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ORIGINAL ARTICLE

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Risk Factors of Recurrent Ischemic Colitis: A Multicenter Retrospective Study

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Background/Aims: Recurrence of ischemic colitis (IC) has not been studied extensively. The aim of this study was to investigate the characteristics of recurrent IC in the community setting and to identify any risk factors.
Methods: We conducted a retrospective study in two community hospitals. Medical records of patients with IC from January 2007 to January 2013 were reviewed. Demographic details, clinical features, co- morbidities, concomitant use of medications, laboratory studies, imaging findings, endoscopic and histological features, surgery, hospital stay, and death within 30 days were collected. Patients were divided into two groups (recurrent IC group, non-recurrent IC group).
Results: A total of 118 patients with IC were identified. IC recurred in 10 patients (8.5%) during the study period. Half of the patients in the recurrent IC group were current smokers as compared to only 18.7% of patients in the non-recurrent group. In the recurrent IC group, 20.0% of patients never smoked as compared to 61.7% in the non-recurrent group (p=0.027). Abdominal aortic aneurysm (AAA) was more frequent in the recurrent IC group (40.0% *vs.* 4.7%; p=0.003). No differences in other clinical symptoms, CT scan findings, comorbidities, endoscopic features, or use of concomitant medications were observed between the two groups. The need for surgical intervention, blood transfusion, intensive care unit stay, mechanical ventilation, length of hospital stay, and anatomic location of affected segments did not differ between the two groups.
Conclusions: IC recurred in 8.5% of patients during the six-year study period. Current smoking status and presence of AAA were identifying risk factors for recurrence of IC. **(Korean J Gastroenterol 2014;63:283-291)**

Key Words: Ischemic colitis; Colitis; Smoking; Abdominal aortic aneurysm; Colonoscopy; Colon

INTRODUCTION

Ischemic colitis accounts for 8.7-18.0% of cases of acute lower gastrointestinal (GI) bleeding; however, in some studies, it was as high as 23.7% of cases.[1-3] Therefore, it is considered one of the most common etiologies for acute lower GI bleeding.[1,3] The prevalence of ischemic colitis is 4.5-44 cases per 100,000 persons.[4,5] In recent decades, its diagnosis has increased with the widespread use of CT scan and colonoscopy. It is possible that the diagnosis of ischemic colitis was overlooked in the past due to less frequent use of the above mentioned modalities. An increasing elderly population is another consideration for the increase in diagnosis of ischemic colitis in recent decades, as ischemic colitis increases with advanced age.[4-6] Although the majority of cases of ischemic colitis have a self-limited course, which is usually resolved with conservative treatment, the major 30-day outcomes are significantly worse than those for patients with other colonic diseases.[2]

The colon is protected against ischemia by an abundant collateral blood supply; however, it is still considered to have relatively poor collateral networks as compared with the small bowel and the stomach. These relatively poor vascular collateral networks are more pronounced in the watershed areas and the right colon. Splenic flexure and rectosigmoid junction are known as watershed areas because of the weak

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points of blood supply between the superior and the inferior mesenteric artery, and the inferior mesenteric artery and the internal iliac artery, respectively.[7-10] The marginal vessel is poorly developed in the right colon in up to 50% of people, making the right colon more susceptible to ischemic colitis.[7]

Risk factors for development of ischemic colitis are divided into two categories, bowel factors and vascular factors. Bowel factors include constipation, irritable bowel syndrome (IBS), fecal impaction, colonic obstruction, and any other condition that increases the intraluminal pressure, which, in turn, compromises the blood flow to the colonic wall, causing an ischemic injury.[4-6,11] Vascular factors include any condition that causes transient or persistent colonic hypoperfusion, local vasoconstriction, focal mesenteric thromboembolism, or mesenteric vasculitis, which all cause inadequate blood supply to the colon and induce ischemic insult. Vascular surgery, including abdominal aortic aneurysm (AAA) repair, coronary artery bypass grafting, aorto-iliac reconstruction surgery, endovascular repair of aorto-iliac aneurysm, or any surgery that requires aortic vascular clamping have been associated with a higher incidence of ischemic colitis.[7,11,12]

Cardiovascular disease and cardiovascular risk factors such as diabetes mellitus, hypertension, hyperlipidemia, peripheral vascular disease, chronic kidney disease, chronic obstructive pulmonary disease, congestive heart failure, cerebrovascular accident, and smoking have been documented more frequently in patients with ischemic colitis as compared to other colonic diseases.[2,4,5,7-11,13-15]

No previous studies in the English literature examining the characteristics of patients with recurrent ischemic colitis have been reported. The aim of our study was to compare the clinical, laboratory, radiological, endoscopic, and histopathologic features and outcomes of recurrent ischemic colitis to those of non-recurrent ischemic colitis and to identify any risk factors that predict its recurrence.

SUBJECTS AND METHODS

A retrospective analysis of all patients with the diagnosis of ischemic colitis from January 2007 to January 2013 was conducted in two different community hospitals (CGH Medical Center in Sterling, IL and Saint Francis Hospital in Evanston, IL, USA) after obtaining Institutional Review Board approval from each institution.

We conducted a comprehensive review of the medical records for the following data: demographic details, clinical signs and symptoms, laboratory studies, imaging findings, endoscopic and histology features, anatomic location of ischemic colitis, comorbidities, concomitant use of medications, need for surgical intervention, blood transfusion, hospital stay, requirement for intensive care unit and mechanical ventilation, and all-causes mortality within 30 days.

The aim of our study was to compare the characteristics of recurrent ischemic colitis to those of non-recurrent ischemic colitis and to identify the risk factors that predict recurrence. The patients were divided into two groups (recurrent ischemic colitis group *vs.* non-recurrent ischemic colitis group). Recurrent ischemic colitis was defined as ischemic colitis that recurred during the study period of six years.

Because there are no specific codes for ischemic colitis, cases of ischemic colitis were identified using the International Classification of Diseases-ninth version (ICD-9) codes (the code 557.0: acute vascular insufficiency, and the code 557.9: unspecific vascular insufficiency). All cases were carefully audited individually by chart review to determine the diagnosis of ischemic colitis. The diagnosis of ischemic colitis was made based on clinical signs and symptoms that were consistent with ischemic colitis along with negative stool studies for infection and with at least one diagnostic study that was consistent with ischemic colitis (CT scan, colonoscopy, or histopathology). Findings that were considered consistent with ischemic colitis on CT scan were thickening of the colonic wall with peri-colonic fat stranding (colitis) in a segmental distribution, particularly in the watershed areas, whereas colonoscopic findings were erythematous, edematous, hemorrhagic mucosa in a segmental pattern, particularly in watershed areas. Histopathologic findings that were considered consistent with ischemic colitis were ischemic changes in biopsy specimens with acute inflammation. Biopsies were read by local general pathologists in each hospital.

Exclusion criteria were age $<$ 18 years, pregnancy, positive studies for enteric pathogens, colonic ischemia due to trauma or mechanical causes (bowel obstruction, volvulus, hernia, etc.), acute bowel (mesenteric) ischemia, chronic bowel (mesenteric) ischemia, acute flare of inflammatory bowel disease, and radiological or colonoscopic evidence of

diverticulitis. In addition, all cases with equivocal or uncertain diagnosis of ischemic colitis or when ischemic colitis was merely considered as a differential diagnosis but never confirmed with objective modalities were excluded. Acute bowel (mesenteric) ischemia, which refers to the sudden onset of acute intestinal hypoperfusion, usually presents with severe acute abdominal pain that is out of proportion to the physical examination. It usually develops as a result of acute thromboembolic events in one or more of the mesenteric vessels that lead to acute arterial occlusion.

Chronic bowel (mesenteric) ischemia refers to a slowly progressive intestinal angina characterized by chronic episodic

Table 1. Clinical Characteristics of the Two Groups

Variable	Recurrent ischemic colitis group (n=10)	Non-recurrent ischemic colitis group (n=108)	p-value
Age (yr)	71.50±13.02	69.21±15.28	0.724
Gender			1.000
Female	9 (90.0)	89 (82.4)	
Male	1 (10.0)	19 (17.6)	
Race group			0.689
White	9 (90.0)	88 (81.5)	
Others	1 (10.0)	20 (18.5)	
BMI	25.58±2.93	28.30±6.81	0.269
Smoking[a]			0.027
Never smoked	2 (20.0)	66 (61.7)	
Ex-smoker	3 (30.0)	21 (19.6)	
Current smoker	5 (50.0)	20 (18.7)	
Missing data	0	1	
Clinical symptoms/signs			
Abdominal pain	8 (80.0)	89 (82.4)	1.000
Nausea	5 (50.0)	38 (35.2)	0.494
Vomiting	3 (30.0)	31 (28.7)	1.000
Diarrhea	6 (60.0)	59 (54.6)	1.000
Rectal bleeding	6 (60.0)	82 (75.9)	0.273
Abdominal distension	1 (10.0)	7 (6.5)	0.519
Fever	1 (10.0)	17 (15.7)	1.000
Peritoneal signs	0 (0.0)	6 (5.6)	1.000
SBP	127.50±12.87	135.78±34.48	0.288
DBP[a]	62.10±10.42	71.31±15.89	0.029
HR	73.60±13.45	84.37±21.96	0.087
Comorbidities			
Hypertension	8 (80.0)	85 (79.4)	1.000
Hyperlipidemia	6 (60.0)	62 (57.9)	1.000
CAD	4 (40.0)	33 (30.8)	0.723
Diabetes mellitus	1 (10.0)	24 (22.4)	0.687
CHF	2 (20.0)	8 (7.5)	0.204
Atrial fibrillation	2 (20.0)	19 (17.8)	1.000
PVD	2 (20.0)	9 (8.4)	0.238
Cerebrovascular disease	2 (20.0)	11 (10.3)	0.307
COPD	1 (10.0)	16 (15)	1.000
CKD	3 (30.0)	12 (11.2)	0.118
DVT	0 (0.0)	4 (3.7)	1.000
IBS	0 (0.0)	3 (2.8)	1.000
AAA[a]	4 (40.0)	5 (4.7)	0.003
Missing data	0	1	
Abdominal surgery (any)	8 (80.0)	58 (54.7)	0.184
Appendectomy	3 (30.0)	19 (17.9)	0.398
Cholecystectomy	4 (40.0)	25 (23.6)	0.265
Hysterectomy	5 (50.0)	31 (29.3)	0.281
Missing data	0	2	
Drugs			
Clopidogrel	3 (30.0)	21 (19.8)	0.429
Aspirin	5 (50.0)	48 (45.3)	1.000
Statins	3 (30.0)	50 (47.20	0.341
Calcium channel blockers	6 (60.0)	33 (31.1)	0.084
B-blockers	5 (50.0)	51 (48.1)	1.000
ACEIs	4 (40.0)	50 (47.2)	0.749
ARBs	0 (0.0)	13 (12.3)	0.600
Diuretics	2 (20.0)	32 (30.2)	0.721
NSAIDs	0 (0.0)	11 (10.4)	0.595
Digoxin	0 (0.0)	6 (5.7)	1.000
Warfarin	0 (0.0)	14 (13.2)	0.607
Antidepressants/ antipsychotics	3 (30.0)	31 (29.3)	1.000
Missing data	0	2	
Hospital stay (day)	7.00±8.23	6.64±7.60	0.855
ICU stay (%)	1 (10.0)	22 (20.4)	0.688
Mechanical ventilation	1 (10.0)	13 (12.0)	1.000
IC occurrence during hospitalization	0 (0.0)	11 (10.2)	0.598
Blood transfusion	2 (20.0)	22 (20.4)	1.000
Surgery	1 (10.0)	13 (12.0)	1.000
Death in 30 days	1 (10.0)	4 (3.7)	0.363
Severe ischemic colitis (required surgery or died)	1 (10.0)	14 (13.0)	1.000
Direct causes			
Constipation	2 (20.0)	14 (13.0)	0.625
Hypotension	0 (0.0)	7 (6.5)	
Drug/vasculitis	0 (0.0)	6 (5.6)	

Values are presented as mean±SD, n (%), or n only.

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CAD, coronary artery disease; CHF, congestive heart failure; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; DVT, deep venous thrombosis; IBS, irritable bowel syndrome; AAA, abdominal aortic aneurysm; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ICU, intensive care unit; IC, ischemic colitis.

[a]Statistical significance.

postprandial abdominal pain, leading to fear of eating (sitophobia) and weight loss, which typically occurs in elderly women. It usually develops as a result of progressive multi-vessel mesenteric atherosclerosis leading to chronic critical arterial occlusion.

1. Statistical analysis

Information for all patients was entered into a Microsoft Excel (Microsoft Co., Redmond, WA, USA) spreadsheet in a coded format, which was locked with a password. The data were analyzed using SAS software (SAS Institute Inc., Cary, NC, USA). A 2-sided p-value of <0.05 was considered statistically significant. Chi-square analysis, Fisher's exact test, and Pearson correlation were performed for categorical variables, such as comorbidities. For quantitative variables, such as laboratory studies, parametric two sample t-tests were performed for comparison of the means of the two groups involved, however, the assumptions associated with t-tests—homogeneity of variances and normality of data—were not satisfied. Therefore, the nonparametric Wilcoxon's rank sum test was performed for comparison of the means of the two groups involved. Results for quantitative variables were reported as mean and standard deviation.

RESULTS

1. Patients' clinical characteristics

From January 2007 to January 2013, a total of 118 patients were diagnosed with ischemic colitis in both hospitals. The mean age of patients was 69.41±15.07 years, with the vast majority being females (83.0%). Ischemic colitis recurred (recurrent ischemic colitis group) in 10 patients (8.5%), whereas there was no recurrence of ischemic colitis (non-recurrent ischemic colitis group) in 108 patients (91.5%) during the study period of six years (Table 1). In the recurrent ischemic colitis group, the mean age of patients was 71.50±13.02 years with a range of 47-87 years. In the non-recurrent ischemic colitis group, the mean age of patients was 69.21±15.28 years with a range of 21-94 years. Age distribution in both groups is shown in Table 2.

Table 2. Age Distribution in the Two Groups

Age group (yr)	Recurrent ischemic colitis (n=10)	Non-recurrent ischemic colitis (n=108)
<45	0 (0.0)	9 (8.4)
45-55	1 (10.0)	11 (10.2)
56-65	2 (20.0)	21 (19.4)
66-75	2 (20.0)	24 (22.2)
76-85	4 (40.0)	30 (27.8)
>85	1 (10.0)	13 (12.0)

Values are presented as n (%).

The majority of patients in both groups were white females. No difference in mean BMI was observed between the two groups. The mean follow-up period was 861.4 ±654.9 days, ranging from 48 to 2,335 days. The median interval between first and second episodes was 121.5 days with a range of 7-730 days. There were no cases with more than one recurrence. Half of the patients in the recurrent ischemic colitis group were current smokers as compared to only 18.7% of patients in the non-recurrent group. In the recurrent ischemic colitis group, 20.0% of patients never smoked as compared to 61.7% in the non-recurrent group (p=0.027). The odds ratio of recurrent ischemic colitis was 8.3 times greater for those who were current smokers compared with those who had never smoked.

Clinical symptoms, including abdominal pain, nausea, vomiting, diarrhea, rectal bleeding, fever, abdominal distention, and peritoneal signs did not differ between the two groups. Lower blood pressure was observed in the recurrent ischemic colitis group; however, only diastolic blood pressure reached statistical significance (62.10±10.42 mmHg *vs.* 71.31±15.89 mmHg; p=0.029).

AAA, detected by CT scan at the time of diagnosis of ischemic colitis or listed as one of the comorbidities if CT scan was not performed, at the initial episode of ischemic colitis was the only comorbidity associated with recurrent ischemic colitis (40.0% *vs.* 4.7%; p=0.003). The odds ratio of recurrent ischemic colitis was 13.8 times greater for those with a history of AAA compared to those with no history of AAA. No significant differences in other comorbidities (hypertension, hyperlipidemia, coronary artery disease, diabetes mellitus, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic kidney disease, atrial fibrillation, chronic obstructive pulmonary disease, deep venous thrombosis, and irritable bowel syndrome) were observed between the two groups. In addition, a history of abdominal surgeries (appendectomy, cholecystectomy, hysterectomy) combined or separate was not statistically significant.

Use of 12 categories of medications (clopidogrel, aspirin,

statins, calcium channel blockers, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, NSAIDs, digoxin, warfarin, and antidepressants/antipsychotics) did not show an association with recurrent ischemic colitis.

Severity of ischemic colitis, the need for surgery or mechanical ventilation, intensive care unit stay, blood transfusion, and length of hospital stay did not predict recurrence of ischemic colitis as these parameters were not statistically different between the two groups. We used the website, www.timeanddate.com, for calculation of the length of hospital stay and we included both admission and discharge dates. We did not calculate the length of stay hourly.

Death within 30 days of the diagnosis of ischemic colitis occurred in five patients of the total 118 patients (4.24%). The causes of death were ischemic colitis (2), sepsis (2), and sudden cardiac death (1) (Fig. 1). One death (10.0%) occurred in the recurrent ischemic colitis group, which was not statistically significant. The median interval from admission to death was 22 days with a range of 3-29 days.

Conditions considered as direct predisposing factors of ischemic colitis (constipation, hypotension, drugs, and vasculi-

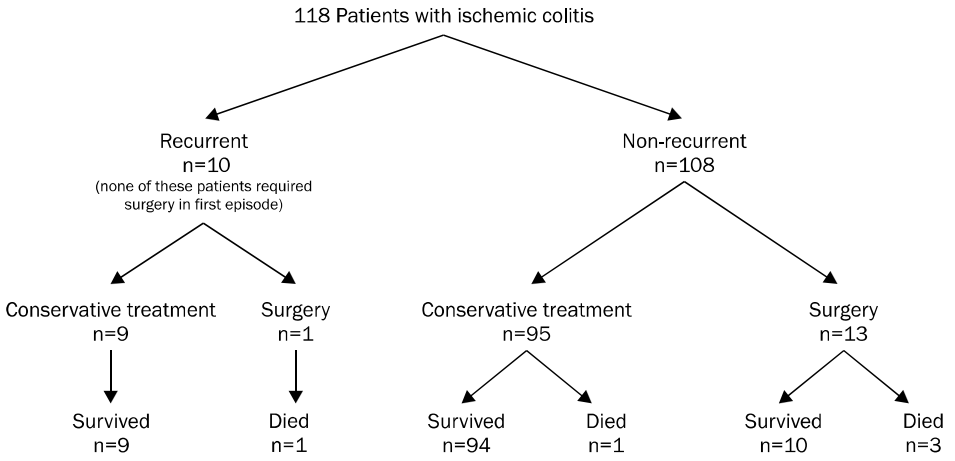

Fig. 1. Outcomes of both groups.

Table 3. Laboratory, Radiology, Colonoscopy, and Histopathology Findings between the Two Groups

Variable	Recurrent ischemic colitis (n=10)	Non-recurrent ischemic colitis (n=108)	p-value
White blood cells ($\times 10^3$/mL)	12.91±5.89	12.96±6.29	0.919
Hemoglobin (g/dL)	13.10±1.26	13.04±1.95	0.904
Albumin (g/dL)	3.59±0.38	3.63±0.55	0.634
Bicarbonate (mEq/L)	26.10±3.07	25.25±3.76	0.471
Sodium (mEq/L)	135.80±3.77	137.33±14.36	0.062
Creatinine (mg/dL)	1.88±1.64	1.33±0.82	0.541
ALT[a] (IU/L)	20.30±9.02	30.86±17.14	0.025
Amylase (IU/L)	58.83±27.79	109.37±180.98	0.634
Lipase (IU/L)	91.22±116.0	122.63±117.34	0.167
Glucose (mg/dL)	116.50±17.58	137.78±73.96	0.252
Lactic acid (mmol/L)	1.10±0.10	4.95±12.33	0.090
CT scan			
Performed	9 (90.0)	81 (75.0)	
Normal CT	1 (11.1)	9 (11.1)	1.000
Wall thickening	7 (77.8)	58 (71.6)	0.716
Induration	1 (11.1)	19 (23.5)	0.677
Pericolonic fat stranding	6 (66.7)	48 (59.3)	0.736
Loss of haustrae	1 (11.1)	4 (4.9)	0.417
Free intra-abdominal fluid	1 (11.1)	15 (18.5)	1.000
Pneumatosis coli	0 (0.0)	7 (8.6)	1.000
Portal/mesenteric venous gas	0 (0.0)	4 (4.9)	1.000
Pneumoperitoneum	0 (0.0)	4 (4.9)	1.000
Bowel dilation	1 (11.1)	12 (14.8)	1.000

Table 3. Continued

Variable	Recurrent ischemic colitis (n=10)	Non-recurrent ischemic colitis (n=108)	p-value
Colonoscopy findings			
Performed	8 (80.0)	81 (75.0)	
Edematous mucosa	5 (62.5)	47 (58.8)	1.00
Erythema	5 (62.5)	52 (65.0)	1.00
Erosions/ulcerations	5 (62.5)	42 (52.5)	0.719
Friability/active bleeding	2 (25.0)	22 (27.5)	1.00
Exudate/necrosis	0 (0.0)	9 (11.3)	1.00
Stricture	0 (0.0)	2 (2.5)	1.00
Missing data	0	1	
Histology findings			
Available	7 (70.0)	87 (80.6)	
Normal histology	0 (0.0)	4 (4.6)	1.00
Edema	1 (14.3)	7 (8.1)	0.475
Epithelium loss/ulceration	1 (14.3)	30 (34.5)	0.419
Crypt loss	0 (0.0)	8 (9.2)	1.00
Acute inflammation	6 (85.7)	62 (71.3)	0.669
Chronic inflammation	2 (28.6)	31 (35.6)	1.00
Capillary thrombosis	0 (0.0)	5 (5.8)	1.00
Necrosis/exudate[a]	0 (0.0)	39 (44.8)	0.039
Submucosal hemorrhage	1 (14.3)	19 (21.8)	1.00
Vascular congestion	0 (0.0)	5 (5.8)	1.00
Mucosal/transmural infarct	0 (0.0)	7 (8.1)	1.00
Chronic ulcer	1 (14.3)	8 (9.3)	0.522
Location			
Left colon	8 (80.0)	88 (85.4)	1.00
Right colon	2 (20.0)	15 (14.6)	0.647
Pancolitis	0 (0.0)	1 (1.0)	1.00
Rectum	0 (0.0)	4 (3.9)	1.00
Rectosigmoid junction	1 (10.0)	14 (13.6)	1.00
Sigmoid colon	6 (60.0)	44 (42.7)	0.337
Descending colon	8 (80.0)	66 (64.1)	0.490
Splenic flexure	4 (40.0)	55 (53.4)	0.513
Transverse colon	4 (40.0)	30 (29.1)	0.488
Hepatic flexure	0 (0.0)	9 (8.7)	1.00
Ascending colon	1 (10.0)	13 (12.6)	1.00
Cecum	2 (20.0)	11 (10.7)	0.327
Missing data	0	6	

Values are presented as mean±SD, n (%), or n only.
[a]Statistical significance.

tis) did not differ between the two groups.

2. Diagnostic studies

While the levels of hemoglobin, white blood cell count, glucose, albumin, amylase, lipase, creatinine, lactic acid, sodium, and bicarbonate at admission were not significantly different between the two groups, lower levels of ALT were observed in the recurrent ischemic colitis group as compared to the non-recurrent group (20.3±9.0 *vs.* 30.9±17.1; p=0.025) (Table 3).

CT scan of the abdomen and pelvis was performed in 90.0% of patients in the recurrent ischemic colitis group as compared to 75.0% in the non-recurrent ischemic colitis group. The scan was normal in 11.1% of patients in both groups. No differences in CT scan findings (colonic wall thickening, induration, pericolonic fat stranding, intra-abdominal fluid or air, pneumatosis coli, portal/mesenteric venous gas, and bowel loop dilation) were observed between the two groups.

Colonoscopy was performed in 80.0% of patients in the recurrent ischemic colitis group as compared to 75.0% in the non-recurrent ischemic colitis group. No significant differences in endoscopic findings (edema, erythema, erosions, ulcerations, friability, active bleeding, fibropurulent exudate,

necrosis, stricture, or stenosis) were observed between the two groups.

Histopathology report (either from endoscopic biopsy or surgery) was available for 70.0% of patients in the recurrent ischemic colitis group as compared to 80.6% in the non-recurrent ischemic colitis group. Of note, some patients underwent surgery without undergoing colonoscopy prior to surgery, and some patients underwent colonoscopy without undergoing biopsy. The histopathological findings were normal in 0.0% of patients in the recurrent ischemic colitis group and 4.6% in the non-recurrent ischemic colitis group. Necrosis and fibropurulent exudate was a less frequent histopathologic finding in recurrent ischemic colitis as compared to non-recurrent (0.0% *vs.* 44.8%; p=0.039). No significant differences in other histologic findings (edema, epithelium loss or ulceration, crypt loss, acute inflammation, chronic inflammation, capillary thrombosis, submucosal hemorrhage, vascular congestion, and mucosal/transmural infarction and chronic ulcer) were observed between the two groups.

The anatomic location of the involved colonic segments was based on the surgery report, CT scan, and colonoscopy findings. If surgery was performed, surgical findings were taken for involved location regardless of the colonoscopy and radiology report findings. If surgery was not performed and there was any discrepancy between CT scan and colonoscopy, the colonoscopy findings were taken. Location of ischemic colitis was divided according to right colon and left colon and then to specific segments of the colon (rectum, recto-sigmoid junction, sigmoid, descending colon, splenic flexure, transverse colon, hepatic flexure, ascending colon, and cecum). Patients may have one or more segments affected. There was one case of pan-colitis, which was considered as involving all segments and counted as right and left colon. Involvement of a specific segment of the colon did not predict the recurrence of ischemic colitis, as no statistically significant difference in terms of anatomic location of the affected segments was observed between the two groups.

DISCUSSION

Our study is unique as no previous studies have addressed the risk factors for recurrence of ischemic colitis. The aim of our study was to investigate the characteristics of recurrent ischemic colitis and to identify risk factors for recurrence. Ischemic colitis recurred in 8.5% of patients during the six-year study period. The rate of recurrent ischemic colitis has been reported between 5.6-13.0%.[13,16] A study by Kimura and his colleagues[13] reported a higher recurrence rate in the elderly group ($>$ 45 years) as compared to patients who were $\leq$ 45 years. However, it did not reach statistical significance (6.2% *vs.* 1.9%; p=0.331).

In our study, patients who continued to smoke represented 50.0% of those with recurrent ischemic colitis compared to only 18.7% in non-recurrent ischemic colitis patients; in the recurrent ischemic colitis group, 20% of patients never smoked, compared to 61.7% of patients in the non-recurrent ischemic colitis group. Smoking has been shown to be associated with occurrence of ischemic colitis in young patients when compared to elderly-onset ischemic colitis or age- and gender-matched healthy individuals.[13]

Cigarette smoking is strongly associated with atherosclerosis. Several pro-atherogenic properties have been attributed to smoking. Cigarette smoking causes increased generation of vascular superoxide anion by activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and concomitantly increases production of cyclooxygenase dependent and independent vasoconstricting prostanoids,[17,18] resulting in decreased nitric oxide (NO) bioactivity in the endothelium and thereby leading to endothelial dysfunction and cigarette smoking-induced vascular toxicity.[17,18] Tobacco smoke contains more than 4,000 chemicals that can accelerate atherosclerotic plaque formation. These plaques develop as a result of impairment of vascular relaxation due to the above mentioned effects of cigarette smoking, up-regulation of inflammatory cytokines, and activation of matrix metallo-proteases.[19] In addition, tobacco smoking may cause platelet dysfunction, stimulate the coagulation cascade, and diminish anticoagulation effects of fibrinolysis mechanisms.[19] Cigarette smoking may also increase the susceptibility of vessels to vasospasm from oxidative stress as one study reported that atherosclerotic arteries may be supersensitive to the constrictor effect of superoxide anion derived from cigarette smoke.[20] In this context, smoking has been shown to be a major risk factor for vasospastic angina without significant coronary narrowing.[21]

Ischemic colitis is associated with cardiovascular disease and its risk factors, such as hypertension, hyperlipidemia, diabetes mellitus, and smoking.[2,7-11,13-15] Not controlling for

these conditions, such as continuation of smoking, may attribute to recurrence of ischemic colitis, as shown in our study. Continuation of smoking causes progression of systemic arterial atherosclerosis, including the mesenteric arteries. Mesenteric atherosclerosis in surgical specimens has shown an association with worse survival and is an independent factor for poor long-term survival.[22] Mesenteric atherosclerosis probably reflects a systemic arterial atherosclerosis as most patients with severe ischemic colitis die from cardiovascular diseases in long-term follow up and treatment of those who survive the first episode of ischemic colitis with aggressive secondary preventive measures is important; such patients should be considered "high-risk" cardiovascular patients. Therefore, smoking cessation after the first episode of ischemic colitis is strongly recommended not only for prevention of recurrence of ischemic colitis but also for improvement of long-term survival. It has been shown that vascular toxicities induced by cigarette smoking may reverse upon its cessation.[19,23]

Ischemic colitis is a well-known complication after aortic surgeries, including AAA repair. In a prospective study reported by Fanti et al.,[24] endoscopic evidence of ischemic colitis was found in 11.4% of patients who underwent early routine sigmoidoscopy after abdominal aortic reconstruction surgery. The main mechanism of development of ischemic colitis after abdominal aortic surgery is ligation or clamping of one of the mesenteric arteries, especially the inferior mesenteric artery. However, the association of ischemic colitis with the presence of AAA without surgical intervention has not been previously conveyed, except in a few case reports. In our study, the presence of AAA on CT scan or by history, if CT scan was not performed, was more prevalent in the recurrent ischemic colitis group as compared with the non-recurrent ischemic colitis group. The proposed mechanism of recurrence of ischemic colitis in patients with AAA is that atherosclerosis plaques in abdominal aorta and its branches, including mesenteric arteries that supply the colon, continue to progress with continuation of offending factors such as smoking. Progression of atherosclerosis in mesenteric arteries may cause a critical reduction of blood flow to the colonic wall, which may result in ischemic injury. Another possible mechanism is dislodging of thromboemboli or atheroemboli from the AAA to the distal mesenteric arteries, resulting in development of ischemic colitis. However, regardless of the mechanism, aggressive treatment of these offending factors after a first episode of ischemic colitis is imperative for prevention of subsequent episodes. Nevertheless, conduct of prospective studies will be needed in order to prove the benefit of these interventions in prevention of recurrent ischemic colitis.

We do not have a meaningful explanation for lower diastolic blood pressure, ALT level, and necrosis in histology in the recurrent ischemic colitis group as compared to the non-recurrent ischemic colitis group.

Limitations of our study include a small number of subjects, particularly in the recurrent ischemic colitis group. Second, the retrospective nature of the study may carry some inherent errors such as deficiency in chart documentation. However, our study is unique as it is the first study to address recurrent ischemic colitis as a distinct entity and identified some risk factors for recurrence of this condition.

In conclusion, smoking and AAA were seen more frequently in subjects with recurrent ischemic colitis. All attempts should be made to treat cardiovascular risk factors such as smoking cessation. Smoking cessation may prevent recurrence of ischemic colitis. Further prospective studies with larger number of study subjects may clarify these associations further.

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