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Research Article

Severe Activity and Cytomegalovirus Colitis May Increase Risk of Venous Thromboembolism in Inflammatory Bowel Disease

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Abstract

There is still a paucity of data on Venous Thromboembolism (VTE) in Asian populations. We compared patients with VTE and IBD to matched IBD controls without VTE. Of 4467 patients diagnosed with IBD, 26 patients with VTE were identified, including 12 with Crohn's Disease (CD) and 14 with Ulcerative Colitis (UC). The incidence of VTE was 0.58%. The recent use of steroids (odds ratio [OR] = 7.00; 95% CI = 1.59–30.77; p = 0.010) and elevated C-reactive protein (CRP) (OR = 1.17; 95% CI = 1.00–1.37; p = 0.046) were associated with an increased risk of developing VTE. Each 1% rise in hematocrit decreased the risk of VTE by 14% (OR = 0.86; 95% CI = 0.77–0.97; p = 0.015). According to second analysis, CMV colitis is associated with an increased risk of developing VTE (OR = 4.01; 95% CI = 1.49–10.78; p =0.006). The incidence of VTE seems to be lower in Asian than in Western patients. Higher disease activity is associated with an increased risk of developing VTE and CMV colitis may also increase this risk. IBD patients with CMV colitis and higher disease activity may require vigilant observation to diagnose VTE.

ABBREVIATIONS

CD: Crohn's disease; CMV: Cytomegalovirus; CRP: C-reactive protein; CT: Computed Tomography; EVT: Extremity Venous Thrombosis; IBD: Inflammatory Bowel Disease; IHC: Immunohistochemistry; IVC: Inferior Vena Cava; IVT: Intraabdominal Venous Thrombosis; OR: Odds Ratio; PTE: Pulmonary Thromboembolism; UC: Ulcerative Colitis; VTE: Venous Thromboembolism

INTRODUCTION

Crohn's disease (CD) and Ulcerative Colitis (UC) present as chronic relapsing conditions and are the major forms of idiopathic Inflammatory Bowel Disease (IBD). IBD predominantly involves the bowels, but is also associated with a number of extraintestinal manifestations. Venous thromboembolism (VTE) isa well-established complication of IBD and is associated with substantial mortality [1,2]. Male gender, old age, and acute disease flare-up are associated with increased risk of VTE in IBD populations [1]. Recently, it was suggested that Cytomegalovirus (CMV) contributes to the development of VTE in immune compromised and immune competent adults, either due to endothelial-damaging or procoagulant properties, thereby resulting in the expression of tissue factors and procoagulant phospholipids on the endothelial surface [3-6].

Korean IBD patients differ from their Western counterparts in terms of clinical features and may also demonstrate better clinical outcomes, as indicated by the lower rates of intestinal resection [7,8]. Moreover, rates of deep venous thrombosis, pulmonary embolism, and venous thromboembolism; incidences in hospitalized patients; and the mortality rate from pulmonary embolism were markedly lower in Asians/Pacific Islanders than in whites and African Americans [9]. However, there have been no studies on VTE in Asian IBD patients.

We here assess the incidence, clinical characteristics, risk factors, and related VTE outcomes in a Korean IBD patient cohort in this nested case-control study. We also investigate the

potential role of CMV colitis in IBD patients with VTE, and analyze colonic tissue samples in order to reliably evaluate CMV colitis.

MATERIALS AND METHODS

Patients

Between July 1989 and January 2013, a total of 4467 IBD patients (2004 CD and 2463 UC patients) were registered at the IBD clinic of the Asan Medical Center, a tertiary university hospital in Seoul, Korea. CD and UC were diagnosed using conventional clinical, radiologic, endoscopic, and histopathologic criteria [10-12]. We identified VTE events in the registry using two methods. First, we selected IBD patients who required anticoagulation therapy or the insertion of an Inferior Vena Cava (IVC) filter during illness (n = 76). Of these, we excluded patients who had received anticoagulants other than VTE (n = 49). Second, we selected IBD patients whose VTE was detected using Doppler ultrasonography, computed tomography (CT) angiography, and/or ventilation/perfusion scans (n = 6). At first, 33 patients were diagnosed with VTE; of these, 3 patients were excluded because of coexisting malignancies (pancreatic cancer, jejunal cancer, or lymphoma, respectively) and 4 patients were excluded because of the lack of information on radiologic and/or symptomatic outcomes. A final cohort of 26 VTE patients waa identified for the analysis and was stratified according to the following anatomic areas: Extremity Venous Thrombosis (EVT) with or without Pulmonary Thromboembolism (PTE); Intraabdominal Venous Thrombosis (IVT); or cerebral venous thrombosis.

Methods

Medical records were retrospectively reviewed. We first calculated the incidence of VTE in patients with IBD and compared their clinical characteristics, including sex, age at diagnosis, age at time of first VTE occurrence, disease duration from IBD diagnosis to first VTE, previous history of intestinal resection, disease location and behavior according to the Montreal classification of IBD [13], laboratory data (e.g., complete blood count, C-reactive protein (CRP), albumin), presence of CMV colitis, and medical treatments administered before the occurrence of VTE. In terms of the disease itself, the involved VTE location, diagnostic and therapeutic modalities, follow-up duration, and final outcomes were reviewed.

We extracted indications and corticosteroid doses for our patients from the medical record. Indications for the use of corticosteroids were similar among the physicians at our hospital (BDY, SKY, KJK). Almost all patients received corticosteroids as treatment for moderate to severe UC or CD activity. In most patients, corticosteroid therapy consisted of oral prednisone or intravenous methylprednisolone (0.8–1 mg/kg/day). CMV colitis (i.e., CMV disease involving the colon) was diagnosed using Immunohistochemistry (IHC) according to current European guidelines [14]. A Single Pathologist (SMH), who was blind to the clinical data, reviewed and evaluated the endoscopic biopsies.

To identify the risk factors for VTE in our IBD patients, we performed nested case-control analysis, the core feature of this current study. Patients (IBD patients with VTE) were classified as IBD patients who developed VTE during their illnesses. The control group consisted of IBD patients without VTE events who were selected from the 2187 patients with CD and 2592 patients with UC; they were matched 3:1 according to disease (UC or CD), calendar year of their first visit to our institution because of the symptoms or signs of IBD (± 2 years), and IBD duration prior to the first visit (± 2 years).

Two sets of analyses were performed. The first set addressed the hypothesis that patients with severe disease would be more likely to develop VTE. The second set addressed the hypothesis that IBD patients with CMV colitis would be more likely to develop VTE than IBD patients without VTE. This second analysis was restricted to patients who provided colonic tissue samples. The institutional review Board of Asan Medical Center approved this retrospective study and waived the requirement for informed patient consent (IRB no.: 2013-0148).

Statistics

Continuous variables are expressed as medians with ranges; discrete data are tabulated as numbers and percentages. The Chi-square and *t* test were used to compare disease proportions. All possible risk factors were examined using logistic regression modeling and generalized estimating equations to identify the risk factors for VTE that were present in the VTE group relative to the non-VTE group. Univariate and multivariate analyses were performed using conditional logistic regression modeling to account for the clustering of matched pairs. The multivariate analysis was performed using backward elimination after multiple imputations for missing data. Clinical outcomes were assessed using logistic regression modeling, generalized estimating equations, and Poisson regression with random effects to account for the clustering of matched pairs. PASW statistics (v. 20.0; SPSS, Chicago, IL) and SAS software (version 9.1; SAS Institute, Inc., Cary, NC) were used to perform all analyses. In this study, p values < 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Incidence and clinical characteristics of VTE

Twenty-six of 4467 IBD patients treated at our center were diagnosed with VTE. The overall incidence of VTE was 0.58% (26 of 4467 patients).Twelve patients with CD (0.60%; 12 of 2004 patients) and 14 patients with UC (0.57%; 14 of 2463) were identified. No differences were found between CD and UC patients in terms of VTE frequency. There were no differences in terms of sex, median age at diagnosis, or median duration of disease. The clinical presentations of IBD-related gastrointestinal symptoms, such as diarrhea, bloody diarrhea, and/or abdominal pain presented in 19 patients (73.1%), leg swelling in 4 patients (15.4%), and headache 2 in patients (7.7%). CT analysis incidentally detected underling disease in 1 patient (3.8%). The demographic and clinical characteristics of the patients with and without VTE are shown in Table 1. Eleven of 14 UC patients (78.6%) and 10 of 12 CD patients (83.3%) were diagnosed with extensive colitis and ileocolonic involvement, respectively.

Medications prescribed at the diagnosis of VTE included corticosteroids in 20 patients (76.9%), immunosuppressants in 9 patients (34.6%), and mesalazine in 14 patients (53.8%). One patient received infliximab within 3 months of VTE. No related deaths occurred.

Table 1: Demographic characteristics of IBD patients with and without VTE.

Variable	Patients with VTE (n = 26)	Patients without VTE (n = 78)	*p*
Diagnosis [n (%)]			1.000†
Ulcerative colitis	14 (53.8)	42 (53.8)	
Crohn's disease	12 (46.2)	36 (46.2)	
Disease duration, mo [median (range)]	21.36 (-0.3–280.1)	18.95 (-0.9–306.8)	0.961‡
Montreal location [n (%)]			
Ulcerative colitis			0.012†
Proctitis	1 (7.1)	14 (33.3)	
Left-side	2 (14.3)	14 (33.3)	
Extensive	11 (78.6)	14 (33.3)	
Crohn's disease			0.760†
Ileum	2 (16.7)	8 (22.2)	
Colon	0	1 (2.8)	
Ileocolon	10 (83.3)	27 (75.0)	
Montreal behavior [n (%)]			0.008†
Nonstricturing nonpenetrating	0	18 (50.0)	
Stricturing	3 (25.0)	5 (13.9)	
Penetrating	9 (75.0)	13 (36.1)	
Upper gastrointestinal modifier [n (%)]	4 (33.3%)	6 (16.7%)	0.241†
Perianal fistula modifier [n (%)]	4 (33.3%)	16 (44.4%)	0.737†

†Determined using the Chi-square test.
‡t test.
Abbreviation: IBD: Inflammatory Bowel Disease; VTE: venous thromboembolism

Anatomic areas of VTE occurrence

VTE developed in 38 anatomic areas in 26 patients, and these areas are presented in Table 2. VTE occurred most commonly in the superior mesenteric vein (28.9%).

Treatment and recurrence of VTE

Anticoagulation therapy was initially administered to 17 patients (65.4%). IVC filters were placed in 4 patients (15.4%) The remaining 5 patients (19.2%) did not receive any treatment and 1 of these cases developed VTE recurrence in 4 months. During the follow-up period following VTE development, 2 of 17 patients who had been administered anticoagulation therapy developed VTE recurrence within 13 and 132 months, respectively. Therefore, 3 of 26 patients (11.5%) developed recurrent VTE.

VTE risk factors

Table 3 shows the results of our univariate and multivariate analyses used to assess all patients with and without VTE. According to the univariate analysis, the recent use of corticosteroids is associated with VTE occurrence. Moreover, increased white blood cell and CRP levels and decreased hematocrit and albumin levels were found to be associated with an increased risk of VTE. The significant variables ($p < 0.02$) shown in Table 3were entered into the multivariate analysis because of the limited number of events. According to this model, the recent use of steroids (odds ratio [OR] = 7.00; 95% CI = 1.59–30.77; $p = 0.010$) and elevated CRP (OR = 1.17; 95% CI = 1.00–1.37; $p = 0.046$) increase the risk of developing VTE. Moreover, every 1% rise in hematocrit decreased the risk of VTE by 14% (OR = 0.86; 95% CI = 0.77–0.97; $p = 0.015$).

CMV colitis and VTE occurrence

Our second set of analyses included only 43 patients (17 and 26 patients in the VTE and control groups, respectively) who had colonic tissues available for IHC analysis. The results of this second analysis (Table 4) were found to be similar to those from the first analysis (Table 3). Although the recent use of corticosteroids tended to increase the risk of VTE, only CMV colitis was associated with an increased risk of VTE (OR = 4.01; 95% CI = 1.49–10.78; $p = 0.006$).

Table 2: Anatomic areas of venous thromboembolism (n = 26).

Anatomic areas of venous thromboembolism	No. (%)
Extremity venous thrombosis/Pulmonary thromboembolism	15 (39.5)
Extremity venous thrombosis	9 (23.7)
Pulmonary thromboembolism	6 (15.8)
Intraabdominal venous thrombosis	21 (55.2)
Portal vein	9 (23.7)
Superior mesenteric vein	11 (28.9)
Uterine vein	1 (2.6)
Cerebral venous thrombosis	2 (5.3)
Total	38 (100)

Table 3: Univariate and Multivariate Analysis of IBD Patients with and without VTE.

Variable	Patients with VTE (n = 26)	Patients without VTE (n = 78)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*p*	OR (95% CI)	*p*
Sex [male (%)]	16 (61.5)	43 (55.1)	0.77 (0.31–1.90)	0.570†		
Age at the diagnosis, y [median (range)]	31.54 (12.74–57.34)	27.50 (9.96–69.25)	1.00 (0.96–1.04)	0.957†		
BMI [kg/m^2± SD]	18.87 ± 3.30	21.27 ± 3.50	0.80 (0.68–0.95)	0.009†		
Smoking [no/yes (%)]	13/13 (50.0/50.0)	53/25 (67.9/32.1)	2.22 (0.86–5.73)	0.100†		
Recent use of corticosteroid (< 3 m) [n (%)]	20 (76.9)	19 (24.4)	11.98 (3.45-41.6)	< 0.001†	7.00 (1.59–30.77)	0.010†
White blood cells [/mm^3 ± SD]	8.64 ± 4.60	6.66 ± 2.55	1.20 (1.04–1.39)	0.012†		
Hematocrit [% ± SD]	33.33 ± 5.00	39.33 ± 5.84	0.82 (0.74–0.91)	< 0.001†	0.86 (0.77–0.97)	0.015†
Platelets [× 10^3/mm^3 ± SD]	270.19 ± 149.68	275.00 ± 88.91	1.00 (0.99–1.00)	0.829†		
C-reactive protein [mg/dL ± SD]	5.50 ± 5.95	1.37 ± 2.99	1.25 (1.07–1.45)	0.004†	1.17 (1.00–1.37)	0.046†
Albumin [g/dL ± SD]	2.79 ± 0.71	3.78 ± 0.76	0.16 (0.06–0.46)	0.001†		

†Logistic regression modeling and the generalized estimating equations were used to account for the clustering of matched pairs.
Abbreviation: BMI: Body Mass Index; CI: Confidence Interval; CMV: Cytomegalovirus; IBD: Inflammatory Bowel Disease; OR: Odds Ratio; SD: Standard Deviation; VTE: Venous Thromboembolism

Table 4: Univariate and Multivariate Analysis of IBD Patients who Provided Colon Tissues.

Variable	Patients with VTE (n = 17)	Patients without VTE (n = 26)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*p*	OR (95% CI)	*p*
Sex [male (%)]	10 (58.8)	18 (69.2)	1.70 (0.48–6.09)	0.412†		
Age at the diagnosis, y [median (range)]	34.12 (12.74–43.49)	30.37 (16.70–60.44)	1.00 (0.97–1.03)	0.885†		
BMI [kg/m^2± SD]	17.96 ± 2.56	21.35 ± 3.50	0.77 (0.64–0.93)	0.007†		
Diagnosis [CD/UC (%)]	7/10 (41.2/58.8)	12/14 (46.2/53.8)	1.10 (0.74–1.63)	0.652†		
Smoking [no/yes (%)]	9/8 (52.9/47.1)	18/8 (69.2/30.8)	1.45 (0.54–3.89)	0.464†		
Recent use of corticosteroids (< 3 m) [n (%)]	15 (88.2)	12 (46.2)	3.69 (1.26–10.84)	0.017†	3.85 (0.90–16.58)	0.070†
CMV colitis [n (%)]	10 (58.8)	2 (7.7)	9.33 (2.84–30.65)	< 0.001†	4.01 (1.49–10.78)	0.006†
White blood cells [/mm^3 ± SD]	8.78 ± 4.63	8.07 ± 2.51	1.06 (0.89–1.26)	0.548†		
Hematocrit [% ± SD]	32.35 ± 6.51	39.51 ± 5.52	0.82 (0.74–0.90)	< 0.001†		
Platelet [× 10^3/mm^3 ± SD]	274.65 ± 164.78	292.27 ± 97.15	1.00 (0.99–1.00)	0.755†		
C-reactive protein [mg/dL ± SD]	5.22 ± 5.30	2.09 ± 3.20	1.11 (1.01–1.21)	0.034†		
Albumin [g/dL ± SD]	2.60 ± 0.56	3.62 ± 0.88	0.16 (0.01–1.70)	0.127†		

†Logistic regression modeling and the generalized estimating equations were used to account for the clustering of matched pairs.
Abbreviations: BMI: Body Mass Index; CI: Confidence Interval; CD: Crohn's Disease; CMV: Cytomegalovirus; OR: Odds Ratio; SD: Standard Deviation; UC: Ulcerative Colitis; VTE: Venous Thromboembolism

Clinical outcomes of IBD patients with and without VTE

The median follow-up duration and clinical outcomes are shown in Table 5. Median follow-up durations following the development of VTE were similar between groups. VTE patients were more likely to receive infliximab in comparison with patients without VTE. Moreover, both the median number of hospitalizations and number of bowel resections were higher in VTE patients than patients without VTE.

Discussion

To the best of our knowledge, this is the first study to evaluate the incidence and risk factors associated with VTE in an Asian population of IBD patients. The incidence of VTE was 0.58% in our Asian IBD population, and higher disease activity was associated with increased risk of developing VTE. Furthermore, CMV colitis might be associated with increased risk of developing VTE. In our present study cohort, the incidence of VTE was much lower than the rates reported previously by retrospective studies from Western countries (range: 1–8%) [15,16]. Since our current study included patients who were referred from IBD centers, it is possible that patients with more severe disease activity were enrolled; however, because patients with more severe IBD activity are at increased risk of developing VTE, the incidence may have been underestimated. Similarly, Korean patients with malignant disease are reportedly at significantly lower risk of developing VTE than Caucasians [17-19]. Also, studies on general populations have shown that the incidence of VTE in Asian-Pacific patients is approximately 5-fold lower than in Caucasians [20-22]. Even though it is difficult to directly compare the incidence determined in this study with previously reported studies due to differences in the study populations, race and ethnicity may play important roles [20,22,23].

According to the results of our multivariate analysis, elevated

Table 5: Clinical Outcomes of IBD Patients with VTE Compared with Matched IBD Controls without VTE.

Clinical outcomes	Patients with VTE (n = 26)	Patients without VTE (n = 78)	*p*
Follow-up duration after VTE [Median (range) months]	39.47 (1.81-174.00)	41.68 (0.0-173.04)	0.985†
Use of infliximab during follow-up§ [n (%)]	6 (23.08%)	6 (7.69%)	0.089‡
Number of hospitalization during follow-upd [Median (range)]	2 (1-3)	0 (0-2)	< 0.001*
Bowel resection during follow-upd [n (%)]	10 (38.46%)	6 (7.69%)	0.005‡

†t-test.
‡Logistic regression using Generalized Estimating Equations that accounted for the clustering of matched pairs.
*Poisson regression with random effects that accounted for the clustering of matched pairs.
§Follow-up after VTE.
Abbreviation: IBD: Inflammatory Bowel Disease; VTE: Venous Thromboembolism

CRP and the recent use of steroids increase the risk of the occurrence of VTE. Furthermore, patients with VTE received more hospitalization and surgery than patients without VTE. The use of steroids is a well-known surrogate indicator of acute disease flare-up in IBD patients [24]. Both hospitalization and surgery are currently considered markers of IBD severity [25]. Taken together, higher disease activity is associated with increased risk of VTE, similar to other reported studies [1,26]. Recently, a nationwide population-based case-control study reported that systemic glucocorticoids increase VTE risk after adjusting for indicators of severe underlying disease [27], which is in line with our results.

Our most salient observation in our current study is that CMV colitis may increase the risk of developing VTE. According to our initial univariate analysis performed on all patients, CMV colitis is associated with an increased risk of VTE. However, CMV colitis was not entered into our multivariate analysis because a significant portion of the patients in our study cohort did not have the required colon tissues. Thus, we performed our second analysis only on patients with colonic tissues, and only CMV colitis was found to increase the risk of VTE.

It has been suggested by several studies that CMV infection may be associated with thrombosis in non-IBD populations [3-5]. There are several plausible mechanisms. First, CMV may promote vascular thromboembolisms via endothelial damage, mostly in immunocompromised patients but also in immunocompetent patients. Second, CMV may exert its procoagulant properties by expressing tissue factor and procoagulant phospholipids on the endothelial surface, thereby leading to enhanced adherence by monocytes and leucocytes to the endothelium. Consequently, the increased production of interleukin-6, which is derived from infected endothelial cells and monocytes, and the increased expression of cell surface receptor CD40 and von Wille brand factor may also contribute to thrombogenesis [3,4,6]. Third, CMV-Ig Gsero status is linked to unexplained elevations in factor VIII [28].

Even though our study was not designed to explain the etiological link between CMV colitis and VTE in IBD patients, we do here describe CMV colitis-related VTE development. We thus suggest that, from the clinical perspective, the presence of CMV colitis should be considered a possible risk factor for thrombophilia. This warrants a high index of suspicion for possible thrombotic events and any subsequent decisions regarding prophylactic anticoagulation. It could be argued that CMV colitis itself is associated with increased risk of VTE, or that it is just a bystander associated with greater underlying disease activity and steroid use. Our second analysis demonstrated that corticosteroid therapy tends to increase the risk of developing VTE. Hence, both higher underlying disease activity and superimposed CMV colitis may be associated with the increased risk of VTE occurrence.

The major strength of this study is our evaluation of a large cohort of IBD patients and the rigorous inclusion of only patients with objectively confirmed thrombotic events. Compared with previous studies, this study was also performed in low IBD-incidence area in Asia. Our findings, however, must be interpreted against the background of potential limitations. First, although this is a case-control study, it is also a retrospective observational study and is therefore prone to bias from unrecognized or unmeasured factors. Second, our data do not include a record of disease activity, such as the Crohn's disease activity index. However anemia, elevated CRP, decreased albumin, and the recent use of corticosteroids are considered reflections of IBD disease activity. Third, we did not evaluate the impact of common predisposing factors during the disease course, such as prolonged immobilization or the use of contraceptive pills. However, at our center, barrier methods are recommend instead of oral pills. The possibility that the IBD patients at our center took oral contraceptives is very low. Fourth, we did not analyze the components of the coagulation cascade, such as serological/phenotypical markers or genetic prothrombotic mutations/polymorphisms. However, most published data report no differences in major prothrombotic genetic predisposition among IBD patients [29-32]. Finally, other sources of bias are possible, such missing case notes and poor therapy documentation; fortunately, these were uncommon in this study.

CONCLUSION

Our present study findings reconfirm that high disease activity is a risk factor for the development of VTE in IBD patients. In addition, CMV colitis may be associated with an increased risk of VTE. Although the incidence of VTE seems to be lower in Asian patients than in Western patients, hospitalized IBD patients with CMV colitis may require vigilant observation to diagnose VTE, and we strongly support the use of prophylactic anticoagulation during hospitalization. However, further research is required to validate our findings.

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