ORIGINAL ARTICLE

Overlooked Management and Risk Factors for Anemia in Patients with Intestinal Behçet's Disease in Actual Clinical Practice

Bun Kim, Soo Jung Park, Sung Pil Hong, Jae Hee Cheon, Tae Il Kim, and Won Ho Kim

Department of Internal Medicine and Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea

Background/Aims: Anemia in patients with inflammatory bowel disease significantly affects the quality of life. The aim of this study was to investigate the frequency of and risk factors for anemia and to describe the management of anemia in patients with intestinal Behçet's disease (BD) in actual clinical practice. **Methods:** We included 64 patients with intestinal BD who visited the outpatient clinic of a tertiary referral center in June 2011 and had available laboratory data for the subsequent 6 months. **Results:** Anemia was detected in 26 patients (40.6%). After 6 months, anemia was still present in 14 of these patients (53.8%). The cause of anemia was investigated in eight patients (30.8%), and oral iron supplementation was prescribed to four patients (15.4%). Of these four patients, two (50%) recovered completely within 6 months. Anemia was associated with a high Disease Activity Index for Intestinal Behçet's Disease (DAIBD, p=0.024), erythrocyte sedimentation rate (p=0.003), and C-reactive protein (p=0.049) in univariate analysis. In multivariate analysis, the factor predictive for anemia in patients with intestinal BD was a higher DAIBD (≥40; odds ratio, 4.08; 95% confidence interval, 1.21 to 13.71; p=0.023). **Conclusions:** Although anemia is common in intestinal BD patients, its clinical importance is overlooked in daily practice. Moderate to severe disease activity is predictive of anemia. **(Gut Liver 2015;9:750-755)**

Key Words: Intestinal Behçet's disease; Anemia; Frequency; Risk factors

INTRODUCTION

Behçet's disease (BD), which can cause chronic gastrointestinal (GI) inflammation, is a chronically relapsing multisystem vasculitis, characterized by recurrent oral and genital ulcers, ocular lesions, skin manifestations, arthritis, and vascular, neurologic, and intestinal involvements.[1] Because GI involvement can cause severe morbidity and mortality, BD is designated "intestinal BD" if GI symptoms predominate and typical ulcerative GI lesions are objectively documented.[2-4] The frequency of GI involvement ranges from 3% to 50% and varies depending on geographic location.[5,6] The most frequently affected site is the ileocecal region, which presents with symptoms of abdominal pain, diarrhea, and bleeding.[7,8]

The prevalence of anemia in patients with inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) ranges from 8.8% to 73.7%, depending on the patient subpopulation.[9-11] It has been considered an important factor affecting patient quality of life.[11] There have been a substantial number of studies on the epidemiology, risk factors and treatments of anemia in CD and UC.[12-14]

Among IBD patients, iron-deficiency anemia is the most common cause of anemia, and is usually manageable through medication. Iron deficiency is caused by iron malabsorption due to active disease, dietary restrictions, or intestinal bleeding. Moreover, in IBD patients, chronic intestinal inflammation leads to the upregulation of both proinflammatory cytokines (e.g., interleukin [IL]-1β, IL-6) and hepcidin, which results in impaired intestinal iron uptake from the gut and impaired iron sequestering in the reticuloendothelial system.[15-17] In addition, anemia in IBD patients can occur due to treatment. Therapy with sulfasalazine or 5-aminosalicylic acid has been related to a minor degree of hemolysis or aplasia.[18] Moreover, both 6-mercaptopurine and azathioprine have a direct myelosuppressive effect.[19] In addition to these possible causes of anemia in IBD, BD, as a type of vasculiits, has the characteristic that reactive oxygen species are produced endogenously at sites of endothelial inflammation by activated leukocytes and it could cause anemia.[20]

Unlike CD and UC, there have been no study on anemia in

patients with intestinal BD; therefore, in this study, we sought to establish the frequency of anemia and describe its management in patients with intestinal BD in actual clinical practice.

MATERIALS AND METHODS

1. Study design and patients

A cross-sectional study was performed based on well-organized electronic medical records. We included 77 patients with intestinal BD who had attended the outpatient clinic of a tertiary referral medical center between June 1, 2011 and June 30, 2011. Among them, we excluded 13 patients based on presence of hematologic malignancy or other severe comorbidities, or loss to 6-month follow-up to investigate not only the causes of anemia, but also treatment agents and the results of treatments after 6 months in these patients (three with myelodysplastic syndrome [MDS]; one each with aplastic syndrome [AA], liver cirrhosis, heart failure with valvular heart disease, and accompanied malignancy; six lost to follow-up).

We collected baseline data for clinical and endoscopic characteristics, comorbidities, gastrointestinal surgical history, family history, extraintestinal manifestations, Disease Activity Index for Intestinal Behçet's Disease (DAIBD)[21] at time of enrollment (June 2011), and any treatment for intestinal BD and anemia. Laboratory data was obtained at baseline and 6 months later, and included white blood cell count, hemoglobin, hematocrit, platelet, mean cell volume, mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), albumin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). To investigate the type of anemia, serum iron, total iron binding capacity, transferrin saturation (TSAT), vitamin B_{12}, folate and reticulocyte count were obtained at time of enrollment. At 6-month follow-up, hemoglobin levels of all patients were assessed. We chose the 6-month follow-up interval to evaluate the improvement of anemia because the hemoglobin level usually returns to normal by 6 to 8 weeks after taking oral iron.

We used DAIBD to evaluate disease activity in patients with intestinal BD. DAIBD is comprised of the following eight variables: general well-being, fever, extra-intestinal manifestations, abdominal pain, abdominal masses, intestinal complications, and number of liquid stools in 1 week. The DAIBD was used to classify disease into quiescent ($\leq$19), mild (20–39), moderate (40–74), or severe ($\geq$75) categories.[21]

2. Definitions of anemia

Anemia was defined according to the World Health Organization criteria: in men as hemoglobin <13 g/dL and in nonpregnant women as hemoglobin <12 g/dL. Iron deficiency anemia (IDA) was defined as a ferritin <30 μg/L when the corresponding CRP was <10 mg/L, or a ferritin <100 ng/mL when the CRP >10 mg/L and/or TSAT <16%.[22] Anemia of chronic disease (ACD) was defined as anemia in the presence of a CRP-adjusted, nor-

mal, or increased serum ferritin and/or a low plasma iron and iron binding capacity.[23] Vitamin B_{12} deficiency was defined as serum vitamin B_{12} <180 pg/mL, and folate deficiency as serum folate <2.34 ng/mL.

3. Statistical analysis

Continuous variables were expressed as the mean$\pm$standard deviation. Baseline characteristics of the nonanemia and anemia groups were compared using a Student t-test for continuous variables and a chi-square test (or Fisher exact test) for categorical variables. In multivariate analysis, logistic regression analysis was used to analyze associative factors of anemia in intestinal BD. Age, sex and the variables for which p<0.1 in univariate analysis except laboratory data were included in multivariate analysis.

Results were considered statistically significant when p<0.05. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Patient characteristics

From June 1, 2011 to June 30, 2011, a total of 64 patients with intestinal BD enrolled in our study. The baseline characteristics at diagnosis are summarized in Table 1. The mean age was 46.12$\pm$12.40 years, and 31.3% were male. Among these 64 patients, anemia was detected in 26 patients (40.6%). Twenty-three patients (35.9%) underwent more than one gastrointestinal surgery, including ileocecectomy (13) and right hemicolectomy (9). The mean DAIBD value was 37.73$\pm$32.39 in June 2011; based on DAIBD, eight patients had severe, 22 had moderate, nine had mild, and 25 had quiescent disease in June 2011. In terms of laboratory data, the mean values of ESR, CRP, and hemoglobin level were 32.27$\pm$27.35 mm/hr, 11.19$\pm$21.16 mg/L, and 12.52$\pm$1.83 mg/dL, respectively.

The cause of anemia was investigated in eight of 26 patients with anemia (one with IDA, two with ACD, four with combined type of IDA and ACD, and the other one with undetermined type); oral ferrous medication was prescribed to four patients. There was no patient who was given intravenous iron and/or erythropoietin (EPO) in this study (Table 1).

2. Comparison of baseline characteristics with regard to anemia

The patients were divided into two groups by blood hemoglobin level: those without (n=38) and those with anemia (n=26). A comparison of baseline characteristics is presented in Table 2. Most baseline characteristics, including age, sex, disease duration, type and frequency of gastrointestinal operation and medication for BD were not significantly different between the two groups. However, the number of patients with moderate to severe disease activity in DAIBD was significantly greater in

Table 1. Baseline Characteristics of Patients with Intestinal Behçet's Disease (n=64)

Characteristic	Value
Age, yr	46.12±12.4
Sex, male/female	20 (31.3)/44 (68.8)
Duration of intestinal BD, mo	80.03±61.84
GI operation	23 (35.9)
No. of GI operations	0.64±21.96
Type of GI operation (duplicates allowed)	
Appendectomy	6 (9.4)
Small bowel resection	5 (7.8)
Right hemicolectomy	9 (14.1)
Ileocecectomy	13 (20.3)
Anal fistulectomy	2 (3.1)
DAIBD	37.73±32.39
Quiescent-mild (0–39)	34 (53.1)
Moderate-severe (≥40)	30 (46.9)
Laboratory data	
WBC, /μL	5,961±2,737.6
Hemoglobin, g/dL	12.52±1.83
Hematocrit, %	37.96±4.96
MCV, fL	91.63±9.26
MCHC, g/dL	32.62±1.56
RDW, %	14.57±2.33
Platelet, $\times 10^3$/μL	254.45±78.88
Albumin, g/dL	4.20±0.48
ESR, mm/hr	32.27±27.35
CRP, mg/L	11.19±21.16
Intestinal BD medication (duplicates allowed)	
Sulfasalazine, mesalazine, 5-ASA	62 (96.9)
Purine analogue	22 (34.3)
Anti-TNF-α inhibitor	1 (1.6)
Corticosteroids	15 (23.4)
Laboratory data of anemia	
Ferritin (n=10)	78.24±119.26
Serum iron, μg/dL	64.9±39.17
TIBC, μg/dL	293.5±109.46
TSAT, %	28.8±26.96
Vitamin B_{12}, pg/mL	640.57±376.93
Folate, ng/mL	9.26±6.08
Reticulocyte count, %	1.73±0.75
Iron replacement	
Oral ferrous	4
Intravenous	0
Erythropoietin	0
Hemoglobin after 6 mo, g/dL	13.03±1.54

Data are presented as mean±SD or number (%).
BD, Behçet's disease; GI, gastrointestinal; DAIBD, Disease Activity Index for Intestinal Behçet's Disease; WBC, white blood cell count; MCV, mean cell volume; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; 5-ASA, 5-aminosalicylic acid; anti-TNF-α, anti-tumor necrosis factor α; TIBC, total iron binding capacity; TSAT, transferrin saturation.

the anemia group than in the nonanemia group (18/26 [69.2%] vs 12/38 [31.6%], p=0.003). Also, ESR and CRP, both thought to be associated with disease activity, were significantly higher in the anemia group than in the nonanemia group (46.15±34.0 mm/hr vs 22.76±16.26 mm/hr, p=0.003; 17.31±21.98 mg/L vs 6.41±19.99 mg/L, p=0.049, respectively). The anemia group had higher mean values of RDW (15.94%±2.70% vs 13.62%±1.43%, p<0.001) and platelet count (288.08±91.82×10^3/μL vs 231.45± 59.66×10^3/μL, p<0.001) than the nonanemia group. Hemoglobin (10.85±1.08 g/dL vs 13.67±1.26 g/dL, p<0.001), hematocrit (33.49%±3.25% vs 41.02%±3.32%, p<0.001), MCHC (31.95±1.58 g/dL vs 33.62±1.40 g/dL, p=0.004), and albumin (3.91±0.57 g/dL vs 4.39±0.29 g/dL, p<0.001) were lower in the anemia group.

The cause of anemia was investigated in only eight patients (30.8%) of the 26 with anemia, and oral ferrous medicines prescribed to four (50%); these four were prescribed ferrous sulfate 256 mg once or twice daily, and two (50%) were able to recover normal hemoglobin levels within 6 months. Overall hemoglobin levels in all patients after 6 months were lower (11.99±1.12 vs 13.75±1.38, p<0.001), and anemia (14/26 [53.8%] vs 2/38 [5.3%], p<0.001) was more frequent in the initial anemia group (Table 2).

3. Factors predictive of anemia in intestinal BD according to multivariate analysis

In multivariate analysis adjusted for age, sex, number of GI operation, DAIBD and corticosteroids use, the independent factor predictive of anemia in patients with intestinal BD was moderate to severe DAIBD (odds ratio, 4.08; 95% confidence interval, 1.21 to 13.71; p=0.023). However, the number of previous gastrointestinal operation and corticosteroids use were not independent factors relating anemia to IBD (Table 3).

DISCUSSION

In the present study, we found the frequency, short-term prognosis, and predictive factors of anemia in intestinal BD patients for the first time. Anemia in patients with intestinal BD was detected as high as 40.6% in this study. Moreover, anemia was meaningfully associated with disease activity of intestinal BD.

Similar to anemia in patients with IBD, anemia in patients with intestinal BD can occur due to chronic disease, iron deficiency, vitamin deficiency and treatment itself such as sulfasalazine, 5-aminosalicylic acid, and azathioprine. Despite, in this study, the number of patients who were surveyed the cause of anemia was small (8/26, 30.77%) in the anemia group, seven out of eight were associated with IDA and/or ACD. This finding was accordance with the result of a previous study in patients with IBD which showed that the main causes of anemia in IBD were mostly IDA, ACD, and a combination of both.[9]

In addition, our study showed that the anemia group had higher platelet count than the nonanemia group and it also

Table 2. Comparisons of Baseline Characteristics with Regard to Anemia

Characteristic	Nonanemia group (n=380)	Anemia group (n=26)	p-value
Age, yr	44.34±12.27	48.73±12.36	0.166
Male sex	11 (28.9)	9 (34.6)	0.783
Medication			
NSAIDs	14 (36.8)	11 (42.3)	0.660
Antiplatelet drug	2 (5.3)	1 (3.8)	0.641
Duration of intestinal BD, mo	77.82±58.18	83.27±67.89	0.732
GI operation	11 (28.9)	12 (46.2)	0.159
No. of GI operations	0.46±0.76	0.96±1.71	0.090
0–1	34 (61.8)	21 (38.2)	0.467
≥2	4 (44.4)	5 (55.6)	
Type of GI operation (duplicates allowed)			
Appendectomy	2 (5.3)	4 (66.7)	0.213
Small bowel resection	3 (7.9)	2 (7.7)	>0.999
Right hemicolectomy	3 (7.9)	6 (23.1)	0.142
Ileocecectomy	6 (15.8)	7 (26.9)	0.277
Anal fistulectomy	1 (2.6)	1 (3.8)	>0.999
DAIBD	30.26±30.36	48.65±32.73	0.024
Quiescent-mild (0–39)	26 (68.4)	8 (30.8)	0.003
Moderate-severe (≥40)	12 (31.6)	18 (69.2)	
Laboratory data			
WBC, /μL	5,424.47±1,998.12	6,745.38±3,449.61	0.087
Hemoglobin, g/dL	13.67±1.26	10.85±1.08	<0.001
Hematocrit, %	41.02±3.32	33.49±3.25	<0.001
MCV, fL	91.26±7.09	92.16±11.88	0.732
MCHC, g/dL	33.62±1.40	31.95±1.58	0.004
RDW, %	13.62±1.43	15.94±2.70	<0.001
Platelet, ×10³/μL	231.45±59.66	288.08±91.82	0.009
Albumin, g/dL	4.39±0.29	3.91±0.57	<0.001
ESR, mm/hr	22.76±16.26	46.15±34.0	0.003
CRP, mg/L	6.41±19.99	17.31±21.98	0.049
Intestinal BD medication (duplicates allowed)			
Sulfasalazine, mesalazine, 5-ASA	36 (94.7)	26 (100)	0.510
Purine analogue	13 (34.2)	9 (34.6)	0.973
Anti-TNF-α inhibitor	0	1 (3.8)	0.406
Corticosteroids	6 (15.8)	9 (34.6)	0.081
Anemia laboratory data	(n=2)	(n=8)	
Ferritin, ng/mL	58.10±38.33	83.28±133.91	0.807
Serum iron, μg/dL	49.50±12.02	68.75±43.21	0.566
TIBC, μg /dL	258.50±34.65	302.25±121.64	0.642
TSAT, %	19.00±1.41	31.25±30.0	0.596
Reticulocyte count, %	1.86±1.0	1.70±0.76	0.807
	(n=1)	(n=6)	
Vitamin B$_{12}$, pg/mL	808.0	612.67±404.91	0.674
Folate, ng/mL	3.02	10.30±5.94	0.308
Iron replacement			0.024
Oral ferrous	0	4 (15.4)	
Intravenous	0	0	
Erythropoietin	0	0	
Hemoglobin after 6 mo, g/dL	13.75±1.38	11.99±1.12	<0.001
Anemia after 6 mo	2 (5.3)	14 (53.8)	<0.001

Data are presented as mean±SD or number (%).

NSAIDs, nonsteroidal anti-inflammatory drugs; BD, Behçet's disease; GI, gastrointestinal; DAIBD, Disease Activity Index for Intestinal Behçet's Disease; WBC, white blood cell count; MCV, mean cell volume; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; 5-ASA, 5-aminosalicylic acid; anti-TNF-α, anti-tumor necrosis factor α; TIBC, total iron binding capacity; TSAT, transferrin saturation.

Table 3. Factors Predictive of Anemia in Intestinal Behçet's Disease according to the Multivariate Analysis

Factor	OR (95% CI)	p-value
Age, yr	1.04 (0.99–1.09)	0.099
Male sex	0.94 (0.28–3.23)	0.925
No. of GI operations	1.43 (0.76–2.70)	0.271
DAIBD (≥40, moderate-severe)	4.08 (1.21–13.71)	0.023
Intestinal BD medication		
Corticosteroids use	1.58 (0.40–6.23)	0.512

OR, odds ratio; CI, confidence interval; GI, gastrointestinal; DAIBD, Disease Activity Index for Intestinal Behçet's Disease; BD, Behçet's disease.

accordance with previous studies of IBD. Several studies suggest that platelets are involved in the pathogenesis of IBD and increased platelet count has been associated with disease activity in IBD.[24-27] Moreover, reactive thrombocytosis has been associated in adults with iron deficiency anemia, inflammatory conditions.[28] As a result, both inflammation and iron deficiency predisposes patients with BD as well as UC and CD to develop thrombocytosis.

Interestingly, BD, which is predominantly associated with MDS,[29] is highly relevant to anemia itself. In such cases those are associated with MDS, patients with BD demonstrate more frequent gut involvement, and were associated with trisomy 8 in their bone marrow.[30,31] Besides MDS, there may also be an association between BD and bone marrow failure, such as in AA. Consistent with these findings, there were three patients (3/87, 3.45%) with MDS and one patient (1/87, 1.15%) with AA who were initially excluded in this study.

Furthermore, despite the exclusion of patients with bone marrow failure-related anemia, this study showed that the frequency of anemia in intestinal BD patients (40.6%) remained as high as that of patients with CD and UC.[9-11]

The ultimate therapeutic goal for intestinal BD patients with anemia is improvement in quality of life; however, in this study, the only objective measures we can gather are changes in laboratory data, including hemoglobin concentrations. In anemic cancer patients, improvements in quality of life were reported beginning at hemoglobin levels of up to 14 g/dL.[32] Since BD patients are younger, on average, than cancer patients, they may experience higher physical and cognitive demands; thus, normalization of hemoglobin levels (12.0 g/dL in women and 13.0 g/dL in men) in patients with intestinal BD should be considered as for the goal of treatment of anemia in CD and UC patients.[9]

According to multivariate analysis, intestinal BD patients with moderate to severe DAIBD are likely to have anemia. This is a similar finding with IBD patients. In IBD patients, previous studies showed that the higher disease activity was associated with lower hemoglobin and hematocrit level and this phenomenon was explained as inflammation inhibits iron absorption

and links to abnormal iron homeostasis.[13,33] Physicians should evaluate the causes and types of anemia, and aggressively manage the intestinal BD patients with anemia using intravenous iron and/or EPO in order to prevent the increase of frequency of anemia and identify malignant conditions such as MDS or AA.

There were several limitations in our study. First, it was a retrospective, cross-sectional, case-control study that was based on medical record review. Nevertheless, we sought to identify predictive factors of anemia by analyzing a well-organized, computer-based medical database. Secondly, data were collected from a single hospital that was part of a tertiary referral center. This might cause our patient group to differ from the general population of Koreans with BD. Due to its rarity and challenging diagnosis, however, most BD patients were managed in tertiary university hospitals rather than primary or secondary medical centers in Korea, and our medical center follows up the largest number of the patients with intestinal BD in Korea. As such, the patient group in this study could show less bias, though patients were recruited from a single tertiary university hospital.

In conclusion, the frequency of anemia in patients with intestinal BD was as high as that of patients with CD and UC. However, the importance of anemia in intestinal BD patients is still overlooked in clinical practice. Therefore, we suggest that physicians pay particular attention to anemia in patients with intestinal BD, in order to improve patient quality of life and monitor for serious underlying problems, such as MDS and AA.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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