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ORIGINAL ARTICLE

Clinical Characteristics of Young-Onset Ischemic Colitis

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Abstract
Background Ischemic colitis (IC) typically develops in the elderly, where hypertension, cerebrocardiovascular disease, and past history of abdominal surgery are regarded as risk factors. Although there have been reports of younger patients with IC, its clinical features remain unclear.

Aim The aim of this study was to clarify the clinical characteristics of IC in young adults.
Methods Three hundred fifty-nine patients were diagnosed as having IC at five hospitals across Nagano prefecture, Japan. Clinical data were compared between the young patient group [20–45 years, $n = 53$ (15%)] and the elderly patient group [>45 years, $n = 306$ (85%)], as well as with age- and gender-matched healthy individuals ($n = 156$).
Results The presence of a smoking habit and hyperuricemia were significantly higher in the young patient group compared with the elderly patient group (42 vs. 19%, $P = 0.001$ and 8 vs. 1%, $P = 0.019$, respectively), which was confirmed by multiple logistic regression analysis ($P = 0.001$, odds ratio 3.239 and $P = 0.028$, odds ratio 16.907, respectively). Additionally, multiple logistic regression analysis of the young IC patient group and age- and gender-matched healthy individuals demonstrated that these two factors were strongly associated with IC development ($P = 0.008$, odds ratio 2.49 for smoking habit and $P = 0.039$, odds ratio 6.37 for hyperuricemia).
Conclusions High prevalences of a smoking habit and hyperuricemia are characteristic features of IC in the young adult population.

Keywords Ischemic colitis · Young · Smoking · Hyperuricemia

Abbreviations

BMI	Body mass index
CRP	C-reactive protein
IC	Ischemic colitis
LDH	Lactate dehydrogenase

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Introduction

Ischemic colitis (IC) was first described by Boley et al. [1] and Marston et al. [2] in the 1960s as a reversible vascular occlusion of the colon. Generally speaking, IC is considered to occur in the elderly having underlying disorders [3–11]. According to previous reports, vascular/hemodynamic and intestinal factors, as well as some kinds of medications, including contraceptive pills, vasoconstrictors, psychotropic drugs, non-steroidal anti-inflammatory drugs, and 5-hydroxytriptamine three receptor antagonists, are associated with the pathogenesis of IC. Vascular disorders include hypertension [3], dyslipidemia [4], diabetes mellitus [5], atrial fibrillation [6], cardiovascular disease [7, 8], cerebral infarction [9], and chronic renal failure [7, 10], while intestinal factors mainly comprise constipation [8] and history of abdominal operation [7, 8, 11].

On the other hand, an increasing number of studies are reporting cases of younger patients who develop IC [12–20]. Constipation [12], history of abdominal operation [12], irritable bowel syndrome [13], vasculitis [14], contraceptive pill use [15, 16], cocaine [17] and methamphetamine use [18], sickle cell anemia [19], long-distance running [20], and polymorphisms in the coagulation factor V and plasminogen activator inhibitor genes [21] are thought to be predisposing factors for young-onset IC. However, such risk factors have not been fully investigated in the Japanese population.

There have been two reports to date comparing factors related to the development of IC between young and elderly patients in Japan. Tohda et al. [22] reported that irritable bowel syndrome, habitual constipation, and prior history of abdominal operation were contributors to IC in young patients. Matsumoto et al. [23] also described that constipation may be related to the pathogenesis of IC in young patients. However, in both studies, the patients were enrolled from a single facility and the number of subjects was small (54 and 31 patients in total and 22 and 16 young IC patients, respectively). Furthermore, the age of the young patient group was relatively high (60 years or less) in the former study [22]. Therefore, we speculated that a larger-scale, multi-center analysis with a lower age limit might better unveil the clinical features of Japanese young-onset IC.

Accordingly, we sought to clarify the clinical characteristics of IC among young Japanese adults (20–45 years of age) and analyzed the data of 359 patients from five independent hospitals across Nagano prefecture, Japan.

Patients and Methods

Ethics

This study was carried out in accordance with the World Medication Association Helsinki Declaration and was approved by the ethics committees of Shinshu University School of Medicine and each participating facility.

Patients

From 2003 to 2010, 359 adult patients [124 (35%) males] were diagnosed as having IC and treated at five regional hospitals (Suwa Red Cross Hospital, Showa Inan General Hospital, Shinshu Ueda Medical Center, Shinshu University Hospital, and Marunouchi Hospital) across Nagano prefecture. Patient age ranged from 20 to 95 years (median, 70 years).

The diagnosis of IC was made based on the following criteria: [22, 23] (1) acute onset of symptoms, such as abdominal pain, diarrhea, and bloody stool; (2) the absence of a medical history of inflammatory bowel diseases; (3) the absence of antibiotic intake immediately prior to the onset of symptoms; (4) negative pathological bacterial cultures, including those for enteropathogenic *Escherichia coli*, *Salmonella*, *Shigella*, *Vibrios*, *Campylobacter*, and *Yersinia* in stools; (5) the presence of endoscopic findings consistent with IC [24–26]; and (6) the presence of histological findings in biopsy specimens consistent with IC [25, 26].

Since patient age data showed a bimodal distribution with peaks centered around approximately 45 years of age, individuals aged 20–45 years or over 45 years on admission were classified into the young IC group or elderly IC group, respectively, similarly to a study by Matsumoto et al. [23]. A total of 359 adult IC patients were subdivided into the young patient group ($n = 53$) or elderly patient group ($n = 306$) for comparison of clinical, laboratory, and lifestyle data.

To further clarify the clinical features of young-onset IC, age- and gender-matched healthy adults ($n = 156$) were selected from individuals who had received a health examination at Showa Inan General Hospital and used for comparisons.

Data Collection

We carefully reviewed the medical records of all patients with regard to age, sex, past history, social history, underlying diseases, symptoms and anthropometric/laboratory data on admission, endoscopic findings, and clinical course. IC subtype (transient, stricture, or gangrenous) was classified according to the criteria proposed by Marston et al. [2]. Location and number of lesions were determined using endoscopic findings. Individuals who smoked regularly were defined as having a smoking habit and those who consumed more than 20 g/day of ethanol were defined as having a drinking habit. We did not review past history or total amount of smoking/drinking. The presence of obesity was

defined as having a body mass index (BMI) of more than 25 kg/m^2 based on criteria released by the Japan Society for the Study of Obesity. Patients were considered to be hypertensive if their systolic/diastolic pressure was greater than 140/90 mmHg, or if they were taking anti-hypertensive drugs [27, 28]. Patients were considered to have dyslipidemia if their fasting serum levels of cholesterol or triglycerides were equal to or higher than 220 or 150 mg/dL, respectively, or if they were taking lipid-lowering drugs [27, 28]. Patients were considered to be diabetic if they had a fasting glucose level equal to or higher than 126 mg/dL, or if they were taking insulin or oral hypoglycemic agents [27–33]. Hyperuricemia was defined as a uric acid concentration of ≥7.0 mg/dL, based on guidelines released by the Japan Society of Gout and Nucleic Acid Metabolism, or if they were taking anti-hypreruricemia drugs. Constipation was defined according to the Rome III criteria when the following three criteria were fulfilled: (1) the presence of two or more of the following symptoms: (i) straining during at least 25% of defecations, (ii) lumpy or hard stools in at least 25% of defecations, (iii) sensation of incomplete evacuation for at least 25% of defecations, (iv) sensation of anorectal obstruction/blockage for at least 25% of defecations, (v) manual maneuvers to facilitate at least 25% of defecations, or (vi) fewer than three defecations per week; (2) loose stools rarely present without the use of laxatives; and (3) insufficient criteria for irritable bowel syndrome [34].

Statistical Analysis

Qualitative findings were expressed as numbers (percentages), and quantitative data were expressed as the median (range). In univariate analysis, qualitative and quantitative variables were compared using Fisher's exact test and the Mann–Whitney *U* test, respectively. Multiple logistic regression analysis was conducted to determine the risk factors associated with development of IC at a younger age. Data were analyzed using a statistical software package (SPSS for Windows, SPSS Inc, Chicago, IL). All *P* values were based on a two-sided test. A *P* value of less than 0.05 was considered to be statistically significant.

Results

Comparison of Clinical Features on Admission

We first compared the clinical features on admission between the young patient group ($n = 53$) and elderly patient group ($n = 306$). Median age was 36 and 73 years, respectively (Table 1). A higher male prevalence was seen in the young patient group (Table 1). Almost all patients experienced abdominal pain and bloody stool, and approximately half had diarrhea in both groups (Table 1). BMI and the frequency of obesity did not differ between the groups (Table 1). In laboratory data, leukocyte count and serum levels of C-reactive protein (CRP) and lactate dehydrogenase (LDH) were significantly lower in the young patient group, but there were no notable differences in hemoglobin value, platelet count, or serum creatine kinase concentration (Table 1).

Comparison of Endoscopic Findings

Based on endoscopic findings, all cases in the young patient group were judged to have transient IC (Table 2). There were ten cases (3.3%) of structuring IC and two

Table 1 Comparison of clinical features on admission between young and elderly patient groups

Clinical features	Young IC ($n = 53$)	Elderly IC ($n = 306$)	*P* value
Age	36 (20–45)	73 (46–95)	–
Male	28 (52.8%)	96 (31.4%)	**0.004**
Symptom			
Abdominal pain	51 (96.2%)	281 (91.8%)	0.398
Diarrhea	25 (47.2%)	154 (50.3%)	0.766
Bloody stool	53 (100%)	293 (95.8%)	0.230
BMI (kg/m^2)	22 (16–31.7)	22 (13.5–36.1)	0.488
Obesity	5 (9.4%)	34 (11.1%)	0.902
Laboratory data			
Leukocyte (/μl)	7,825 (1,330–22,230)	10,070 (3,400–21,890)	**0.001**
Hemoglobin (g/dL)	13.6 (8.3–16.8)	13.6 (8–16.8)	0.226
Platelet ($\times 10^4$/μl)	18.5 (13–37)	22 (10–37)	0.166
CRP (mg/dL)	0.16 (0–3.8)	0.30 (0–25)	**<0.001**
LDH (IU/L)	177 (4–242)	197 (120–879)	**0.003**
CK (IU/L)	100 (22–243)	112 (10–11,290)	0.962

IC ischemic colitis, *BMI* body mass index, *CRP* C-reactive protein, *LDH* lactate dehydrogenase, *CK* creatine kinase

Data are expressed as median (range) or number (percentage). Statistically significant values are in bold text

Table 2 Comparison of endoscopic findings between young and elderly ischemic colitis (IC) patient groups

Findings	Young IC ($n = 53$)	Elderly IC ($n = 306$)	P value
Form of disease			0.506
Transient	53 (100%)	294 (96%)	
Stricturing	0 (0%)	10 (3.3%)	
Gangrenous	0 (0%)	2 (0.7%)	
Lesion location[a]			
Number of sections	2 (1–3)	1 (1–4)	0.268
A	0 (0%)	0 (0%)	0.235
T	1 (1.9%)	9 (2.9%)	
T + D	4 (7.5%)	18 (5.9%)	
T + D + S	3 (5.7%)	32 (10.5%)	
T + D + S + R	0 (0%)	2 (0.7%)	
D	9 (17%)	46 (15%)	
D + S	21 (39.6%)	61 (19.9%)	
D + S + R	0 (0%)	5 (1.6%)	
S	14 (26.4%)	117 (38.2)	
S + R	1 (1.9%)	11 (3.6%)	
R	0 (0%)	1 (0.3%)	
Unknown	0 (0%)	4 (1.1%)	

Data are expressed as median (range) or number (percentage)

[a] Lesion location was separated into the following 5 sections: A (ascending colon), T (transverse colon), D (descending colon), S (sigmoid colon), and R (rectum)

cases (0.7%) of gangrenous IC in the elderly patient group, but the difference between the two groups was not significant. Similarly, location and number of ischemic lesions were comparable between the two groups.

Comparison of Lifestyle Habits and Underlying Diseases

In lifestyle comparisons, the prevalence of IC patients having a smoking habit was significantly higher in the young patient group (41.5 vs. 19.3%, $P = 0.001$) (Table 3). The frequency of a drinking habit did not differ between the groups (Table 3).

As expected, the prevalence of underlying hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, ischemic heart disease, cerebral infarction, history of abdominal operation, and use of warfarin or aspirin were lower in the young group. However, the prevalence of hyperuricemia was significantly higher in the young group (7.5 vs. 1.3%, $P = 0.019$). The frequency of regular use of other IC-associated drugs, such as contraceptive pills or non-steroidal anti-inflammatory agents, showed no significant differences between the two groups. The prevalence of constipation was similarly high in both groups.

Table 3 Comparison of lifestyle habits and underlying diseases between young and elderly ischemic colitis (IC) patient groups

Characteristic	Young IC ($n = 53$)	Elderly IC ($n = 306$)	P value
Lifestyle habit			
Smoking	22 (41.5%)	59 (19.3%)	**0.001**
Drinking	11 (20.1%)	51 (16.7%)	0.438
Underlying disease			
Hypertension	1 (1.9%)	155 (50.7%)	**0.000**
Dyslipidemia	3 (5.7%)	64 (20.9%)	**0.007**
Diabetes mellitus	1 (1.9%)	38 (12.4%)	**0.017**
Hyperuricemia	4 (7.5%)	4 (1.3%)	**0.019**
Atrial fibrillation	0 (0%)	23 (7.5%)	**0.033**
Ischemic heart disease	1 (1.9%)	51 (16.7%)	**0.002**
Cerebral infarction	0 (0%)	27 (8.8%)	**0.021**
Constipation	22 (41.5%)	147 (48%)	0.456
Irritable bowel syndrome	0 (0%)	1 (0.3%)	1.000
Chronic kidney disease	0 (0%)	2 (0.7%)	1.000
Pregnancy	2 (3.8%)	0 (0%)	1.000
Past history			
Abdominal operation	5 (9.4%)	101 (33%)	**0.000**
Radiation therapy	0 (0%)	2 (0.7%)	1.000
Medication			
Warfarin	0 (0%)	26 (8.5%)	**0.020**
Aspirin	0 (0%)	27 (8.8%)	**0.021**
Contraceptive pill	1 (1.9%)	0 (0%)	0.148
NSAID	1 (1.9%)	14 (4.6%)	0.708
Narcotics	0 (0%)	1 (0.3%)	1.000

Data are expressed as number (percentage). Statistically significant values are in bold text

NSAID non-steroidal anti-inflammatory drug

Comparison of Clinical Course of IC

The hospitalization period was shorter for the young patient group than for the elderly patient group (6.0 vs. 8.0 days, $P < 0.001$; Table 4). Although the rates of recurrence, surgery, and death in the elderly group tended to be higher than those in the young group, this difference did not reach statistical significance.

Multiple Logistic Regression Analysis

We next conducted multiple logistic regression analysis to identify the clinical features of young-onset IC. According to the results obtained from univariate analysis, we selected the following items as independent variables: sex, smoking habit, hypertension, dyslipidemia, diabetes mellitus, hyperuricemia, atrial fibrillation, ischemic heart disease, cerebral infarction, history of abdominal operation, and use of

warfarin or aspirin. As summarized in Table 5, multivariate logistic regression analysis demonstrated that the presence of a smoking habit and hyperuricemia were more frequent in young IC patients than in elderly ones. Furthermore, the presence of abdominal surgery history and hypertension were independently less frequent in the young patient group (Table 5).

Comparison of Lifestyle Habits and Underlying Diseases Between Young Adults With and Without IC

To examine whether the presence of a smoking habit and hyperuricemia were associated with the development of young-onset IC, we compared lifestyle habits and underlying diseases between young IC patients and age- and gender-matched healthy individuals. In univariate analysis, the presence of a smoking habit and hyperuricemia were significantly higher in young adults with IC compared with healthy adults without IC (41.5 vs. 22.4%, $P = 0.012$ and 7.5 vs. 1.3%, $P = 0.037$, respectively; Table 6). Furthermore, these two factors were selected as independent variables associated with IC development in the young IC patient group by multivariate logistic regression analysis (Table 7). The prevalence of constipation tended to be higher in the IC group than in the healthy control group, but this difference did not reach statistical significance (Tables 6 and 7).

Table 4 Comparison of clinical course between young and elderly ischemic colitis (IC) patient groups

Clinical course	Young IC ($n = 53$)	Elderly IC ($n = 306$)	P value
Hospitalization (days)	6 (1–26)	8 (1–270)	**<0.001**
Recurrence	1 (1.9%)	19 (6.2%)	0.331
Prognosis			
Surgery	0 (0%)	3 (1%)	1.000
Death	0 (0%)	5 (1.6%)	1.000

Data are expressed as median (range) or number (percentage). Statistically significant values are in bold text

Table 5 Multivariate logistic regression analysis between young and elderly patient groups

Variable	Odds ratio	95% confidence interval	P value
Hyperuricemia	16.907	1.356–210.789	**0.028**
Smoking habit	3.239	1.581–6.635	**0.001**
Abdominal operation	0.246	0.090–0.675	**0.004**
Hypertension	0.012	0.001–0.119	**<0.001**

Statistically significant values are in bold text

Discussion

Although there have been reports of young patients with IC, its clinical features have not been fully clarified. As such, we designed this retrospective study using data from 359 adult IC patients enrolled at five medical centers. We found that young IC patients aged 20–45 years had a higher prevalence of a smoking habit and hyperuricemia and a lower prevalence of accompanying conventional risk factors, such as hypertension and past history of abdominal surgery compared with elderly IC patients. Furthermore, multivariate logistic regression analysis revealed that a smoking habit and hyperuricemia were factors significantly associated with IC development in young adults. These

Table 6 Comparison of lifestyle habits and underlying diseases between young ischemic colitis (IC) patients and age- and gender-matched healthy individuals

Characteristics	Young IC ($n = 53$)	Young healthy individuals ($n = 156$)	P value
Age	36 (20–45)	36 (20–45)	0.388
Male	28 (52.8%)	79 (50.6%)	0.783
BMI (kg/m^2)	22 (16–31.7)	22 (16–38)	0.767
Obesity	5 (9.4%)	19 (12.6%)	0.803
Habitual			
Smoking	22 (41.5%)	35 (22.4%)	**0.012**
Drinking	11 (20.1%)	27 (17.3%)	0.545
Underlying disease			
Hypertension	1 (1.9%)	11 (7.1%)	0.303
Dyslipidemia	3 (5.7%)	17 (11%)	0.417
Diabetes mellitus	1 (1.9%)	3 (1.9%)	1.000
Hyperuricemia	4 (7.5%)	2 (1.3%)	**0.037**
Atrial fibrillation	0 (0%)	0 (0%)	1.000
Ischemic heart disease	1 (1.9%)	0 (0%)	0.254
Cerebral infarction	0 (0%)	0 (0%)	1.000
Constipation	22 (41.5%)	43 (27.6%)	0.062
Irritable bowel syndrome	0 (0%)	0 (0%)	1.000
Chronic kidney disease	0 (0%)	0 (0%)	1.000
Pregnancy	2 (3.8%)	0 (0%)	0.063
Past history			
Abdominal operation	5 (9.4%)	23 (14.7%)	0.484
Radiation therapy	0 (0%)	0 (0%)	1.000
Medications			
Warfarin	0 (0%)	0 (0%)	1.000
Aspirin	0 (0%)	0 (0%)	1.000
Contraceptive pill	1 (1.9%)	0 (0%)	0.256
NSAID	1 (1.9%)	0 (0%)	0.256
Narcotics	0 (0%)	0 (0%)	1.000

Data are expressed as median (range) or number (percentage). Statistically significant values are in bold text

NSAID non-steroidal anti-inflammatory drug

Table 7 Multivariate logistic regression analysis between young ischemic colitis (IC) patients and young healthy individuals

Variable	Odds ratio	95% confidence interval	*P* value
Hyperuricemia	6.370	1.120–37.041	**0.039**
Smoking habit	2.490	1.271–4.852	**0.008**
Constipation	1.900	0.981–3.684	0.058

Statistically significant values are in bold text

results provide novel information regarding the clinical features of IC in the young Japanese population.

It is generally accepted that IC predominantly develops in the elderly, especially in those aged more than 60 years [3–11]. However, in our study, approximately 15% of all adult patients diagnosed as having IC were 20–45 years of age. These findings indicate that IC in the young population is in fact not rare; when clinicians encounter young adults suffering from abdominal pain and bloody stool, they should bear in mind the possibility of IC.

The remarkable finding in this study was the strong association of a smoking habit and hyperuricemia with young-onset IC. As far as we know, this is the first report proposing such associations from a large, multi-center cohort. Several pro-atherogenic properties have been attributed to smoking and hyperuricemia. For example, these factors have been shown to decrease nitric oxide bioactivity and induce oxidative stress generation due to stimulation of NADPH oxidase, in turn impairing endothelial function and promoting arteriosclerosis [35–43]. Additionally, they have been reported to influence platelet adhesiveness and hemorheology, which may disrupt coagulation/fibrinolysis balance [37, 38, 40, 41]. Therefore, it is plausible that patients having a smoking habit and/or hyperuricemia are likely to have more progressive atherosclerosis and be in a hypercoagulative state that is conducive to IC development.

Another possibility is that smoking and/or hyperuricemia may increase endothelial sensitivity, causing susceptibility to vasospasms [44–48]. Epidemiological studies have shown that cigarette smoking is a major risk factor for vasospastic angina [44]. In animal models, cigarette smoke suppressed acetylcholine-induced endothelium-dependent vasodilatation [45, 46]. These observations might, at least in part, explain the putative mechanism of IC development in the young population.

The prevalence of other conventional accompanying IC risk factors, such as hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, ischemic heart disease, cerebral infarction, and history of abdominal operation, were significantly lower in the young IC group. Indeed, multiple logistic regression analysis demonstrated that the rate of abdominal operation history and hypertension were features of typical IC in the elderly group. This study showed clear differences in IC characteristics between young and elderly patients.

Constipation is reported to be one of the risk factors of IC [4, 8]. The prevalence of constipation in young IC patients was comparatively high and tended to be higher than that in young healthy adults, but this difference did not reach statistical significance. This result suggests that a smoking habit and hyperuricemia are stronger contributors to young-onset IC than constipation.

We could not assess the physical activity of daily life in our IC patients. However, it has been reported that physical activity is inversely related to the prevalence of hyperuricemia [49]. As moderate intense physical activity may also be associated with lower uric acid concentrations in obese individuals [50], further studies are needed to clarify the relationship between physical activity and IC development in the young population.

Although we showed the association between hyperuricemia and smoking habit and young-onset IC, it remains undermined whether correction of hyperuricemia by pharmacological intervention or lifestyle modification, such as reduction of purine-containing food intake and increased physical activity, and/or smoking cessation can prevent the development of IC. Further prospective data accumulation of young IC patients might clarify the relationship between these factors and IC pathogenesis. Additionally, polymorphisms of the coagulation factor V and plasminogen activator inhibitor genes are thought to be predisposing causes of young IC in Europe [21]. Thus, it may be of value to examine such gene polymorphisms in young Japanese IC patients as well.

In conclusion, IC in the young adult population was in fact not a rare disease entity, and its clinical background was clearly different from that of typical elderly-onset IC. A smoking habit and hyperuricemia are considered as predisposing factors of IC developing at a young age, and should be managed accordingly in such patients.

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Conflict of interest The authors have declared that no conflict of interest exists.

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