 subjects were treated with 5-aminosalicyclic acid (5-ASA). Eight subjects received steroids. All of the subjects' symptoms went into remission and did well with conventional therapy. No subject experienced adverse events during 5-ASA treatment.

4 Discussion

Since it was first proposed, the definition of IC/IBDU has changed over the years, and it has been universally accepted in pediatrics (Romano *et al*., 2008). Children with IC/IBDU have an early age of disease onset, which rapidly progresses to pancolitis (Carvalho *et al*., 2006). For adult patients, however, the debates around the term 'IC/IBDU' have been never-ending. Some experts observed that the great majority of IC/IBDU patients (>80%) had long-term functional results identical to those of patients with chronic UC (Tekkis *et al*., 2005). A longitudinal study showed that 13% of subjects will remain unclassified

after one year of follow-up (Notteghem *et al*., 1993). In comparison, more experts consider that IC/IBDU is an interim or preliminary appellation rather than a distinctive clinical entity of IBD because less than 5% maintained that diagnosis over time (Burakoff, 2004; Talbot, 2005).

The term IC/IBDU is widely used with a relatively lower threshold without uniformed criterion by pathologists, surgeons and clinicians. And the incidence of use of the term IC/IBDU is thought to be increasing despite the meaning indicated by the Montreal Working Party (Satsangi *et al*., 2006), with referral bias being a possible reason. Some experts are afraid that construction of an ileoanal pouch in those patients who were initially misdiagnosed as IC/IBDU may result in significant morbidity and pouch failure when the ultimate diagnosis is CD (Marcello *et al*., 1997). Thus, caution is warranted before using this term.

Due to the poorly established histopathological criteria of IC/IBDU, more researches are required to sufficiently describe this sort of disease and to improve our recognition, while reducing the taxonomic dilemma and indiscriminate use in clinic practice. To date, few cases labeled with IC/IBDU in adults have been reported.

The proportion of IC/IBDU cases among all IBD cases in our series, 5.7%, is equal to that reported by the previous studies (Yantiss and Odze, 2006). In our clinical setting, patients should undergo a combined upper endoscopy, colonoscopy, and biopsy and/or imaging modalities as the initial diagnostic procedure. The diagnosis of IC/IBDU relies on the presence of the following (Geboes *et al*., 2008): clear evidence of IBD but insufficient evidence to make a definite diagnosis of either UC or CD; clinical and macroscopic features of either CD or UC, without clear histology; inflammatory colitis containing features on macroscopic and microscopic evaluations of the colon that are consistent with both CD and UC; colitis without an identifiable cause and with clinical features of both UC and CD; mucosal ulcerative colitis with histological features of CD such as skip lesions, transmural inflammation, granulomata or mucin depletion, but no clinical or radiological evidence of CD; and colitis for which endoscopic, histologic, and radiologic criteria fail to discriminate between UC and CD of the colon.

Colonoscopy with multiple biopsy specimens from different sites is the first-line procedure used to make a precise diagnosis. Pathologists play an important role in the diagnosis of IBD. Clinicians should offer detailed evidence for easier diagnosis. Upper gastroscopy, CE, CT, magnetic resonance imaging (MRI), and other ancillary tests are recommended. They sometimes provide important information in diagnostically-difficult cases. Technological advances, based on genetic markers and a better knowledge of immune responses, have allowed better characterization (Geboes *et al*., 2008). Patients with IC/IBDU are often diagnosed as anti-neutrophil cytoplasmic antibody (ANCA)-negative and anti-*Saccharomyces* cerevisiae antibody (ASCA)-negative. *Pseudomonas fluorescens*-associated sequence I2 (anti-I2), the *Bacteroides caccae* TonB-linked outer membrane protein OmpW, ASCA, and fecal calprotectin, a new promising marker for intestinal inflammation, are non-invasive, sensitive, and specific tools used for early identification of IBD (Ashorn *et al*., 2009). It has been reported that anti-synthetic mannoside antibodies (AΣMA) revealed the heterogeneity of the anti-oligomannose antibody response in CD subjects and increased the sensitivity of CD diagnosis when combined with ASCA (Vandewalle-El Khoury *et al*., 2008). Suzuki *et al*. (2008) found that anti-porcine pancreatic amylase (PPA) antibodies combined with ASCA/anti-I2 may be useful for differentiating CD from UC. There are also reports that infectious gastroenteritis was a close relative of IBD, but the value of serologic markers in distinguishing IBD remains controversial (Arai, 2010; Dotan, 2010; Dubinsky, 2010). Serum C-reactive protein (CRP) correlates well with other measures of biological activity but not as well with clinical activity (Moscandrew and Loftus, 2009). It was reported that CE is superior to IBD serological markers in identifying small bowel CD in IC subjects (Leighton *et al*., 2007). In a large prospective study, only 50% of subjects with an initial diagnosis of IC and positive serology testing were ultimately reclassified as either UC or CD (Joossens *et al*., 2002).

To our knowledge, literature rarely refers to the management of IBDU alone. Treatment philosophies now attempt to alter the natural history of the disease and prevent long-term complications. Except for adequate food supplement, a broad range of therapies

are available, including aminosalicylates, corticosteroids, immunomodulators, biologics, and surgery, though it is not entirely clear how well IBDU clinically responds to them. Whether it is a coined term or a real entity, to establish such a 'grey zone' is a philosophy of management. It is convenient and effective for doctors to pay more attention to the patients with overlapping histological features of CD and UC. For the sake of tailoring the pharmacological treatment especially prior to surgical intervention, CD- or UC-oriented IBDU is advised. This may be important when considering a subsequent restorative proctectomy (Wells *et al*., 1991), but it can easily cause doctors to be less likely to explore the disease. IBDU-favoring CD may be treated according to the scheme of CD, while IBDU-favoring UC may be treated as similar to UC. Aminosalicylates are widely used as a basal medicine for treating mild to moderate IBDs in China. Sulfasalazine gradually trends to be substituted by 5-ASA products because of the side effects, while corticosteroids remain a conventional therapy. It is well-known that early corticosteroid administration improves the healing rate of peristomal pyoderma gangrenosum in IBD. We have less experience in using immunomodulators to treat IBD, but an Asian study showed that azathioprine is effective in corticosteroid-dependent Asian IBD subjects (Thia *et al*., 2011). It was also reported that mycophenolate mofetil appeared safe, well tolerated, and efficacious for both short- and long-term therapies, without the need for dose escalation (Tan and Lawrance, 2009). Bastida *et al*. (2010) reported that thiopurine immunomodulators alone, or with other treatments, have a positive and long-lasting impact on the health-related quality of life (HRQoL) of IBD patients. Biological agents offer therapeutic options as rescue therapy after failing to respond to steroids. Though infliximab does not appear to increase rates of emergent surgery or multistep procedures in patients undergoing treatment for IC (Bordeianou *et al*., 2010), it was shown to be effective in improving clinical symptoms (Gornet *et al*., 2003). General opinion is that anti-tumour necrosis factor-alpha (TNF-α) medications, such as infliximab and adalimumab, are more efficacious in the treatment of CD than in the treatment of UC. Furthermore, the safety profile associated with infections and certain malignancies is under discussion (Ngo *et al*., 2010). Pearce and Lawrance (2007) proposed that careful patient selection may improve infliximab's efficacy. Clinical remission appears greater after induction with three infliximab doses in CD subjects. Clinical efficacy is suggested for UC/IBDU.

A prospective evaluation of the long-term outcome revealed that patients with IBDU and IC can undergo ileal pouch-anal anastomosis and expect a long-term outcome equivalent to patients with UC (Murrell *et al*., 2009).

Leukocytapheresis is a technology in development since 1999. Data show that granulocyte/monocyte adsorption (GMA; Adacolumn, JIMRO, Takasaki, Japan) in patients with steroid-dependent or steroid-refractory IBD is associated with striking efficacy and tapering or discontinuation of steroids, whereas in steroid-naive patients, GMA spared patients from steroids (Hanai, 2008). It is an additional remission option for chronically active IBD patients (Lindberg *et al*., 2010).

With better use of standard therapies, approximately 50% of resection surgery was "potentially avoidable" (Gapasin *et al*., 2010). Ileorectal anastomosis (IRA) in patients with UC gives an acceptable quality of life and functional outcome as compared to ileal pouch-anal anastomosis (IPAA) (da Luz Moreira *et al*., 2010). Although the chance of an adverse outcome increases after IPAA on patients with UC/IC, such as risks of perineal complications and pouch loss, the operation continues to be performed on these patients (Pezim *et al*., 1989; Dayton *et al*., 2002). The reason that patients with IC should not be precluded from having IPAA surgery is that they are more likely to develop CD (Gramlich *et al*., 2003). It was reported that ileoproctostomy is preferred over ileoanal pull-through in patients with IC (Bodzin *et al*., 1995).

The problem of too many IC/IBDU diagnoses in clinic practice is mainly due to the low threshold for this label, which then covers all cases of diagnostic uncertainty (Stange *et al*., 2006). It is especially apposite in cases of acute fulminant disease of the colorectum (Martland and Shepherd, 2007). To avoid the indiscriminate use of IC/IBDU, and to conquer the diagnostic obstacles, a combination of clinical presentation, endoscopic appearance, radiology, histology, surgical findings, and even serologic testing is advocated. The following points should be kept in mind: (1) Not all pathologically-ambiguous

specimens are diagnosed as IC. Histological interpretation should not be relied upon too greatly. Although good pathologic materials make diagnosis much easier, it is quite difficult to obtain well-known histology especially during onset of the disease. We should think twice before making a diagnosis for those in a first attack because microscopic features and the features characteristic of disease activity vary with time and treatment. (2) Several circumstances, such as microscopic colitis, diverticulitis, and diversion colitis, may also show IBD-like changes (Yantiss and Odze, 2006) on occasion. (3) Failure to recognize the morphologic variants of CD and UC and accept any of the "hardcore" features as definitive evidence of the two entities may lead to a potentially erroneous diagnosis of IC (Yantiss and Odze, 2006). For instance, granulomas are not always CD-related. (4) Multiple deep biopsies may provide effective information that will assist in improving the accuracy of diagnoses. For CD diagnosis, specimen with submucosa or muscularis propria is beneficial for the judgment during diagnosis. (5) It is commonly believed that IC does not involve the upper gastrointestinal (GI) tract; therefore, for those with suspected IBD or new-onset IBDU, routine upper-endoscopy and CE at initial presentation facilitate the diagnosis. (6) To improve the compliance rate (especially in maintenance), medicine is required to be fast-acting, easily used, inexpensive, effective, and safe. (7) Surveillance and reassessment are necessary for benefit to the subjects, even for those who have a reasonable diagnosis of CD or UC. It might be of more benefit to reexamine the patients within one year initially, and then at follow-up intervals of a maximum 2.5 years. Because many cases presumed as IBDU are seen early in the disease course (Guindi and Riddell, 2004; Talbot, 2005), 50%–80% of them can be reclassified as definite UC or CD with time (Geboes and de Hertogh, 2003). (8) Initial therapy has an influence on the further diagnostic testing and long-term prognosis (permanent ostomy vs. ileoanal pouch anastomosis). Inappropriateness of early management of newly diagnosed IBD may increase potential risk of adverse events. The presentation under endoscopy, radiology and pathology will change after treatment (medication or surgery). Therefore, one must be cautious during selection of therapy. Careful patient selection may improve response rates to medicine in IBD. Moreover, a series problem should be solved including phenotypes, epidemiology, location, behavior, severity, the nature history (remission or relapse), extraintestinal manifestations of the disease, a guideline for macroscopic and microscopic criteria, and management, as well as prognosis. Guidelines and diagnostic route charts for routine and special cases are expected.

Further studies, such as the head-to-head comparison between patients with CD or UC and those clinical features inclining towards the diagnosis of CD or UC, would be very meaningful to improve our recognize of IBD.

The drawback of our review is that the true nature history and outcome of IBDU are not known, as some of the long-term follow-up data are unavailable. It was reported that approximately 80% of IBDU cases were ultimately reclassified as either UC or CD within eight years of follow-up (Meucci *et al*., 1999). There is now good evidence that the majority of IBDU diagnoses are likely to behave as unusual examples of UC, with only 10%–40% of them ultimately proving to be CD (Yantiss and Odze, 2006).

In conclusion, our clinical observations suggest that IC/IBDU is a clinicopathological entity. IC/IBDU should be diagnosed on the basis of a constellation of clinical, endoscopic, histological, radiological, and biochemical findings. Specimens in conjunction with appropriate techniques can avoid delays in diagnosis as time-dependent reappraisal of the lesions within weeks, and follow-up is needed to allow a more precise diagnosis.

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