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Original Article

Characteristics of Clinical Features between Isolated Left Side Ischemic Colitis and Non-Isolated Left Side Ischemic Colitis

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좌측 대장에 국한된 허혈성 대장염과 국한되지 않은 허혈성 대장염 사이의 임상적 특징 비교

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Objectives: Compared with all other patterns, isolated right colon ischemia has been found to be more associated with coronary artery disease and a poor prognosis. However, there has been no research on comparing isolated left side ischemic colitis (ILIC) and non-ILIC with vascular assessment. The aim of the present study was to evaluate the clinical and laboratory findings between these two different forms of ischemic colitis (IC).
Methods: We retrospectively investigated differences in clinical features, course, and mesenteric vascular (superior mesenteric artery, SMA; inferior mesenteric artery, IMA) findings between ILIC and non-ILIC patients who were hospitalized at Kosin University Gospel Hospital from 2004 to 2010.
Results: Our study population comprised 221 patients, all of whom met our entry criteria of biopsy-proven or -compatible IC. Of the 221 patients, 46 (20.8%) had non-ILIC. Congestive heart failure and hypercholesterolemia were more frequently observed in the non-ILIC group (P = 0.003 and P = 0.020, respectively). SMA atherosclerosis and SMA stenosis were more frequently observed in the non-ILIC group (P = 0.006 and P = 0.001, respectively). Recovery periods were longer in the non-ILIC group (P = 0.039), and mortality was lower in the ILIC group (6.9% vs. 17.3%, P = 0.026).
Conclusions: ILIC has favorable outcomes compared with non-ILIC. Furthermore, non-ILIC showed a close relationship with SMA atherosclerosis and SMA stenosis, which should be investigated carefully in the clinical field.

Key Words: Atherosclerosis, Ischemic colitis, Stenosis, Superior mesenteric artery

Ischemic colitis (IC) is the most frequent form of vascular alteration in the digestive system. It occurs mainly in the elderly with pluripathology when there is no major vascular occlusion as a result of reduced blood flow responsible for the colon's need, and is conditioned by many factors.[1] Clinical presentations vary from mild and limited forms not needing medical treatment to fulminant trans-mural colonic necrosis which may lead to death. The variability in presentations of IC makes epidemiologic research difficult in the general population.[2] If IC is clinically suspected, its diagnosis can be established by colonoscopy. IC most commonly involves the left side of the colon, the splenic flexure, the descending colon and the

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sigmoid colon, although any segment of the colon can be affected.[3] Isolated right colon ischemia has been reported to occur in about 10% of cases.[4] Isolated right colon ischemia, however, also may be the heralding event of an otherwise clinically silent focal obstruction or vasoconstriction of the superior mesenteric artery (SMA), because the SMA constitutes the blood supply of both the small intestine and much of the colon, including the right side. Compared with all other patterns, isolated right colon ischemia has been found to be more associated with coronary artery disease or end-stage kidney disease requiring dialysis, longer hospitalization, a greater need for surgery, and the highest mortality rate.[5] Because IC most commonly involves the left side of the colon, the comparison between IC localized in left colon and IC extended beyond left colon needs to be investigation. However, there has been no research comparing isolated left side ischemic colitis (ILIC) and non-isolated left side ischemic colitis (non-ILIC). Furthermore, vascular findings assessed by dynamic computed tomography (CT) or angiography between ILIC and non-ILIC have not yet been investigated. In the present study, we aimed to evaluate the clinical and laboratory findings, including the conditions of SMA and inferior mesenteric artery (IMA) and outcomes between these two different forms of ischemic colitis.

MATERIALS AND METHODS

1. Patients and inclusion criteria

We performed a retrospective study assessing the records of consecutive patients with IC who were hospitalized at Kosin University Gospel Hospital from 2004 to 2010. Inclusion criteria included: (i) a colonoscopic evaluation of the entire colon; (ii) a colonoscopy report that described signs of ischemia, including subepithelial hemorrhage, edema, ulceration, and / or gangrene; (iii) a pathology report that concluded that the findings were pathognomonic or consistent with a diagnosis of IC; and (iv) a vascular assessment by dynamic CT or angiography. Pathognomonic features of IC observed on biopsy were infarction and ghost cells, i.e., preserved individual cellular outlines without cell content.[6] Biopsy specimens that were consistent with IC showed mucosal and submucosal hemorrhage and edema, and capillary fibrin thrombi with neutrophilic infiltration.[6]

This investigation was approved by ethics committee of our hospital (IRB number: 11-54).

2. Definition of non-ILIC and ILIC

On the basis of the colonoscopy reports, IC patterns were tabulated and categorized into two groups: non-ILIC and ILIC. The left side colon was composed of the descending colon, sigmoid colon, and rectum. Patterns were classified based on the most proximal location of injury. Thus, for example, a colon that showed involvement of the transverse colon to the sigmoid colon was classified as non-ILIC because the most proximal site of ischemia affected the transverse colon. This classification system was chosen because of the prognostic importance of non-ILIC.[7,8] Resoution day was defined the point when patients did not feel pain and started general diet.

3. Severity of colonoscopic findings

We investigated the severities of IC retrospectively based on colonoscopic findings. Mild ischemic colitis is defined as segmental hyperemic erosive mucosal change without deep ulceration (Fig. 1A). Moderate

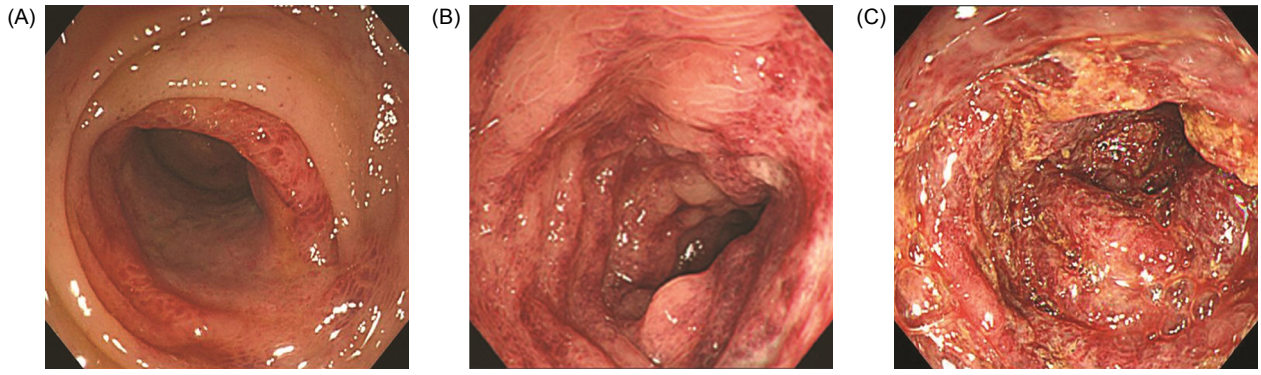

Fig. 1. Severity of ischemic colitis assessed by colonoscopy. (A) Mild ischemic colitis is defined as segmental hyperemic erosive mucosal change without deep ulceration. (B) Moderate ischemic colitis is defined as hyperemic mucosal change and focal ulceration with severe edema. (C) Severe ischemic colitis is defined as extensive exfoliation of colonic mucosa combined with deep ulceration or gangrene.

ischemic colitis is defined as hyperemic mucosal change and focal ulceration with severe edema (Fig. 1B). Severe ischemic colitis is defined as extensive exfoliation of colonic mucosa combined with deep ulceration or gangrene (Fig. 1C).

4. Vascular findings

Vascular findings of SMA atherosclerosis, SMA stenosis, SMA calcification, and IMA atherosclerosis were assessed by dynamic CT scan or angiography. Atherosclerosis was defined as low attenuated intraluminal thickening detected in arterial phase of dynamic CT scan. Vascular calcification was defined as bone-like high attenuated finding of vasculature in pre-contrast CT scan. Stenosis was defined as an occlusion of the lumen over 75%.

5. Comorbidities and Clinical Outcomes

ECOG performance status, recent operative history, specific cardiac problems (hypertension, ischemic heart disease, arrhythmia, and congestive heart failure), and other comorbidities (diabetes mellitus, peripheral vascular disease, chronic renal insufficiency, chronic obstructive pulmonary disease, hyperthyroidism, and hypothyroidism), were tabulated for all 221 cases after a comprehensive chart review of the hospital stay in which there was histologic confirmation of clinically suspected or diagnosed IC. Age, gender, length of stay, recovery period, and mortality were also investigated and compared across the two groups. Recovery of IC was proved by colonoscopy in all patients.

6. Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (version 16.0, SPSS, Chicago, IL, USA). Continuous baseline descriptive variables were expressed as means with standard deviation (SD) and were compared using Student's t -test. Categorical variables were expressed as absolute numbers and proportions. The χ^2 statistic was used to compare most categorical variables, whereas Fisher's exact test was used for small numbers. Survival analyses were performed using the Kaplan-Meier method and compared by log-rank tests. Cox proportional regression analysis was performed to estimate the hazard ratio (HR) for events observed in each group. Survival data

are presented as the 120-day survival from admission date. A two-sided *P*-value of < 0.05 was considered statistically significant.

RESULTS

1. Patient characteristics

Our study population comprised 221 patients, all of whom met our entry criteria of biopsy-proven or -compatible IC. Of the 221 patients, 46 (20.8%) had non-ILIC. The entire colon was visualized in all 221 (100%) cases. Biopsies were pathognomonic of ischemia in 48 (21.7%) cases and consistent with ischemia in 173 (78.3%) cases. The average age of our cohort was 65.9 years with a range of 33-82 years, and 60.2% of patients were women (133 women and 88 men). The mean length of stay for all 221 cases of IC was 14 days, with a range of 1 to 98 days. The total number of deaths was 20 (9.0%).

2. Comparison of characteristics between non-ILIC and ILIC groups

There were no significant differences in baseline characteristics between the non-ILIC and ILIC groups including age and gender (Table 1). Recent operative history and ECOG performance status were not different between the two groups. Total protein was lower in the non-ILIC group (5.8 ± 0.9 vs. 6.5 ± 0.8, $P < 0.001$), but total cholesterol was higher in the non-ILIC group (143.2 ± 61.5 vs. 109.3 ± 63.0, $P = 0.001$). C-reactive protein was also higher in the non-ILIC group (7.7 ± 7.7 vs. 5.1 ± 7.1, $P = 0.049$).

3. Medical comorbidities in the non-ILIC and ILIC groups

Congestive heart failure was more frequently observed in the non-ILIC group (17.4% vs. 4.6%, $P = 0.003$, odds ratio [OR] = 4.395, 95% CI = 1.551-

Table 1. Baseline characteristics of patients in two groups at symptomonset

	Non-ILIC n = 46	ILIC n = 175	*P*-Value
Age, year, mean ± SD	66.5 ± 11.9	64.0 ± 12.4	0.656
Sex, male, n (%)	17 (36.9)	71 (40.6)	0.224
Recent operation, n (%)	0 (0.0)	9. (5.1)	0.210
ECOG performance status			0.124
Score 1, n (%)	2 (4.3)	20 (11.4)	
Score 2, n (%)	11 (24.0)	36 (20.6)	
Score 3, n (%)	23 (50.0)	62 (35.4)	
Score 4, n (%)	10 (21.7)	58 (32.6)	
Laboratory findings			
Albuming, g/dL, mean ± SD	3.1 ± 0.7	3.9 ± 2.8	0.058
Total protein, g/dL, mean ± SD	5.8 ± 0.9	6.5 ± 0.8	< 0.001*
Total cholesterol, mg/dL, mean ± SD	143.2 ± 61.5	109.3 ± 63.0	0.001**
Triglyceride, mg/dL, mean ± SD	81.2 ± 60.9	78.7 ± 46.2	0.102
Hgb, g/dL, mean ± SD	12.2 ± 2.2	12.9 ± 2.1	0.216
WBC, counts/dL, mean ± SD	13,145.1 ± 6,702.2	11,828.3 ± 63,265	0.052
CRP, mg/dL, mean ± SD	7.7 ± 7.7	5.1 ± 7.1	0.049***
ESR, mg/dL, mean ± SD	22.3 ± 21.2	32.8 ± 37.0	0.066

ILIC, isolated left side ischemic colitis; Non-ILIC, non isolated left side ischemic colitis; ECOG, eastem cooperative oncology group; Hgb, hemoglobin; WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

12.391) (Table 2). Furthermore, hypercholesterolemia was also more common in the non-ILIC group (19.5% vs. 6.9%, P = 0.001, OR = 3.304, 95% CI = 1.297-8.417). However, there were no differences in other comorbidities such as hypertension, ischemic heart disease, atrial fibrillation, diabetes mellitus, peripheral vascular disease, chronic renal insufficiency, chronic obstructive pulmonary disease, hyperthyroidism, or hypothyroidism.

4. Comparison of mesenteric vascular and endoscopic findings between the non-ILIC and ILIC groups

All patients underwent abdominal CT scan, and

Table 2. Medical comorbidities in the tow groups

	Non-ILIC n = 46	ILIC n = 175	*P*-Value
Cardiovascular disease			
Hypertension, n (%)	19 (41.3)	82 (46.9)	0.512
Ischemic heart disease, n (%)	7 (15.2)	24 (13.7)	0.794
Atrial fibrillation, n (%)	18 (39.1)	69 (39.4)	0.971
Congestive heart failure, n (%)	8 (17.4)	8 (4.6)	0.003*
Cerebrovascular accident, n (%)	10 (21.7)	23 (13.1)	0.164
Diabetes mellitus, n (%)	16 (34.8)	47 (26.9)	0.359
Peripheral vascular disease, n (%)	2 (4.3)	6 (3.4)	0.673
Autoimmune disease, n (%)	2 (4.3)	8 (4.6)	1.000
Hypercholesterolemia, n (%)	9 (19.5)	12 (6.9)	0.020**
Chronic renal insufficiency, n (%)	4 (8.7)	11 (6.3)	0.522
Chronic obstructive pulmonary disease, n (%)	7 (15.2)	15 (8.5)	0.180
Hyperthyroidism, n (%)	1 (2.2)	3 (1.7)	1.000
Hypothyroidism, n (%)	2 (4.3)	6 (3.4)	0.673

ILIC, isolated left side ischemic colitis; Non-ILIC, non isolated left side ischemic colitis.
* Odds ratio = 4.395, 95% confidence interval = 1.551-12.391.
** Odds ratio = 3.304, 95% confidence interval = 1.297-8.417.

Table 3. Comparison of endoscopic findings and mesenteric vascular finding between two groups

	Non-ILIC n = 46	ILIC n = 175	*P*-Value
Endoscopic findings			0.524
Severe	16 (34.8)	50 (28.6)	
Moderate	24 (52.2)	91 (52.0)	
Mild	6 (13.0)	34 (19.4)	
Vascular findings†			
SMA calcification, n (%)	23 (50.0)	86 (49.1)	0.918
SMA atherosclerosis, n (%)	6 (13.0)	4 (2.3)	0.006*
SMA stenosis, n (%)	6 (13.0)	2 (1.2)	0.001**
IMA atherosclerosis, n (%)	1 (2.1)	4 (2.3)	0.964
Mesenteric ischenmia, n (%)	10 (21.7)	4 (2.3)	0.497

ILIC, isolated left side ischemic colitis; Non-ILIC, non isolated left side ischemic colitis; SMA, superior mesenteric artery; IMA, inferior mesenteric artery.
† Vascular findings were accessed by dynamic computed tomography and angiography.
* Odds ratio = 6.412, 95% confidence interval = 1.728 to 23.793.
** Odds ratio = 12.975, 95% confidence interval = 2.525 to 66.677.

angiography was performed in 55 of 221 patients (24.8%). SMA atherosclerosis and SMA stenosis were more frequently observed in the non-ILIC group (13.0% vs. 2.3%, P = 0.006, OR = 6.412, 95% CI = 1.728-23.793; 13.0% vs. 1.2%, P = 0.001, OR = 12.975, 95% CI = 2.525-66.677) (Table 3). However, there were no differences in SMA calcification, IMA atherosclerosis, or mesenteric ischemia, in endoscopic findings.

5. Clinical outcomes between the non-ILIC and ILIC groups

Days symptom onset to the resolution of ischemic colitis was longer in the non-ILIC group (9.5 ± 13.1 vs. 5.3 ± 8.5; P = 0.039, 95% CI = 0.210-8.272) (Table 4). However, the total hospitalization period was not different between the two groups. Patients who underwent operation due to IC were more frequently observed in non-ILIC group (10.8% vs. 2.9%, P = 0.035, OR = 4.146, 95% CI = 1.146-16.997). Mortality was lower in the ILIC group than non-ILIC group (6.9% vs. 17.3%, P = 0.026, HR = 0.286, 95% CI = 0.095-0.855) (Fig. 2).

Table 4. Clinical course between Non-ILIC and ILIC

	Non-ILIC n = 46	ILIC n = 175	*P*-Value
Recovery period of ischemic colitis†, days, mean ± SD	9.5 ± 13.1	5.3 ± 8.5	0.039*
Hospitalization period, days, mean ± SD	24.8 ± 17.1	19.6 ± 16.6	0.061
Operation, n (%)	5 (10.8)	5 (2.9)	0.035**

ILIC, isolated left side ischemic colitis; Non-ILIC, non isolated left side ischemic colitis.
†Recovery period is the days between symptom onset and the resolution of ischemic colitis proved by colonoscopy.
* 95% confidence interval = 0.210-8.272.
** Odds ratio = 4.146, 95% confidence interval = 1.146-14.997.

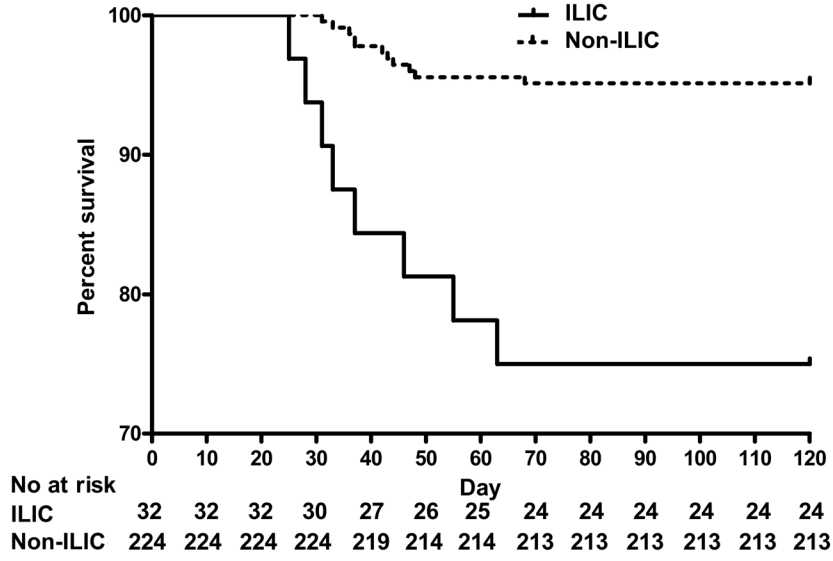

Fig. 2. Kaplan-Meier survival curve comparing ILIC with non-ILIC. Mortality is lower in the ILIC group than non-ILIC group (6.9% vs. 17.3%, P = 0.026, hazard ratio = 0.286, 95% confidence interval = 0.095-0.855).
ILIC, isolated left side ischemic colitis.

DISCUSSION

Most patients with IC present with mild-to-moderate lower abdominal pain and bloody diarrhea; however, these symptoms are not specific for IC and can be observed with infectious colitis and inflammatory bowel disease in addition to a variety of other entities.

In the present study, segmental involvement was typical. The common form of ILIC was observed in 175 (79.2%) out of 221 cases. Non-ILIC comprised 46 cases (20.8%). The segmental nature of IC can be explained by the vascular anatomy and blood flow to the colon and rectum. Colonic blood flow is supplied by three vessels: the SMA, IMA, and the superior hemorrhoidal artery.[5] Watershed zones are areas that are frequently susceptible to ischemic insult as a result of their location between two different vascular supplies. The representative areas are the splenic flexure (Griffiths' Point), the sigmoid colon (Sudeck's Point), and the left side colon, both of which may have potentially limited collateral blood flow. The predominance of ILIC in our study seems to reflect this traditional viewpoint.

When assessing comorbid illness and vascular findings, congestive heart failure and hypercholesterolemia were more commonly found in the non-ILIC group. Furthermore, SMA atherosclerosis and SMA stenosis were more frequently observed in the non-ILIC group. An important factor that is often responsible for aggravating colonic ischemia is the phenomenon of vasospasm.[9] It has been well documented that both occlusive and non-occlusive forms of arterial ischemia can result in prolonged vasospasm, even after the occlusion has been removed or the perfusion pressure restored. This vasospasm may persist for several hours, resulting in extended ischemia.[10] Atherosclerosis is a well known precipitating factor for vasospasm. Contrasting to ILIC, usual form of IC mostly caused by hypovolemia, the tight relationship between SMA atherosclerosis and non-ILIC presents that non-ILIC would be caused by transient vasospasm related with SMA atherosclerosis. These findings also suggest that if non-ILIC is present on colonoscopy or abdominopelvic CT, radiologists should investigate SMA atherosclerosis or SMA stenosis more carefully, which can be corrected by angioplasty.

The segment of the colon involved in IC also has prognostic implication. Previously, other studies have shown that patients with isolated right-sided IC have a relatively poor prognosis compared with patients whose ischemic injury involves other areas of the colon.[3,7,8,11-14] Although our study compared non-ILIC and ILIC, our results also potentiated the previous findings and showed that ILIC had favorable outcome, a shorter recovery period, lower operation rate, and a lower mortality rate.

The limitations of our study included its retrospective design, the definition of the pattern of disease distribution (the pattern was based upon the most proximal site of disease regardless of distal extent), and the fact that our study population comprised only inpatients. Given the usually benign and transient nature of IC, outpatients having a self-limited symptomatic episode would not have been captured by our methodology.

Although our study population represents only a portion of all cases of IC, the segment of the colon involved influences the clinical features and outcomes of the disease. In this study, we have revealed that non-ILIC showed worse prognosis and a close

relationship with SMA atherosclerosis and SMA stenosis. Therefore, we recommend performing dynamic abdominal CT or angiography to find correctable lesions when non-ILIC is suspected.

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