Optimal Treatment Approaches to Intestinal Behçet's Disease Complicated by Myelodysplastic Syndrome: The KASID and KSBD Multicenter Study

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Purpose: Studies on intestinal Behçet's disease (BD) complicated by myelodysplastic syndrome (MDS) are rare, and no established therapeutic guidelines exist. This study aimed to evaluate the clinical presentation and outcomes of patients with intestinal BD complicated by MDS (intestinal BD–MDS) and suggest a treatment strategy.

Materials and Methods: Data from patients with intestinal BD–MDS from four referral centers in Korea who were diagnosed between December 2000 and December 2022 were retrospectively analyzed. Clinical features and prognosis of intestinal BD–MDS compared with age-, sex-matched intestinal BD without MDS were investigated.

Results: Thirty-five patients with intestinal BD–MDS were included, and 24 (70.6%) had trisomy 8. Among the 35 patients, 23 (65.7%) were female, and the median age at diagnosis for intestinal BD was 46.0 years (range, 37.0–56.0 years). Medical treatments only benefited eight of the 32 patients, and half of the patients underwent surgery due to complications. Compared to 70 matched patients with intestinal BD alone, patients with intestinal BD–MDS underwent surgery more frequently (51.4% vs. 24.3%; p=0.010), showed a poorer response to medical and/or surgical treatment (75.0% vs. 11.4%; p<0.001), and had a higher mortality (28.6% vs. 0%; p<0.001). Seven out of 35 patients with intestinal BD–MDS underwent hematopoietic stem cell transplantation (HSCT), and four out of the seven patients had a poor response to medical treatment prior to HSCT, resulting in complete remission of both diseases.

Conclusion: Patients with intestinal BD–MDS frequently have refractory diseases with high mortalities. HSCT can be an effective treatment modality for medically refractory patients with intestinal BD–MDS.

Key Words: Behçet's syndrome, myelodysplastic syndrome, trisomy 8, case–control study

INTRODUCTION

Behçet's disease (BD) is a multisystem variable vasculitis of unknown cause characterized by four main symptoms: recurrent oral ulcers, genital ulcers, uveitis, and cutaneous lesions.[1] Although the gastrointestinal tract, central nervous system, and vessels are less frequently affected, their involvement can lead to life-threatening complications.[1] The ileocecal region is the most commonly affected part of the gastrointestinal tract; however, the colon and esophagus are sometimes involved. The symptoms associated with these extra-oral gastrointestinal manifestations of BD are abdominal pain, nausea, vomiting, diarrhea, and hematochezia, and sometimes intestinal lesions result in severe complications, such as perforation and massive hemorrhage.[1-4] Gastrointestinal symptoms in patients with BD and typical volcano-shaped intestinal ulcerative lesions that may be measured objectively are used for the diagnosis of intestinal BD.[5] 5-aminosalicylic acids (5-ASAs), corticosteroids (CS), immunomodulators, such as azathioprine and 6-mercaptopruine, surgical therapy, and anti-tumor necrosis factor (TNF)α agents, such as adalimumab and infliximab, were included in conventional therapy for intestinal BD, such as Crohn's disease and ulcerative colitis.[6-11]

Myelodysplastic syndromes (MDS) are clonal marrow stem cell disorders characterized by ineffective hematopoiesis that causes peripheral blood cytopenias and, in one-third of patients, progresses to acute myeloid leukemia.[12,13] Recent research on MDS suggests that aberrant innate immune system activation and accompanying inflammation may play a role in its pathogenesis.[14,15] Patients with MDS have 10%–30% autoimmune disease prevalence; the autoimmune diseases described previously vary in nature and outcome.[16,17] There are heterogeneous opinions on the effect of autoimmune disease on the prognosis of patients with MDS. Some studies have reported that the presence of autoimmune disease is not of prognostic relevance[18] or is even associated with better outcomes,[17] while others have reported poorer outcomes.[19] The management of MDS includes hypomethylating agents, and hematopoietic stem cell transplantation (HSCT) and is based on the revised International Prognostic Scoring System (IPSS-R).[12,20]

Over the past 30 years, several case reports on the association between BD and MDS have been published internationally.[21-28] Clinical characteristics of this group of patients differ from those with MDS or BD alone. In comparison to patients with idiopathic BD without MDS, those with BD and MDS were older, had fewer ocular lesions, and had more frequent gastrointestinal involvement.[29,30] Particularly, patients with intestinal BD complicated by MDS (intestinal BD–MDS) with cytogenetic aberration trisomy 8 often have refractoriness to conventional medical treatments and poor prognoses.[25,27,31] Immunomodulators and anti-TNFα agents had no beneficial effects on patients with intestinal BD–MDS compared to those with intestinal BD without MDS and improved through treatment targeted to MDS.[24-27] However, studies on Korean patients with intestinal BD–MDS are rare, and no established therapeutic guidelines exist. Therefore, we conducted a case-control study to evaluate the clinical presentation and outcomes of patients with intestinal BD–MDS and suggest a treatment strategy.

MATERIALS AND METHODS

Study subjects
Data of patients with intestinal BD–MDS from four participating centers in Korea who were diagnosed between December 2000 and December 2022 were retrospectively analyzed. The diagnosis of intestinal BD was performed based on the established criteria in the Japanese Consensus of Intestinal BD published in 2007 and 2014.[6,7,32] MDS was diagnosed through a bone marrow aspiration, and IPSS-R was used for assessing the hematologic prognosis.[20] Patients diagnosed with other hematologic diseases were excluded from this study. The final cohort comprised 35 patients with intestinal BD–MDS.

To conduct a matched case-control study, we defined controls as intestinal BD without MDS, and control participants were recruited from Asan Medical Center, a tertiary university hospital in Seoul, Korea. A total of 370 patients with intestinal BD were available for selection as controls at the time of this study. The control groups were matched to cases in a ratio of 2:1 for sex, age at diagnosis of intestinal BD (±5 years), and duration of follow-up (±5 years).

Information collection
The clinical features, treatments, and prognosis of intestinal BD–MDS compared with matched intestinal BD without MDS were investigated. The following data were collected at the time of the intestinal BD diagnosis through medical record review: age at diagnosis of intestinal BD and MDS, Disease Activity Index of intestinal Behçet's disease (DAIBD) score at diagnosis, symptoms associated with systemic BD, gastrointestinal symptoms, surgical history, and location of intestinal ulcers at endoscopic and/or radiologic findings. In addition, data on treatment modality during follow-up and outcome for intestinal BD and MDS at the last visit were also collected.

Statistical analysis
Continuous variables were presented as medians with interquartile ranges, and categorical variables were presented as numbers with percentages. Chi-square or Fisher's exact test was used to compare the categorical variables. Student's t test or Mann–Whitney U-test was used to compare the continuous variables. All p-values <0.05 were considered statistically significant. Cumulative survival was estimated using Kaplan–Meier curves, and comparison between cases and controls was performed using the Cox proportional hazards regression, as appropriate. Analysis of the predictive factors of poor progno-

sis (no response to medical treatment) of intestinal BD was carried out by univariate and multivariate analyses using logistic regression after the inclusion of significant variables and clinical risk factors (age, sex). Associations were expressed as odds ratio (OR) with a 95% confidence interval (CI). All statistical analyses were performed using R statistics software 4.2.1 (R foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

This study was approved by the Institutional Review Board of Asan Medical Center (Approval No. 2022-0641) and other collaborating hospitals.

RESULTS

Baseline characteristics

Of the 105 patients with intestinal BD, 35 and 70 had intestinal BD–MDS and intestinal BD without MDS, respectively. The characteristics associated with MDS in 35 patients with intestinal BD–MDS are presented in Table 1. Among the 35 patients, 23 (65.7%) were female; the median age at diagnosis was 46.0 years (range, 37.0–56.0 years) and 49.0 years (range, 42.0–55.0

Table 1. Baseline Characteristics of Patients with Intestinal BD Complicated by MDS (n=35)

	Value
Sex (M/F)	12/23
Age at intestinal BD diagnosis, yr	46.0 (37.0–56.0)
Age at MDS diagnosis, yr	49.0 (42.0–55.0)
Sequence of diagnosis	
Intestinal BD first	19 (54.3)
MDS first	6 (17.1)
At the same time	10 (28.6)
Diagnosis interval between intestinal BD and MDS, yr	1.8 (0.6–5.7)
Follow-up duration, months	64.0 (27.0–102.5)
Baseline DAIBD	90.0 (60.0–117.5)
Chromosomal abnormality of MDS	
Trisomy 8	24/34 (70.6)
Non-trisomy 8	10/34 (29.4)
NA	1/35 (2.9)
IPSS-R risk of categories	
Very low	0 (0)
Low	8/29 (27.6)
Intermediate	8/29 (27.6)
High	10/29 (34.5)
Very high	3/29 (10.3)
NA	6/35 (17.1)

M, male; F, female; IQR, interquartile range; BD, Behçet's disease; MDS, myelodysplastic syndrome; DAIBD, disease activity index for intestinal Behçet's disease; NA, not available; IPSS-R, revised International Prognostic Scoring System.
Data are presented as median (IQR) or n (%).

years) for intestinal BD and MDS, respectively, and 24 (70.6%) patients had the trisomy 8 karyotype. Intestinal BD preceded the diagnosis of MDS in 19 (54.3%) patients, whereas MDS preceded the diagnosis of intestinal BD in 6 (17.1%) patients. Both diseases were diagnosed simultaneously in 10 (28.6%) patients. The median follow-up duration was 64.0 months (range, 27.0–102.5 months). Of 29 patients, 21 (72.4%) were classified as intermediate, high, or very high risk (IPSS-R >3).

Table 2 shows demographic and clinical characteristics of patients and controls. The follow-up periods of the two groups were comparable. The most common symptoms of systemic BD and intestinal BD, such as oral ulcer, genital ulcer, abdominal pain, and diarrhea, and the most frequent location of intestinal ulcer involvement, such as the ileocecal region and colon, were also not different between the two groups. In comparison to the control group, the patients with intestinal BD–MDS had higher baseline DAIBD [90.0 (range, 60.0–117.5) vs. 40.0 (range, 10.0–90.0); *p*=0.009] and more frequent erythema nodosum (41.2% vs. 17.1%; *p*=0.016).

Intestinal BD–MDS vs. intestinal BD alone on clinical outcomes

Treatments, treatment responses, and clinical outcomes of patients with intestinal BD–MDS and intestinal BD without MDS are presented in Table 3 and Fig. 1. The percentage of patients with intestinal BD–MDS who received 5-ASA, CS, immunomodulator, and anti-TNFα agent was 100%, 85.7%, 14.3%, and 42.9%, respectively. Compared to 70 matched patients with intestinal BD alone, patients with intestinal BD–MDS underwent surgery more frequently (51.4% vs. 24.3%; *p*=0.010), and more patients had surgeries following medical treatment failure in the intestinal BD–MDS group (45.7% vs. 12.9%; *p*<0.001). We could not assess the treatment response of three patients in the case group owing to an insufficient follow-up period after starting the medication or a lack of data on symptoms and endoscopic findings. Among 32 patients with intestinal BD–MDS who received 5-ASA and/or CS, only 4 (12.5%) exhibited clinical and/or endoscopic/radiological improvements. In contrast, of 70 patients with intestinal BD without MDS, 29 (41.4%) showed improvement of symptoms and intestinal ulcers (*p*=0.004). Out of 28 patients with intestinal BD–MDS who showed no response to 5-ASA and/or CS, 16 received an immunomodulator and/or an anti-TNFα agent. Among them, four showed improvement in intestinal BD. Accordingly, out of 32 patients, 8 (25.0%) with intestinal BD–MDS exhibited clinical improvements with medical treatment. Out of 41 patients with intestinal BD without MDS who showed a poor response to 5-ASA and/or CS, 38 were treated with an immunomodulator and/or an anti-TNFα agent. Among them, clinical and/or endoscopic/radiological improvements were observed in 33 patients. Out of 70 patients with intestinal BD without MDS, 62 exhibited improved clinical and/or endoscopic/radiological findings after medication and/or surgical treatment

Table 2. Demographic and Clinical Characteristics of Patients with Intestinal BD Complicated by MDS and Controls

	Intestinal BD with MDS (n=35)	Intestinal BD alone (n=70)	*p* value
Sex (M/F)	12/23	24/46	>0.999
Age at diagnosis of intestinal BD, yr	46.0 (37.0–56.0)	45.5 (36.0–56.0)	0.734
Follow-up duration, yr	5.3 (2.6–8.5)	6.5 (3.9–11.3)	0.095
Baseline DAIBD	90.0 (60.0–117.5)	40.0 (10.0–90.0)	0.009*
Symptoms associated with BD			
Oral ulcer	33/34 (97.1)	69 (98.6)	>0.999
Genital ulcer	20/34 (58.8)	28 (40.0)	0.112
Ocular lesion	4/34 (11.8)	8 (11.4)	>0.999
Erythema nodosum	14/34 (41.2)	12 (17.1)	0.016*
Folliculitis	7/34 (20.6)	10 (14.3)	0.594
Arthritis	6/34 (17.6)	15 (21.4)	0.849
Central nervous system	2/34 (5.9)	1 (1.4)	0.517
Positive pathergy test	1/34 (2.9)	4 (5.7)	0.895
NA	1/35 (2.9)	0 (0)	
Symptoms associated with intestinal BD			
Abdominal pain	31 (88.6)	53 (75.7)	0.196
Hematochezia	4 (11.4)	13 (18.6)	0.512
Diarrhea	13 (37.1)	23 (32.9)	0.827
Fever	8 (22.9)	13 (18.6)	0.796
Vomiting	1 (2.9)	3 (4.3)	>0.999
Chest pain	1 (2.9)	3 (4.3)	>0.999
Location of intestinal ulcers			
Esophagus	1 (2.9)	4 (5.7)	0.871
Small intestine	5 (14.3)	7 (10.0)	0.745
Terminal ileum and Ileocecal	34 (97.1)	63 (90.0)	0.363
Colon	19 (54.3)	25 (35.7)	0.108
Rectum	4 (11.4)	3 (4.3)	0.333

M, male; F, female; DAIBD, disease activity index for intestinal Behçet's disease; IQR, interquartile range; BD, Behçet's disease; MDS, myelodysplastic syndrome; NA, not available.
Data are presented as median (IQR) or n (%).
*$p<0.05$.

(62/70; 88.6%; $p<0.001$) (Table 3 and Fig. 1). The anti-TNFα agent was much more effective in the control group (25.0% vs. 85.0%; $p<0.001$), and patients with intestinal BD–MDS manifested a deteriorating course of intestinal ulcers after medical or surgical treatments during their last visits (75.0% vs. 11.4%; $p<0.001$), along with higher mortality (28.6% vs. 0%; $p<0.001$). Seven of 35 patients with intestinal BD–MDS underwent HSCT, and four of seven exhibited a poor response to medical treatment prior to HSCT, resulting in all patients experiencing complete remission in both intestinal BD and MDS groups. The median follow-up period for patients who underwent HSCT was 24.0 months (range, 12.0–54.0 months).

Ten patients (28.6%) with intestinal BD–MDS died during the follow-up period: eight patients died from infectious complications associated with intestinal inflammation, such as septic shock due to perforation or peritonitis (6), toxic megacolon (1), and bleeding after surgery (1); and two patients died from hematological causes. Mortality was not observed in the intestinal BD alone group. The cumulative probabilities of death in both groups are presented in Fig. 2.

The prognosis for intestinal BD in patients with intestinal BD-MDS was associated with whether surgery was performed rather than with patient characteristics, the location of intestinal ulcers, or IPSS-R (Supplementary Table 1, only online).

Intestinal BD–MDS with trisomy 8 vs. non-trisomy 8 on clinical outcomes

Sex ratio, age, symptoms, treatment, and response to medial or surgical treatment did not differ between patients with intestinal BD–MDS with and without trisomy 8, except that patients with trisomy 8 were more likely to have genital ulcers than those without (Table 4).

DISCUSSION

Our study showed that patients with intestinal BD–MDS frequently have refractoriness to conventional medical or surgical treatment, with high mortality rates. Many case reports, case series, and systemic reviews have reported the clinical

Table 3. Treatments and Outcomes of Patients with Intestinal BD Complicated by MDS and Controls

	Intestinal BD with MDS (n=35)	Intestinal BD alone (n=70)	*p* value
Medical treatment for intestinal BD			
5-ASA	35 (100)	67 (95.7)	0.534
Corticosteroid	30 (85.7)	48 (68.6)	0.097
Immunomodulator	5 (14.3)	34 (48.6)	0.001*
Anti-TNFα agent	15 (42.9)	20 (28.6)	0.213
Surgery for intestinal BD			0.010*
No surgery	17 (48.6)	53 (75.7)	
Surgery	18 (51.4)	17 (24.3)	
Surgery before diagnosis	1 (2.9)	5 (7.1)	0.656
Surgery after medical treatment failure	16 (45.7)	9 (12.9)	<0.001*
Both	1 (2.9)	3 (4.3)	>0.999
Treatment for MDS		NA	NA
Conservative treatment only	21 (60.0)		
Hypomethylation	9 (25.7)		
Immunosuppressant	3 (8.6)		
HSCT	7 (20.0)		
Medical treatment and HSCT	4 (11.4)		
HSCT only	3 (8.6)		
Response to medical treatment			
Response to 5-ASA and/or corticosteroid	4/32 (12.5)	29/70 (41.4)	0.004*
Response to immunomodulator	0/5 (0)	16/34 (47.1)	0.066
Response to anti-TNFα agent	4/16 (25.0)	17/20 (85.0)	<0.001*
No response to 5-ASA and/or corticosteroid, not yet tried a different medical treatment	12/32 (37.5)	3/70 (4.3)	<0.001*
No response to immunomodulator and/or anti-TNFα agent	12/16 (75.0)	5/38 (13.2)	<0.001*
NA	3/35 (8.6)	0/70 (0)	
Outcome of intestinal BD			
No response to medical/surgical treatment	24/32 (75.0)	8/70 (11.4)	<0.001*
Improved after medical/surgical treatment	8/32 (25.0)	62/70 (88.6)	<0.001*
Improved after HSCT who had no response to medical treatment	4/4 (100)	NA	NA
NA	3/35 (8.6)	0/70 (0)	
Outcome of MDS		NA	NA
No change	21/35 (60.0)		
No response to medical treatment	11/11 (100)		
CR after HSCT	7/7 (100)		
Outcome at last follow-up			<0.001*
Survival	25/35 (71.4)	70/70 (100)	
Death	10/35 (28.6)	0/70 (0)	

BD, Behçet's disease; MDS, myelodysplastic syndrome; HSCT, hematopoietic stem cell transplantation; TNF, tumor necrosis factor; 5-ASA, 5-aminosalicylic acid; NA, not available.
Data are presented as n (%).
*p<0.05.

characteristics or treatments for patients with intestinal BD–MDS;[21-30] however, no study has systematically summarized the treatment response or outcome between intestinal BD with and without MDS. Therefore, the present study aimed to investigate the response to treatment and prognosis of intestinal BD–MDS and suggest a treatment strategy. HSCT can be an effective treatment modality for medically refractory patients with intestinal BD–MDS.

A previous review reported a higher proportion of females

(61.5% vs. 59.1%; *p*=1.000) and older individuals (44.5±12.7 vs. 37.7±11.2; *p*=0.055) in a group of patients with BD-MDS associated with bone marrow failure than in those without bone marrow failure, although these differences were statistically insignificant.[24] Another study also reported that patients with BD–MDS were significantly more likely to be female (75.0% vs. 48.2%; *p*=0.040) and were of older age (49.9±12.4 vs. 37.9±12.8; *p*=0.007) than patients having BD without MDS.[30] In this sex- and age-matched case-control study, a direct comparison of
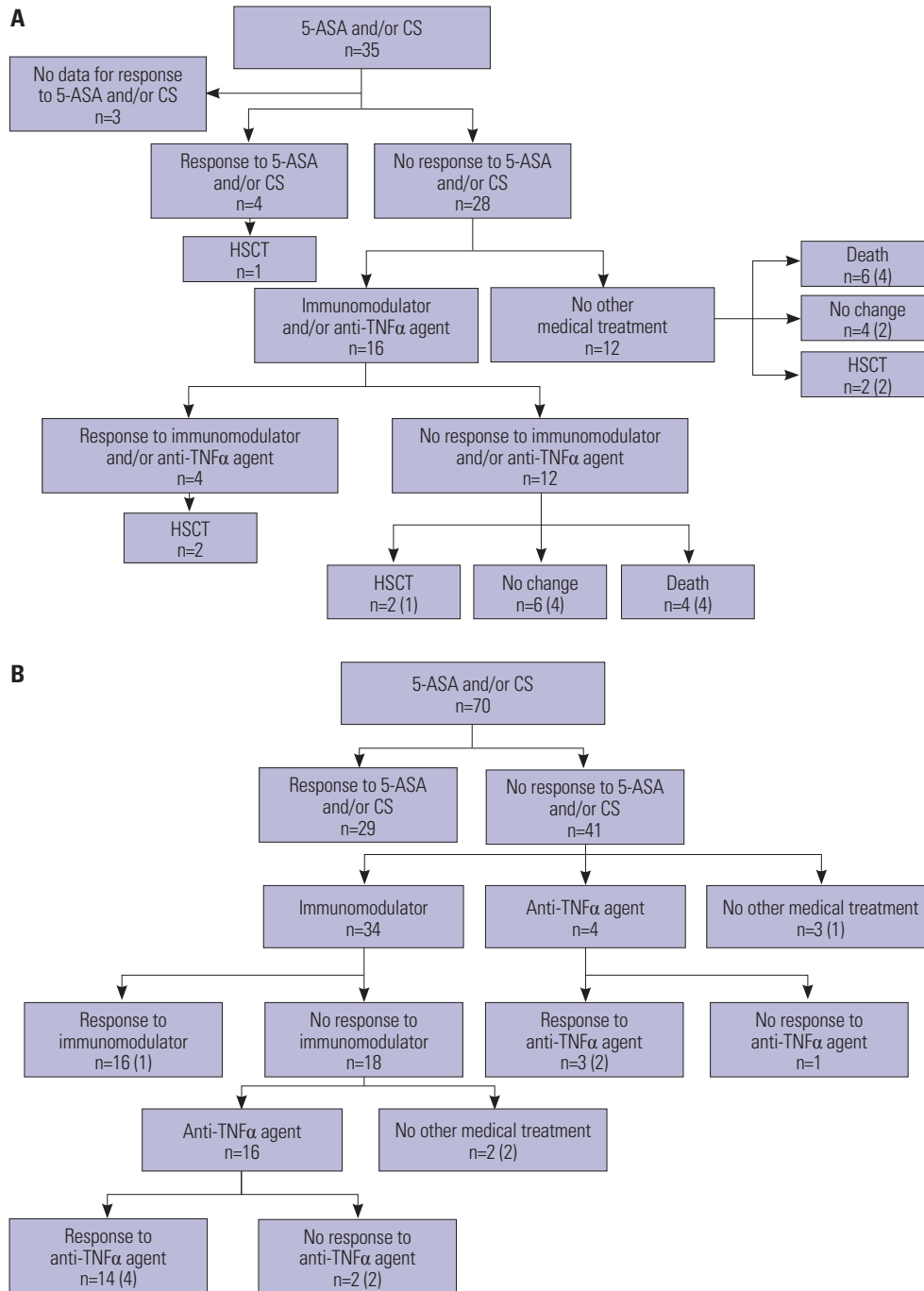
Fig. 1. Flowchart showing medical treatment and outcomes of patients with intestinal BD complicated by MDS (A) and controls (B). The number of patients who underwent surgery is represented in parentheses "( )." BD, Behçet's disease; MDS, myelodysplastic syndrome; 5-ASA, 5-aminosalicylic acid; CS, corticosteroid; TNF, tumor necrosis factor; HSCT, hematopoietic stem cell transplantation.

characteristics between the intestinal BD-MDS and intestinal BD groups was not feasible. However, our study found that a higher proportion of females (23/35; 65.7%) were diagnosed with intestinal BD–MDS. Additionally, the median age at diagnosis for intestinal BD was 46.0 years, with an age range of 37.0–56.0 years, aligning with previous research findings.[24,30]

According to previous studies, the prevalence of trisomy 8 in patients with MDS alone was only 7.0%–8.4%, whereas the prevalence of trisomy 8 in patients with BD and MDS was 76.2%–81.3%.[30,33-35] These studies further highlighted the higher frequency of gastrointestinal involvement (60%–85%) in patients with BD and MDS compared to the general BD populations (3%–60%); moreover, a trend for an increased frequency of gastrointestinal involvement in the BD–MDS with trisomy 8 group was observed, although the difference between non-trisomy 8 group was not statistically significant (74.4% vs. 50.0%;
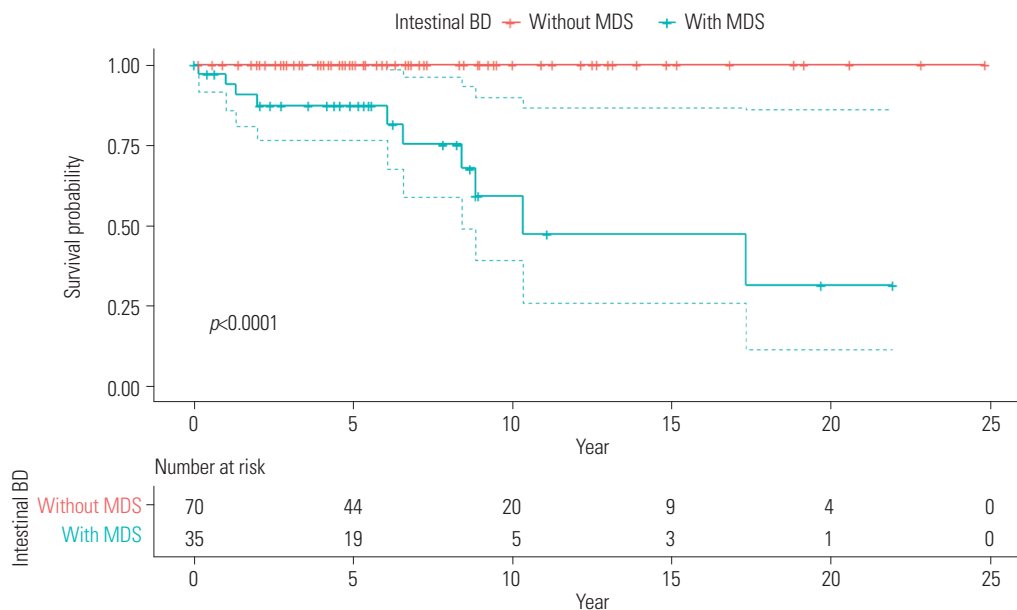
Fig. 2. Cumulative survival from index date in the intestinal BD complicated by MDS and intestinal BD alone groups using the Kaplan–Meier method. Index date: the earlier date of diagnosis between intestinal BD and MDS in the intestinal BD complicated by MDS group and the date of intestinal BD diagnosis in the intestinal BD alone group. BD, Behçet's disease; MDS, myelodysplastic syndrome.

p=0.150), indicating that MDS associated with trisomy 8 increases the risk of gastrointestinal involvement in patients with BD.[29,30,35-37] Previous studies have suggested that trisomy 8 may be associated with the pathogenesis of intestinal ulcers through the production of pro-inflammatory cytokines or reactive oxygen species; however, the underlying mechanisms remain unclear.[21,30,38,39] Therefore, it is conceivable that pathogenic mechanisms from cytogenetic abnormalities render intestinal ulcers more refractory to conventional BD treatments, potentially leading to a poor prognosis. Trisomy 8 has also been detected at a high frequency of 70.6% in patients with intestinal BD–MDS in our study; however, sex ratio, age, treatment response, and prognosis did not differ between intestinal BD–MDS patients with and without trisomy 8.

Anti-TNFα agent was considered the standard therapy for intestinal BD according to the 2nd edition of the Japanese Consensus Statements for Intestinal BD published in 2014.[7,40] As extensive intramedullary cell death in patients with MDS is related to TNFα, and the serum TNFα concentrations are elevated in patients with BD, anti-TNFα agents would theoretically be appropriate for treating intestinal BD–MDS.[41,42] However, previous studies showed that 5-ASA or CS and anti-TNFα agents were ineffective in treating intestinal BD–MDS, and only hematological therapy could improve both intestinal lesions and cytopenias.[25-27,29,43] Consistently, in our study, 5-ASA and/or CS, immunomodulators, and anti-TNFα agents provided clinical benefits in 4/32, 0/5, and 4/15 patients, respectively, whereas in all four patients who had been resistant to medical treatments, improvement in intestinal ulcers was observed following HSCT. Seven of the 35 patients with intestinal BD–MDS underwent HSCT. Three of these patients received HSCT due

to higher risk IPSS-R and cytopenias, despite showing a good medical response to intestinal BD treatment. Additionally, four patients underwent HSCT owing to higher risk IPSS-R, recurrent gastrointestinal infections, and refractory intestinal BD. All these patients achieved complete remission of both MDS and intestinal BD and survived until the last follow-up. Table 5 provides comprehensive details on the patients with intestinal BD-MDS who underwent HSCT. Among them, four were experiencing chronic graft-versus-host disease (GVHD), and one patient was being considered for lung transplantation due to lung fibrosis following Pneumocystis pneumonia. Ten patients with intestinal BD–MDS died at the last follow-up and could not receive HSCT. The majority of deaths were caused by complications of intestinal BD. None of the controls died, suggesting that MDS plays an important role in the prognosis of patients with intestinal BD–MDS, and that controlling intestinal ulcers and receiving early HSCT can improve survival rates.

One study suggested that the prognosis of patients with MDS with autoimmune inflammatory manifestations is closely related to the IPSS subcategory of the underlying hematological malignancy.[44] There was a significant difference in survival between low and non-low patients with IPSS for both groups (*p*<0.01).[44] Although one might anticipate that patients with intestinal BD–MDS would exhibit a poor prognosis as per the IPSS, our study did not find the IPSS-R to be a significant predictor of poor prognosis in BD–MDS (low and intermediate risk vs. high and very high risk, OR 0.46, CI 0.08–2.62; *p*=0.383). The lack of statistical significance in our findings may be attributed to the limited sample size of our study cohort. Nevertheless, we did identify another factor significantly associated with the poor prognosis of intestinal BD: the performance of surgery.

Table 4. Treatments and Outcomes of Patients with Intestinal BD Complicated by MDS with and without Trisomy 8

	Trisomy 8 (n=24)	Non-trisomy 8 (n=10)	*p* value
Sex (M/F)	8/16	3/7	>0.999
Age at diagnosis of intestinal BD, yr	41.0 (36.0–56.0)	50.5 (46.0–54.0)	0.069
Treatment for intestinal BD			
5-ASA	24 (100)	10 (100)	0.975
Corticosteroid	21 (87.5)	8 (80.0)	0.274
Immunomodulator	2 (8.3)	3 (30.0)	>0.999
Anti-TNFα agent	11 (45.8)	4 (40.0)	>0.999
Surgery	12 (50.0)	5 (50.0)	>0.999
Treatment for MDS			
Conservative treatment only	13 (54.2)		0.312
Hypomethylation	7 (29.2)		0.449
Immunosuppressant	1 (4.2)	2 (20.0)	0.412
HSCT	7 (29.2)	0	0.147
Medical treatment and HSCT	4 (16.7)		
HSCT only	3 (12.5)		
Symptoms associated with BD			
Oral ulcer	24 (100)	8/9 (88.9)	0.604
Genital ulcer	18 (75.0)	2/9 (22.2)	0.018*
Ocular lesion	2 (8.3)	1/9 (11.1)	>0.999
Erythema nodosum	11 (45.8)	3/9 (33.3)	0.801
Folliculitis	4 (16.7)	2/9 (22.2)	>0.999
Arthritis	4 (16.7)	2/9 (22.2)	>0.999
Central nervous system	1 (4.2)	1/9 (11.1)	>0.999
Positive pathergy test	0 (0)	1/9 (11.1)	0.604
NA	0	1/10 (10.0)	
Symptoms associated with intestinal BD			
Abdominal pain	20 (83.3)	10 (100)	0.429
Hematochezia	1 (4.2)	3 (30.0)	0.122
Diarrhea	7 (29.2)	6 (60.0)	0.194
Fever	6 (25.0)	2 (20.0)	>0.999
Vomiting	1 (4.2)	0	>0.999
Chest pain	1 (4.2)	0	>0.999
Response to medical treatment			
Response to 5-ASA and/or corticosteroid	3/22 (13.6)	1/9 (11.1)	0.946
Response to immunomodulator	0/2 (0)	0/3 (0)	>0.999
Response to anti-TNFα agent	3/11 (27.2)	1/4 (25.0)	0.933
NA	2/24 (8.3)	1/10 (10.0)	
Outcome of intestinal BD			
No response to medical/surgical treatment	12/22 (54.5)	7/9 (77.8)	0.149
Improved after medical/surgical treatment	6/22 (27.2)	2/9 (22.2)	0.924
Improved after HSCT who had no response to medical treatment	4/4 (100)	NA	
NA	2/24 (8.3)	1/10 (10.0)	
Outcome of MDS			
No change	17/24 (70.8)	10/10 (100)	0.078
No response to medical treatment	4/8 (50.0)	2/2 (100)	0.501
CR after HSCT	7/7 (100)	NA	
Outcome at last follow-up			>0.999
Survival	17 (70.8)	7 (70.0)	
Death	7 (29.2)	3 (30.0)	

BD, Behçet's disease; MDS, myelodysplastic syndrome; 5-ASA, 5-aminosalicylic acid; TNF, tumor necrosis factor; HSCT, hematopoietic stem cell transplantation; NA, not available.
Data are presented as median (IQR) or n (%).
*$p<0.05$.

This finding was consistent with our expectations, as surgical intervention was typically necessary in cases involving perforation, peritonitis, fistula, abscess, or refractory abdominal pain.

To the best of our knowledge, no study has included this many cases of intestinal BD–MDS and systematically evaluated the response to treatment and prognosis of intestinal BD–MDS among Asian patients in a single study. The results of our study demonstrate that Korean patients with intestinal BD–MDS, compared to patients with intestinal BD alone, had higher rates of surgery following medical treatment failure, showed poorer response to conventional medical treatment, including 5-ASA, CS, immunomodulators, and anti-TNFα agents, and had poorer outcomes. Although there was a difference in mortality between the two groups (intestinal BD–MDS vs. intestinal BD alone: 28.6% vs. 0%; $p<0.001$), we could not confirm a statistically significant difference in survival as no patient in the intestinal BD alone group died during the follow-up period. However, our overall data suggest a worse prognosis in the intestinal BD–MDS group regarding refractoriness to conventional treatment and mortality. We suggest initially considering conventional treatments, as our study showed that a subset of patients (8/32, 25.0%) responded to medical therapies, such as 5-ASA, CS, and anti-TNFα agents. Should these treatments fail and result in complications, such as recurrent infection, perforation, or persistent abdominal pain, physicians are advised to assess the appropriateness of HSCT for treating both intestinal BD and MDS. Nonetheless, it is vital to recognize the inherent risks of HSCT, including GVHD and infections. Therefore, conducting a thorough evaluation of these risks, in consultation with a hematologist, is imperative.

This retrospective study has a few limitations. First, although the present study included the largest study population for the investigation of intestinal BD–MDS epidemiology and prognosis among patients with intestinal BD, it may be limited by its small number of intestinal BD–MDS cases, which precludes a subdivided analysis of patient characteristics. Second, we could not find the role of trisomy 8 in patients with intestinal BD–MDS as reported by previous studies that trisomy 8 is associated with BD prognosis and refractoriness to conventional medical therapy. Third, patients after HSCT were observed for a short period of time, resulting in no long-term prognosis for them.

In conclusion, patients with intestinal BD–MDS frequently have refractory diseases with high mortalities. HSCT can be an effective treatment modality for medically refractory patients with intestinal BD–MDS, but caution is warranted due to its associated risks. The decision to pursue HSCT should be made through comprehensive discussions with a hematologist. Further accumulation of long-term data from patients undergoing HSCT is necessary to evaluate the effectiveness of HSCT.

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Table 5. Clinical Review of Seven Patients with Intestinal BD-MDS Who Received HSCT

No.	Age/sex	IBD onset in relation to MDS	Symptoms of BD	MDS type	IPSS-R	Ulcer location	Medical treatment for IBD	Response to medical treatment	Surgery	Treatment for MDS	Outcome-IBD	Outcome-MDS	Follow-up duration after HSCT
1	42/F	7 months before	O, G	MDS-MLD →AML-MRC	High	TI~HF	5-ASA, CS, ADA	No response	Yes	D, HSCT	Remission	CR	1 year 7 months
2	37/M	2.3 years after	O, S	MDS-SLD	High	TI~SC	5-ASA, CS, ADA	No response	No	HSCT	Remission	CR	5 years
3	60/F	1.4 years before	O	MDS-EB-1	Very high	TI~SC	5-ASA, CS	Good response	No	D, HSCT	Remission	CR	4 years 6 months
4	37/F	7.7 years before	O, G, S	MDS-EB-2	High	TI, ICV	5-ASA, CS, AZA, ADA	Good response	No	D, HSCT	Remission	CR	1 year
5	64/M	3.1 years before	O, G, S	MDS-MLD	Intermediate	ICV~SC	5-ASA, ADA	Good response	No	A, HSCT	Remission	CR	6 months
6	25/F	18.5 years before	O, G, S	MDS-EB-1	Very high	TI~TC	5-ASA, CS	Good →No response	Yes	HSCT	Remission	CR	3 years
7	37/F	17 years before	O, G, S	MDS-MLD	Very high	TI, ICV	5-ASA, CS	No response	Yes	HSCT	Remission	CR	2 years

IBD, intestinal Behcet's disease; MDS, myelodysplastic syndrome; IPSS-R, revised International Prognostic Scoring System; HSCT, hematopoietic stem cell transplantation; O, oral ulcer; G, genital ulcer; S, skin lesion; MDS-MLD, myelodysplastic syndrome with multilineage dysplasia; AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; MDS-SLD, myelodysplastic syndrome with single lineage dysplasia; MDS-EB-1, myelodysplastic syndrome with excess blasts-1; MDS-EB-2, myelodysplastic syndrome with excess blasts-2; TI, terminal ileum; ICV, ileocecal valve; HF, hepatic flexure; TC, transverse colon; SC, sigmoid colon; 5-ASA, mesalamine derivatives; CS, corticosteroids; AZA, azathioprine; ADA, adalimumab; D, decitabine; A, azacitidine; CR, complete response.

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