



Change in the diagnosis of inflammatory bowel disease: a hospital-based cohort study from Korea

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Background/Aims: Accurately diagnosing inflammatory bowel disease (IBD) remains a challenge, but is crucial for providing proper management for affected patients. The aim of the present study was to evaluate the frequency of change in diagnosis in Korean patients who were referred to our institution with a diagnosis of IBD. **Methods:** We enrolled 1,444 patients diagnosed with ulcerative colitis (UC) and 1,452 diagnosed with Crohn's disease (CD), who had been referred to the Asan Medical Center between January 2010 and December 2014. These patients were assessed and subsequently classified as having UC, CD, indeterminate colitis, possible IBD, or non-IBD. **Results:** During a median follow-up of 15.9 months, 400 of the 2,896 patients (13.8%) analyzed in this study experienced a change in diagnosis. A change in diagnosis from UC to CD, or vice-versa, was made in 24 of 1,444 patients (1.7%) and 23 of 1,452 patients (1.6%), respectively. A change to a non-IBD diagnosis was the most common modification; 7.5% (108 of 1444) and 12.7% (184 of 1452) of the patients with a referral diagnosis of UC and CD, respectively, were reclassified as having non-IBD. Among the 292 patients who were ultimately determined not to have IBD, 135 (55 UC and 80 CD cases) had received IBD-related medication. **Conclusions:** There are diagnostic uncertainties and difficulties in relation to IBD. Therefore, precise assessment and systematic follow-up are essential in the management of this condition. (**Intest Res 2016;14:258-263**)

Key Words: Crohn disease; Ulcerative colitis; Diagnosis; Inflammatory bowel diseases

INTRODUCTION

The exact diagnosis of IBD is crucial for patient safety and treatment and for the interpretation of epidemiological data.¹⁻³ However, diagnosis and sub-classification of IBD are sometimes not obvious even after clinical, endoscopic,

radiologic, macroscopic, and histologic evaluations.^{4,5} In practice, 3%–10% of patients with colonic inflammation have overlapping clinical and pathological features, making it difficult to distinguish between UC and CD, and resulting in the diagnosis of indeterminate colitis (IC).⁶⁻⁸ Furthermore, a change in diagnosis was reported after reevaluation during follow-up in 10% of patients originally diagnosed with UC or CD in the Inflammatory Bowel South-Eastern Norway (IBSEN) cohort.^{1,3,9,10} This finding highlights not only the heterogeneity of these diseases, but also the difficulty of ascertaining their correct diagnoses.

The incidence of IBD has been rapidly increasing in Asian countries, and physicians have become more aware of and more knowledgeable about this condition.^{11,12} However, to the best of our knowledge, no studies to date have systemati-

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cally evaluated the difficulties and pitfalls in diagnosing IBD with its rapid shifts in incidence in this region. The aim of the present study was to address this issue by evaluating the frequency with which alterations in the diagnosis of IBD occur in Korea, and to create a list of diseases mimicking this disorder.

METHODS

1. Patients

The medical records of 2,896 patients who were referred to Asan Medical Center with a diagnosis of IBD between January 2010 and December 2014 were collected from the Asan IBD registry.^{13,14} These patients were referred from private clinics, local hospitals, and university hospitals.

2. Study Design

Data regarding clinical information, including radiologic imaging, endoscopy, and histological reports from the referring physicians were reviewed. The diagnoses originally provided by the referring physicians or patients were either changed or confirmed according to assessments by eight expert gastroenterologists (H.S.L., S.H.P., D.H.Y., K.J.K., B.D.Y., J.S.B., S.J.M., and S.K.Y.). The patients were subsequently reclassified as having UC, CD, IC, possible IBD, or non-IBD. To minimize misjudgment, a diagnosis was changed only when two or more reviewers agreed, and any discrepancies regarding reclassification were resolved by consensus. The diagnosis of CD and UC was determined based on conventional clinical, radiologic, endoscopic, and histopathologic

criteria.^{12,15-19} The diagnostic criteria for the classification of IC were clear evidence of IBD and divergent or inconclusive endoscopy and histopathology results for a diagnosis of definite UC or CD.⁸ The term “possible IBD” was used in cases where the quality of the diagnostic examination was not satisfactory or the findings were ambiguous.^{1,3} The most probable final diagnosis and the time lag from the initial diagnosis of IBD to reclassification of the diagnosis as non-IBD were investigated for each patient who was ultimately deemed not to have IBD (non-IBD). The follow-up duration was calculated from the day of the first visit to our center to the last follow-up visit.

3. Statistical Analysis

Continuous variables were expressed as medians with ranges; discrete data were tabulated as numbers and percentages. Statistical evaluations were performed using the statistical software package SPSS 21.0 for Windows (IBM SPSS, ver. 21.0; IBM Corp., Armonk, NY, USA). The institutional review board of Asan Medical Center approved this retrospective study (IRB No. 2016-0021).

RESULTS

1. Baseline Characteristics

The baseline characteristics of the patients are listed in Table 1. Of the 2,896 patients included in the current study, 57.4% (829 of 1,444) and 70.0% (1,017 of 1,452) were men with alleged UC and CD, respectively. The median age at ini-

Table 1. Baseline Characteristics of the Study Patients

Variable	Referred as UC (n=1,444)	Referred as CD (n=1,452)
Men	829 (57.4)	1017 (70.0)
Age at initial diagnosis, yr	36 (9–80)	22 (9–77)
Median interval from diagnosis to referral, mo	11.0 (0.1–1380.3)	5.8 (0.1–1381.1)
Institution of first diagnosis		
Private clinics	471 (32.6)	217 (14.9)
Local hospitals	586 (40.6)	513 (35.3)
University hospitals	387 (26.8)	722 (49.7)
Institution of referral		
Private clinics	371 (25.7)	182 (12.5)
Local hospitals	551 (38.2)	472 (32.5)
University hospitals	522 (36.1)	798 (55.0)

Values are presented as n (%) or n (range).

tial diagnosis was 36 years (range: 9–80 years) in the cases of alleged UC and 22 years (range: 9–77 years) in the cases of alleged CD.

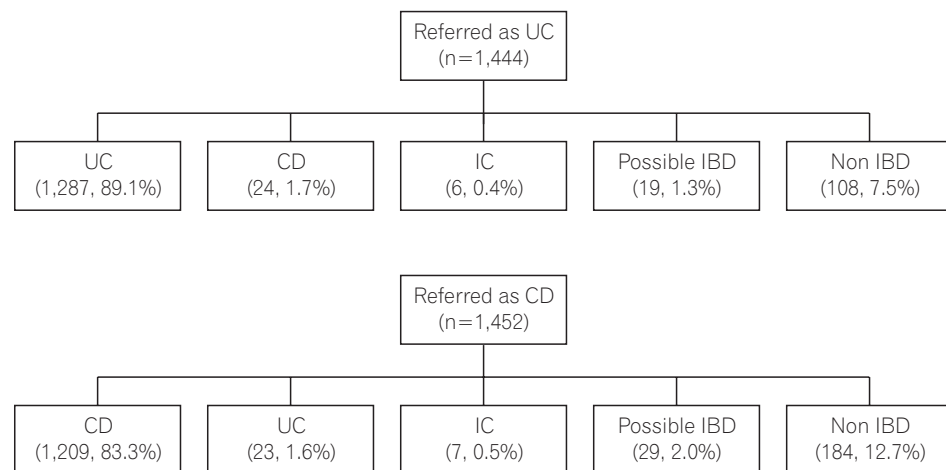


Fig. 1. Final diagnosis according to the initial diagnosis. Patients who were referred with the diagnosis of UC or CD were subsequently classified as having UC, CD, indeterminate colitis (IC), possible IBD, or non-IBD.

Table 2. Diseases that Mimicked UC and CD in the Study Population

Misdiagnosed as UC	n=108	Misdiagnosed as CD	n=184
Acute self-limited colitis	66 (61.1)	Acute self-limited colitis	57 (31.0)
Intestinal tuberculosis	6 (5.6)	Intestinal tuberculosis	53 (28.8)
Mucosal prolapse syndrome	6 (5.6)	Isolated terminal ileal ulcerations	18 (9.8)
Pseudomembranous colitis	6 (5.6)	Behçet's disease	14 (7.6)
Drug-induced colitis	5 (4.6)	Lymphoid hyperplasia of terminal ileum	6 (3.3)
Ischemic colitis	5 (4.6)	Drug-induced colitis	5 (2.7)
Lymphoid hyperplasia of rectum	3 (2.8)	Cancer	5 (2.7)
Cap polyposis	2 (1.9)	Amebic colitis	4 (2.2)
Eosinophilic colitis	2 (1.9)	Eosinophilic colitis	3 (1.6)
Radiation colitis	1 (0.9)	Appendicitis	3 (1.6)
Diversion colitis	1 (0.9)	Diverticulitis	2 (1.1)
Diabetes-associated diarrhea	1 (0.9)	Pseudo-obstruction	2 (1.1)
Amebic colitis	1 (0.9)	Cryptogenic multifocal ulcerous stenosing enteritis	2 (1.1)
Polyposis syndrome	1 (0.9)	Bile salt diarrhea	1 (0.5)
Systemic lupus erythematosus-associated colitis	1 (0.9)	Cytomegalovirus colitis	1 (0.5)
Behçet's disease	1 (0.9)	Radiation colitis	1 (0.5)
		Ischemic colitis	1 (0.5)
		Small intestinal bacterial overgrowth	1 (0.5)
		Henoch-Schönlein purpura	1 (0.5)
		Sodium phosphate-induced colitis	1 (0.5)
		Heterotopic pancreas	1 (0.5)
		Actinomycosis	1 (0.5)
		Pseudomembranous colitis	1 (0.5)

Values are presented as n (%).

2. Change in the Diagnosis of IBD

Over a median of 15.9 months of follow-up, 400 of 2,896 patients (13.8%) diagnosed with IBD experienced a change in the original diagnosis. Of the patients initially diagnosed with UC, 89.1% (1,287 of 1,444) had their diagnosis confirmed, compared with 83.3% (1,209 of 1,452) of patients initially diagnosed with CD (Fig. 1). The referral diagnosis of UC was confirmed in 82.2% (305 of 371), 89.5% (493 of 551), and 93.7% (489 of 522) of patients referred from primary clinics, local hospitals, and university hospitals, respectively. Likewise, the referral diagnosis of CD was confirmed in 65.9% (120 of 182), 82.2% (388 of 472), and 87.8% (701 of 798) of patients referred from primary clinics, local hospitals, and university hospitals, respectively. In the majority of cases with amendments, the diagnosis was changed from UC or CD to non-IBD (diagnosis changed from UC to non-IBD: 7.5%; diagnosis changed from CD to non-IBD: 12.7%). A relatively small proportion of patients originally diagnosed with UC or CD required their diagnosis to be changed to another form of IBD (from UC to CD: 1.7%; from CD to UC: 1.6%). Thirteen patients (0.4%) were reclassified as having IC, and 48 patients (1.7%) as having possible IBD.

3. The Mimics of IBD

The distribution of IBD mimics is presented in Table 2. In the cases of alleged UC, acute self-limited colitis (n=66) was the main mimic identified, followed by intestinal tuberculosis (ITB) (n=6), mucosal prolapse syndrome (n=6), pseudo-membranous colitis (n=6), drug-induced colitis (n=5), and ischemic colitis (n=5). In the case of alleged CD, the most common mimic was acute self-limited colitis (n=57). Other common mimics included ITB (n=53), isolated terminal ileal ulcerations (n=18), Behçet’s disease (n=14), lymphoid hyperplasia of the terminal ileum (n=6), drug-induced colitis (n=5), and cancer (n=5).

4. Reclassification as Non-IBD

The median time lag from the initial diagnosis of IBD to a reclassification as non-IBD was 2.0 months (range: 0.0–92.4 months) for UC and 3.3 months (range: 0.2–132.1 months) for CD patients. Among the 292 patients ultimately deemed not to have IBD, 52 cases (14 of 108 patients diagnosed with UC and 38 of 184 patients diagnosed with CD) had been suspected of having IBD for more than 1 year. IBD-related medications (namely, 5-aminosalicylates, thiopurines, corti-

Table 3. IBD-related Medications Used in the Patients Ultimately Deemed not to have IBD

Variable	Misdiagnosed as UC (n=108)	Misdiagnosed as CD (n=184)
None	53 (49.1)	104 (56.5)
5-aminosalicylates	52 (48.1)	75 (40.8)
Thiopurines	1 (0.9)	11 (6.0)
Corticosteroids	15 (13.9)	28 (15.2)
Anti-tumor necrosis factor agents	1 (0.9)	0

Values are presented as n (%).

costeroids, and anti-tumor necrosis factor [TNF]) were used in 55 of the 108 patients (50.9%) misdiagnosed with UC and in 80 of the 184 patients (43.5%) misdiagnosed with CD (Table 3). We also evaluated the time lag from the first visit to the Asan Medical Center to reclassification as non-IBD. The change in diagnosis from IBD to non-IBD was made at the first visit or within 2 months after the first visit to the Asan Medical Center in 267 of 292 patients (91.4%). In the remaining 25 patients (8.6%), the change in diagnosis was made after a follow-up period of between 2 months and 36 months.

DISCUSSION

We show from our current analysis that a change in diagnosis after a careful review and evaluation was required for 400 of 2,896 patients (13.8%) initially alleged to have IBD. The main change in the diagnosis of patients who were referred with a diagnosis of IBD was a reclassification as non-IBD.

An exact diagnosis of IBD is essential for its proper management. However, there are several hurdles when diagnosing and classifying this condition. Inflammatory changes in the bowel observed by radiology and endoscopy are frequently non-characteristic. Therefore, inflammatory changes in the bowel such as an infectious condition or ischemic colitis cannot be immediately or easily distinguished from IBD.^{4,5,20} Second, the dynamic nature of IBD often makes it complex to differentiate between patients with IBD who achieve a complete remission after a short period of first attack and patients with self-limiting colitis.^{9,10,21} Moreover, the overlap between CD and UC in terms of clinical, endoscopic, and pathological findings could make distinguishing between these two diseases difficult, particularly when the lesions are subtle or fulminant.⁸ However, these conditions become more discernible with follow-up; thus, patients with suspected IBD need to be evaluated through observation

over time.

Consistent with previous studies from IBSEN,^{1,3} 13.8% of the patients in our current series who were initially diagnosed with IBD had a change in diagnosis, mainly a reclassification to non-IBD. The most frequent cause of misclassification in patients misdiagnosed with either UC or CD was acute self-limited colitis. A systematic follow-up should lead to reductions in such misdiagnoses. ITB also remains a major hurdle in the accurate diagnosis of IBD in Korea.^{12,22-25} Although previous studies have suggested and evaluated diagnostic tools,^{22,24,26-29} the differential diagnosis of CD and ITB remains challenging, particularly in areas with a high prevalence of ITB.^{28,29} Owing to the rarity of CD among Koreans, a significant proportion of Korean patients with CD have been misdiagnosed with ITB. However, with the rising incidence and prevalence of CD and with the increasing awareness of CD among physicians in Korea,^{11,12,30} ITB cases initially misdiagnosed as CD are increasing. Therefore, physicians should be more cautious while evaluating the differential diagnosis because the diagnostic confusion between CD and ITB may result in the inappropriate use or even misuse of medications that could be harmful to the patient.

The accuracy of the diagnosis and sub-classification of IBD could also have a significant impact on the results of clinical studies. In hospital-based studies, a diagnosis is usually reassessed because the patient's clinical course has been followed over time. However, in epidemiology studies using administrative databases, the information in the databases has the inherent challenge of misclassification bias even by using validated codes.³¹⁻³³ An administrative database cannot capture detailed and revised medical records, and thus, precise approaches in designing (particularly patient selection), analyzing, and carefully interpreting the results are necessary. Moreover, confounding by misdiagnosis and misclassification is critically relevant in genetic studies.^{2,34} Making an accurate diagnosis and constantly updating clinical medical records are the principles for analyzing and interpreting genetic data.

Clinically relevant findings from our current analyses include the fact that 46.2% of the patients (135 of 292) analyzed received an IBD-related medication during a misdiagnosis. Furthermore, over 10% of misdiagnosed patients received thiopurines, corticosteroids, or anti-TNF agents. These medications could have significant adverse effects, especially in patients with infections.³⁵ Above all, the misdiagnosis of ITB as IBD can lead to serious consequences because immunosuppressive drugs, such as corticosteroids, thiopurines, and anti-TNF agents can actually aggravate ITB.

Thus, patients with a questionable diagnosis of IBD should be carefully observed at follow-up, and caution should be exercised by physicians during the administration of any medications.

Our study had a few limitations of note. First, our analysis was retrospective in nature. Therefore, the diagnostic tools and work-ups were not controlled, and a pathologic evaluation was not performed on all patients. Second, there was a chance that we still incorrectly diagnosed some of our patients. However, the diagnosis was only deemed conclusive when two or more gastroenterologists independently classified a case identically, and any discrepancies were resolved by discussion. Third, the follow-up period may not have been sufficient. Confidence in a diagnosis has been shown to increase with a longer duration of follow-up. Thus, future studies with a longer follow-up are necessary to determine the risk of IBD misdiagnosis.

In conclusion, numerous diseases can mimic IBD clinically, but careful and repeated evaluations reduce the chance of the misdiagnosis and misclassification of this disorder. Careful assessment of patients, systematic follow-up, and continuous correction or updating of the information in medical records will facilitate correct diagnoses and a reduction in misclassification bias.

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