Behçet’s disease (BD) is a multi-systemic inflammatory disorder of an unknown etiology and shows a chronic recurrent clinical course. When the disease involves the alimentary tract, it is called intestinal BD because of its clinical importance. Intestinal BD is more frequently reported in East Asian countries than in Western or Middle Eastern countries. While any part of the gastrointestinal tract can be involved, the most common location of intestinal BD is the ileocecal area. A few, large, deep ulcerations with discrete border are characteristic endoscopic findings of intestinal BD. Currently, there is no single gold standard test or pathognomonic finding of intestinal BD. However, recently developed novel diagnostic criteria and a disease activity index have helped in assessing intestinal BD. As intestinal BD shares a lot of characteristics with inflammatory bowel disease, including genetic background, clinical manifestations, and therapeutic strategies, distinguishing between the two diseases in clinical practice is quite difficult. However, biologic agents such as anti-tumor necrosis factor α antibody shows a considerable efficacy similar to inflammatory bowel disease cases. It is important to distinguish and treat those two disease entities separately from the standpoint of precise medicine. Clinicians should require comprehensive knowledge regarding the similarities and differences between intestinal BD and inflammatory bowel disease for making an accurate clinical decision.

**Key Words:** Intestinal Behçet’s disease, inflammatory bowel disease, Crohn’s disease, ulcerative colitis

**INTRODUCTION**

Behçet’s disease (BD) is a chronic relapsing multi-systemic inflammatory disease of an unknown etiology characterized by repeated oral and genital ulcerations, ocular lesions, skin manifestations, arthritis, vasculitis, and gastrointestinal involvement. Intestinal BD occurs in 3–60% of patients with BD. East Asian countries such as Korea and Japan tend to have a higher frequency of gastrointestinal involvement of BD than Western or Middle Eastern countries. Although clinical manifestations of intestinal BD vary widely from mild abdominal pain to bowel perforation or massive hemorrhage, gastrointestinal involvement of BD often predicts poor treatment response and unfavorable prognosis of the affected patients.

Intestinal BD and inflammatory bowel disease (IBD) share a considerable number of genetic backgrounds, pathogenesis, and clinical features. Moreover, current therapeutic strategies for intestinal BD have many similarities to those of IBD. Some experts classify the two diseases as the same category of a single disease or as different spectrums of the same disease; others regard them as totally different diseases. In this review, we will discuss the similarities and differences between intestinal BD and IBD (Table 1).
ETIOLOGY AND PATHOPHYSIOLOGY

Genetics
The exact etiology and pathophysiology of BD remains unclear. Nevertheless, similar to IBD, both genetic and environmental factors might contribute to the development of BD.9 Classically, an human leukocyte antigen (HLA)-B51 allele has been thought to be the most important genetic factor of BD.9 Although it is still unclear whether this locus independently acts as the fundamental cause of BD development, studies of BD report that the prevalence of the HLA-B51 allele is much higher in patients with BD than in unaffected populations.3,10 Genome-wide association studies (GWAS) from Japan and Turkey have also confirmed HLA-B51 as a susceptible locus for BD.11,12 Another susceptibility locus, HMC class I related gene A (MICA), has been evaluated in several studies.8,11,14 However, an independent contribution for these loci has not proven to be easy to confirm due to the strong linkage disequilibrium with HLA-B51.15 HLA-B51 or MICA has not been shown to be associated with IBD susceptibility.

Recent studies report an association for BD with interleukin (IL) 10 and the IL23R-IL12RB2 loci.11,12 Decreased mRNA expression and low protein production was correlated with BD expression. Similarly, IL10 or IL23R variants were also observed in IBD patients, suggesting that the two diseases have similar genetic backgrounds and pathogenesis.16 However, polymorphisms of genetic variants of IL10 and IL23R in patients with intestinal BD were not associated with those of IBD.17 The IL10-1082AA and -819T genotype were associated with BD, while IL10-819CT and -592CA polymorphisms were related with ulcerative colitis. IL10-1082GA was not associated with IBD.8,10 IBD is known to exhibit an association with variants in IL23R, IL12B, and TYK2, while BD is associated with the intergenic region between IL23R and IL12RB2.20 In the Korean population, haplotypes of IL17A demonstrated a risk of developing intestinal BD, while those of IL23R were associated with disease protection.21

Close overlap of genetic variants provides considerable explanation about phenotypic and clinical similarities between intestinal BD and IBD. Despite many parallels between the two diseases, detailed distinctions regarding genetics have been steadily traced. Therefore, further studies are needed to discover the exact genetic contributions for each disease.

Microorganisms and immune response
Although BD shows familial aggregation and a genetic background, environmental factors also contribute to triggering inflammation. Increased Th1, Th17, CD4+ and CD8+ T cell, and γδ+ T cell activities were found both in the serum or inflamed tissues of BD patients,11,23-25 which suggests that innate and adaptive immune responses contribute to BD. The role of innate immune system in BD is supported by the recent studies showing an increased expression of IFN-γ, IL-1β, and TNF-α in BD tissues.20,26,27 These findings suggest that the innate immune response plays a crucial role in the pathogenesis of BD.20,26,27

Table 1. Similarities and Distinctions of Intestinal Behçet’s Disease (BD) with Crohn’s Disease

| Similarities | Distinctions |
|--------------|--------------|
| Genetics | Interleukin (IL) 10 and the IL23R-IL12RB2 loci | Human leukocyte antigen-B51 allele |
| Immunology | Activation of innate and adaptive immune system | Serum anti-Herpes simplex virus-1 antibodies in the patients with BD were significantly higher than controls |
| | Increased Th1, Th17, CD4+ and CD8+ T cell, and γδ+ T cell activities | Heat shock protein (HSP) stimulate γδ+ T cells in BD patients because of homology between Streptococcus sanguis and human HSP |
| | Increased Th1-type cytokines | Anti-endothelial cell antibody |
| | The rate of anti-Saccharomyces cerevisiae antibodies detection is remarkably higher | |
| | Bacterial contribution to the disease development | |
| Clinical findings | Wide variation of abdominal symptoms from mild discomfort to hematoclasia | Rare anorectal involvement in intestinal BD |
| | Similar extra-intestinal manifestations | Possible ischemic damage from vasculitis |
| Endoscopic findings | Segmental involvement | Fewer number of lesion |
| | Various type of ulcers are able to seen | Large size of ulceration |
| | Grossly normal looking intervening mucosa | Round or oval shaped ulceration |
| | Mucosal healing is closely related with favorable clinical course | Relatively more discrete and elevated border of ulceration |
| Histologic findings | Non-specific inflammation (lymphocytic or neutrophilic infiltrations) | Vasculitis can be seen |
| | | Absence of non-caseating granuloma |
| Disease activity index | Concordance with clinical disease activity | Highly weighted general condition of patient and abdominal pain |
| | Discordance with endoscopic disease activity | Less concern for laboratory test and diarrhea |
| Treatment | 5-amino-salicylates/sulfasalazine, corticosteroids, thiopurines, thalidomide, and biologic agents are used for intestinal lesion | Concomitant use of medications for systemic BD is frequent |
| Prognosis | Similar admission, operation, and post-operative recurrence rate | Higher cumulative rate in use of corticosteroids and immunomodulators |

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adaptive immunity act together to initiate BD. Similar to other autoimmune disorders, BD shows Th1-type cytokine profiles. IL-2 and interferon (INF)-γ producing T cells were increased in patients with active BD, while IL-4 producing T cells were lower than in controls. IL-12 and tumor necrosis factor (TNF)-α levels were also increased in BD. However, contrary to typical autoimmune disorders, CD5+CD19+ B cell levels were low, and autoimmune markers such as antinuclear antibodies were negative. The immunologic pathogenesis of BD is summarized as exhibiting epithelial barrier, innate immune cells, and adaptive T cells. In patients with IBD, innate (macrophage, neutrophil) and acquired (T and B cell) immune responses are activated. Most pro-inflammatory cytokines involved in innate immune system are activated in both Crohn’s disease and ulcerative colitis. As in BD, Th1 and Th17 related cytokines, such as IL-12, IL-23, and IL-27, are also up-regulated in Crohn’s disease. Moreover, Th1 cell-related cytokines, such as IFN-γ and IL-2, are also increased in Crohn’s disease. In patients with ulcerative colitis, however, T cells from the lamina propria highly produce IL-5 and IL-13, which are regarded as Th2-cell related cytokines. So far, relatively less research has been conducted on the immunology of BD.

Serum anti-herpes simplex virus (HSV)-1 antibodies in patients with BD were significantly higher than those in controls, and HSV DNA was found in the genital and intestinal ulcers of patients. Sohn, et al. developed and reported a BD murine model through HSV inoculation in ICR mice. However, antiviral therapy seems controversial for the treatment of BD. Though other viruses, including hepatitis C, parvovirus B19, cytomegalovirus, Epstein-Barr virus, and varicella-zoster virus, may contribute to BD, results are inconsistent. The exact role of viruses in the pathogenesis of IBD is not clearly demonstrated. Cytomegalovirus is frequently related with severe or steroid refractory ulcerative colitis. Cytomegalovirus seems to be associated with steroid refractoriness. However, the causal relationships between ulcerative colitis and cytomegalovirus are not clear.

Generally, BD starts from oral ulcerations. Therefore, bacteria from normal flora of the oral mucosa have been evaluated as causative organisms. A number of Streptococcus species have been implicated. Streptococcus sanguis and its antibodies are repeatedly detected in the oral mucosa and sera of patients with BD. Streptococcus sanguis-related antigen (KTH-1) stimulates IL-6 and INF-γ production in patients with BD. Streptococcus sanguis antigen has a homology with a cellular membrane protein called heat shock protein (HSP). Mycobacterial HSP-65 and human HSP-60 share over 50% of sequence homology, and HSPs have been found to stimulate γδ+ T cells in BD patients. Therefore, researchers have postulated that specific bacterial antigens induce mucosal HSP against bacterial stimulation and concurrently activate T cells against intestinal mucosa in BD patients. However, the exact role of those antigens as an inducer of primary autoimmunity remains obscure.

In the same manner, intestinal microbiota may play an important role in IBD development. Dysbiosis of conventional microbiota, pathogenic stimulation of functionally altered commensal bacteria, host genetic defects in containing microbiota, and defective host immune regulation are generally accepted explanations of the pathogenesis of IBD. In a study comparing mucosal flora between 40 controls and 305 patients with an inflamed bowel, including 54 Crohn’s disease and 119 ulcerative colitis, concentrations of mucosa-associated bacteria were higher in patients with intestinal inflammation than in controls. Recent studies have revealed that the dysbiosis of intestinal microbiota in patients with IBD is characterized by reduction in diversity, prominent depletion of Bacteroides and Firmicutes including Clostridium XIVa/IV, and growth of Actinobacteria and Proteobacteria. Mycobacterium avium subspecies paratuberculosis, adherent-invasive Escherichia coli, Clostridium difficile toxin A and enterotoxigenic Bacteroides fragilis have been thought to be possible pathogens of IBD. However, the exact relationships between these bacteria and induction of IBD have not been confirmed due to differences among individuals and considerable alterations of intestinal microbiota.

Clinical findings
Abdominal pain, diarrhea, melena, and hematochezia can occur in patients with intestinal BD. Clinical signs such as abdominal tenderness or a palpable mass on the affected area, fever, and weight loss are also noted. Gastrointestinal manifestations of BD usually develop 4.5–6 years after the onset of oral ulcerations. Sometimes, however, intestinal lesions can precede extra-intestinal manifestations. Theoretically, there are two forms of intestinal lesions: one is mucosal inflammations and ulcerations by neutrophilic phlebitis. The other involves ischemic damage from vasculitis. The most frequently involved location is the ileocecal area. However, any part of the alimentary tract and extra-intestinal organs, such as liver, pancreas, or spleen, can be affected. While anal complication is frequently observed in patients with Crohn’s disease, rectal or anorectal involvement of intestinal BD is rare. Also, intestinal complications such as stricture, fistula, and abscess formation are more frequent in patients with Crohn’s disease due to its transmural nature of inflammation. Oral ulceration is usually considered separately, because oral ulceration plays a major role in diagnosing BD. Although the frequencies of gastrointestinal involvement in patients with BD have been reported variously, depending on geographical location, its actual incidence might be higher than study results, because of the possible presence of asymptomatic lesions. A Chinese study evaluating screening colonoscopies of systemic BD patients found 35.1% had gastrointestinal lesions. Of them, four of 18 patients with active ulcerations showed no gastrointesti-
nal symptoms. Importantly, extra-intestinal manifestations of BD, such as oral and genital ulcerations, ocular and joint involvement, and skin lesions, are all potentially experienced in the course of IBD. Thus, differential diagnosis between BD and IBD remains a challenge.

**Endoscopic findings**

Typical ulcerations of intestinal BD are described as a single or few, large, discrete, and round or oval shaped ulcerations in the ileocecal area. However, various ulcerations from small aphthous ulcerations to multiple irregular shaped ulcerations can be observed. As intestinal BD and Crohn’s disease share similar clinical courses, extra-intestinal manifestations, and non-specific gastrointestinal symptoms, it is often difficult to differentiate between the two. Lee, et al. compared colono-scopic findings of 115 intestinal BD and 135 Crohn’s disease patients. Multivariate analysis revealed that round shape, fewer number (≤5), focal distribution, and absence of aphthous and cobble stone appearance were independent discriminating factors of intestinal BD. Furthermore, they proposed a diagnostic algorithm using classification analysis (Fig. 1). Dominant colonoscopic findings of intestinal BD also can be used. A study suggested a novel diagnostic criteria for intestinal BD using systemic and colonoscopic features of BD. Investigators regarded five or fewer lesions, oval shape, deep penetrating, discrete border, and ileocecal location as typical ulcerations. Overall, the positive predictive value and accuracy of the diagnostic algorithm were 86.1% and 91.1%, respectively. Kim, et al. classified macroscopic findings of intestinal BD ulcers into volcano, geographic, and aphthous types. Volcano type ulceration (well-demarcated deeply penetrating ulcers with nodular margins, converging folds, or pseudopolyps) was associated with poor prognosis.

Yim, et al. reported complete resolution of inflammation by macro- and microscopic evaluation, so called “mucosal healing,” to be significantly associated with favorable clinical course, which is consistent with Crohn’s disease cases. Identifying active intestinal ulcerations during clinical remission was independently related with clinical relapse. Classical endoscopic findings of Crohn’s disease in colonoscopic examination include discontinuous chronic mucosal inflammation, aphthoid ulcerations, longitudinal ulcerations, and cobblestone appearance with normal surrounding mucosa. Skipped inflammatory lesions with normal intervening mucosa are frequently observed in Crohn’s disease, similar to those of intestinal BD. However, distribution patterns in patients with Crohn’s disease are more diffuse than in patients with intestinal BD (Fig. 2).

**Histologic findings**

There are no pathognomonic histologic findings regarding intestinal BD. Vasculitis affecting small veins and venules are commonly accepted features. However, these findings are not consistently observed in affected organs. Histology from esophageal biopsy, for example, often shows non-specific inflammation (lymphocytic or neutrophilic infiltrations) rather than vasculitis. Generally, absence of non-caseating granuloma implies intestinal BD rather than Crohn’s disease. However, non-caseating granulomas are observed in only 15–36% of patients with Crohn’s disease. Other histologic characters of Crohn’s disease, such as transmural inflammation, chronicity, and focality, are also able to be observed in intestinal BD. Normal circumferential mucosa surrounding a large ulceration is one of the characteristic histologies of intestinal BD. A study comparing histology from rectal biopsy between 75

![Fig. 1. Diagnostic algorithm for differential diagnosis between intestinal Behçet’s disease and Crohn’s disease.](http://dx.doi.org/10.3349/ymj.2016.57.1.22)
patients with BD and 14 ulcerative colitis revealed that destruction of surface epithelium, polymorphonuclear infiltration, loss of goblet cells, and loss of crypts are more frequently observed in ulcerative colitis than in BD.\(^{73}\)

**Disease activity index for intestinal Behçet’s disease (DAIBD)**

The Korean IBD Study Group developed a novel tool for assessing disease activity in patients with intestinal BD.\(^{74}\) As IBD exhibits an unpredictable wax-and-wane clinical course and various manifestations, disease activity should be monitored by an organized measuring method. Investigators have developed and applied several validated disease activity indices for each Crohn’s disease and ulcerative colitis.\(^{75}-^{79}\) Before developing disease activity index for intestinal Behçet’s disease (DAIBD), some clinicians had used disease activity index of Crohn’s disease for evaluating intestinal BD activity. DAIBD includes the general condition of a patient, extra-intestinal manifestations, intestinal complications, symptoms and signs, and stool frequency. Whereas taking antidiarrheal agents and the presence of complications are highly weighted in Crohn’s disease activity index (CDAI), DAIBD considers the general condition of patient and abdominal pain more importantly. Based on the cumulative score of each item, disease activity is categorized into “severe,” “moderate,” “mild,” and “quiescent.” DAIBD showed much higher responsiveness than the CDAI (r=0.812 vs. r=0.645, respectively). However, a recent study of the same group revealed that DAIBD was not highly associated with endoscopic severity, which is similar to Crohn’s disease cases.\(^{80}\)

**Serologic tests**

The rate of anti-*Saccharomyces cerevisiae* antibodies (ASCA) detection is remarkably higher in patients with BD, especially in patients with gastrointestinal involvement, than in controls.\(^{81}\) In a study evaluating ASCA and the clinical course of intestinal BD patients, similar to those of Crohn’s disease, ASCA was positive in 44.3% of intestinal BD patients. ASCA positive patients were also more likely to receive surgical treatment.\(^{82}\)

The results further implied a similarity between Crohn’s disease and intestinal BD. However, atypical or perinuclear antineutrophil cytoplasmic autoantibody was not shown to be related with intestinal BD.\(^{75}\) Studies regarding anti-endothelial cell antibody (AECA) revealed a high prevalence of AECA in systemic vasculitis including BD.\(^{84}\) \(\alpha\)-enolase protein is the target of AECA.\(^{85,86}\) Serum soluble triggering receptor expressed in myeloid cells-1 was significantly associated with DAIBD in intestinal BD patients, although not with C-reactive protein (CRP) or erythrocyte sedimentation rate.\(^{87}\)

**TREATMENT AND PROGNOSIS**

**Medical treatments**

There is a lack of randomized prospective studies regarding the treatment of intestinal BD.\(^{88,89}\) Traditionally, therapeutic implications of intestinal BD have been similar to those of Crohn’s disease.\(^{60,89}\) There is a controversy about the therapeutic effects of 5-amino-salicylates (5-ASA)/sulfasalazine, which is routinely used in patients with IBD.\(^{90-92}\) In a retrospective cohort study investigating 143 patients with intestinal BD receiving 5-ASA/sulfasalazine alone for maintaining remission, cumulative relapse rates at 1, 3, 5, and 10 years after remission were 8.1%, 22.6%, 31.2%, and 46.7%, respectively. Younger age at diagnosis (<35 years), higher serum CRP level (1.5 mg/dL), and greater DAIBD score (≥60) independently predicted clinical relapse.\(^{93}\)

Systemic corticosteroids are available for inducing remission in patients with moderate to severe disease or when treatment with 5-ASA/sulfasalazine fails.\(^{94}\) Starting 0.5–1 mg/kg of prednisolone or its equivalent and rapid tapering strategies are prevalent, similar to IBD treatment.\(^{86}\) The dose of corticoste-
roides should be adapted according to the severity of the disease. In a retrospective cohort study, systemic corticosteroid therapy (mean starting dose, 0.58 mg/kg) in 54 patients with active intestinal BD showed 46.3% complete remission, 42.6% partial remission, and 11.1% no response after a month from treatment. After one year, however, prolonged responses were found in 4 only 8.1% of the cohort, while 35.2% of patients showed corticosteroid dependency. Compared with a similar study evaluating clinical outcomes in patients with Crohn’s disease receiving oral prednisolone, prolonged response (56.6%) and corticosteroid dependency (24.1%) at a year after receiving treatment showed a better clinical course in patients with Crohn’s disease than in intestinal BD.

Thiopurines or azathioprine/6-mercaptopurine (AZA/6-MP) are indicated in patients who show corticosteroid dependency or resistance. In a double-blind, randomized, placebo-controlled trial, AZA had a beneficial effect in controlling BD including eye and extra-ocular diseases. In patients with intestinal BD, Jung, et al. reported cumulative relapse rates of 5.8%, 28.7%, 43.7%, and 51.7% at 1, 2, 3, and 5 years after remission among patients who received AZA/6-MP for remission maintenance, respectively. Multivariate analysis showed a young age at diagnosis (<25 years) and lower serum hemoglobin level (<11 g/dL) to be independent predictors of relapse. Similarly, a retrospective study revealed cumulative relapse rates of 18.0% and 49.2% in patients with Crohn’s disease who were treated continuously with AZA/6-MP to maintain clinical remission after 1 and 3 years of treatment, respectively. Independent predictive factors of relapse during AZA/6-MP treatment were younger age at treatment and increased serum CRP level at remission status.

Thalidomide (100–300 mg/day) was found to be effective on treating oral and genital ulcerations, as well as follicular lesions, of BD in a randomized, double-blind, placebo-controlled study. Another small case series reported that thalidomide (1–3 mg/kg) was able to replace steroid therapy without serious complications in juvenile-onset intestinal BD. A small study investigating thalidomide in patients with IBD reported clinical response rates of 83.3% and 100.0% after 12 weeks of 100–400 mg per day thalidomide treatment in patients with Crohn’s disease and ulcerative colitis, respectively. However, continuous vigilance for long-term side effects of thalidomide is warranted.

Monoclonal antibodies to TNF-α, including infliximab (IFX) and adalimumab (ADA), are important biological agents for treating IBD. After several reports on therapeutic effects of anti-TNF-α in patients with intestinal BD, accumulation of evidence on the therapeutic impacts of anti-TNF-α treatment has increased. Nevertheless, there is a need to investigate the impact of anti-TNF-α treatment on cumulative surgery rates and post-operative recurrence. Currently, there is no large scale, randomized trial of anti-TNF-α agents in patients with intestinal BD. However, several case series reported favorable results of IFX on induction and maintain remission of intestinal BD. A retrospective multicenter study in Korea, evaluating 28 cases of patients with intestinal BD treating with IFX who were refractory to conventional medical treatments, reported a clinical response rate of 64.8% at 4 weeks after treatment. Older age (≥40 years), female gender, longer disease duration (≥5 years), using concomitant immunomodulators, and achieving clinical remission were independently associated with sustained response. A prospective, multicenter, randomized, double-blind, placebo-controlled study (ACCENT I) revealed that IFX induced clinical remission (CDAI<150) in 58% of patients with Crohn’s disease. Also, patients who received scheduled IFX were more likely to sustain clinical remission than those who did not. The impacts of maintenance therapy with IFX were consistently confirmed, even in patients with fistulizing Crohn’s disease who responded to induction therapy (ACCENT II).

Recently, the clinical efficacy of ADA was also ascertained by case reports and a small randomized trial similar to IFX. A phase III, multicenter, open-label, uncontrolled study investigating the efficacy and safety of ADA for treating active intestinal BD patients who were refractory to conventional therapy in Japan revealed complete remission in 20% at week 52 with similar rates of adverse events as in other clinical trials regarding ADA. Two randomized, double-blind, placebo-controlled studies similarly evaluated the efficacy of remission induction and maintenance of ADA in patients with Crohn’s disease. A study investigating 299 patients with moderate-to-severe Crohn’s disease naïve to anti-TNF-α agents who were randomized to receive ADA (40/20 mg, 80/40 mg, or 160/80 mg) or placebo at weeks 0 and 2 showed remission rates of 18%, 24%, and 36% of (CDAI<150) at week 4, respectively. A follow-up study revealed that 40 mg of ADA injection every other week or weekly showed significantly higher remission rates (79% and 83%, respectively) at week 56 than placebo (44%, p<0.05). Another study evaluating 854 patients with moderate to severe Crohn’s disease who received 80 mg of ADA at week 0 and 40 mg at week 2 showed clinical response in 58.4% (drop in CDAI of 70 points) at week 4. Also, 40% of the 40 mg every other week group, 47% of the 40 mg weekly group, and 17% of the placebo group were in remission at week 26. A consensus statement of anti-TNF-α therapy in patients with intestinal BD by the Japanese group proposed its indication as a standard therapy for intestinal BD. However, a large scale, randomized, prospective trial is needed for the establishment of the long-term efficacy of anti-TNF-α therapy.

Surgical treatment

Surgical resection of an affected bowel is considered when patients with intestinal BD are refractory to medical treatment or serious complications, such as bowel perforation or severe bleeding, cannot be controlled by conservative treatment.
Lee, et al. reported peritonitis due to multiple perforations as the most common indication of surgery in patients with intestinal BD, following gastrointestinal bleeding, enterocutaneous fistula, and intractable pain with recurrence. Bowel perforation is one of the most disastrous complications of intestinal BD. A retrospective analysis regarding free bowel wall perforation in 129 patients with intestinal BD reported that 33 (25.6%) of patients experienced bowel perforation and consecutive surgery. Of them, 14 (42.4%) showed post-operative recurrence and 11 (33.3%) underwent re-operation. Younger age at diagnosis (<25 years), experience of prior laparotomy, and volcano-shaped ulceration predicted bowel perforation independently.

Compared to Crohn’s disease, intestinal BD shows similar cumulative surgery rates (29.4% and 36.0% in Crohn’s disease vs. 31.6% and 44.4% in intestinal BD at five and ten years, respectively: \( p=0.287 \)). Naganuma, et al. reported that small bowel involvement and ocular lesion in patients with intestinal BD were significantly associated with requiring surgery. Likewise, pouchitis after ileal pouch-anal anastomosis in patients with IBD was highly related with extra-intestinal manifestations. However, intestinal BD surgery shows distinct features. While the extent of bowel resection should be restricted in patients with Crohn’s disease, that of intestinal BD is suggested to include leakage, perforation, and fistula formation, with relatively high rates of complications at anastomosis sites, in-terative recurrence in patients with intestinal BD. Due to bowel involvement, because resection length was not related with post-operative recurrence in patients with intestinal BD. Due to relatively high rates of complications at anastomosis sites, including leakage, perforation, and fistula formation, in intestinal BD surgery, bowel diversion (stoma formation) is suggested by several investigators. Especially, because pathergy is often seen with BD patients, ulcerations at the site of surgical incision can develop.

**Prognosis**

A study investigating the clinical course of intestinal BD during the first 5 years after diagnosis reported that 74.6% of patients were in remission or showed mild disease activity at year 5. The independent predictor of severe clinical course was higher DAIBD (≥40) at diagnosis (OR: 6.2, 95% CI: 1.1–33.5, \( p=0.035 \)). The same group also compared long-term clinical outcomes between intestinal BD and Crohn’s disease. The cumulative probabilities of surgery, hospital admission, and post-operative recurrence were not significantly different between intestinal BD and Crohn’s disease (44.4% vs. 36.0%, 69.2% vs. 73.8%, and 66.5% vs. 79.1% at 10 years, \( p=0.287, 0.295, \) and 0.724, respectively). However, there were significant differences in cumulative probabilities of corticosteroid use and immunosuppressant use between intestinal BD and Crohn’s disease (59.4% vs. 42.6% and 37.7% vs. 27.1%, \( p<0.001 \) and \( <0.001, \) respectively).

**CONCLUSIONS**

The clinical manifestations of intestinal BD and IBD frequently overlap. Therefore, clinicians often encounter formidable obstacles regarding differential diagnosis at first presentation. Intestinal BD and Crohn’s disease share similar genetic backgrounds, such as IL10 and the IL23R-IL12RB2 locus. Innate and adaptive immune responses activate Th1, Th17, CD4+ and CD8+ T cell, and γδ T cells from the stimulation of microorganisms alike. However, precise generic variants and the mechanisms of immune responses are different between the two diseases. Although clinical manifestations and endoscopic findings resemble each other, independent characteristics can be found through careful clinical evaluation. So far, treatment strategies for IBD have proven to be the most effective for controlling intestinal BD. However, in terms of understanding disease, continued efforts to out the pathogenesis and to distinguish intestinal BD from other inflammatory conditions, including Crohn’s disease, must be pursued.

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