Observational Study

Clinical course of ulcerative colitis patients who develop acute pancreatitis

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Abstract

AIM
To investigate the clinical course of ulcerative colitis (UC) patients who develop acute pancreatitis.

METHODS
We analyzed 3307 UC patients from the inflammatory bowel disease registry at Asan Medical Center from June 1989 to May 2015. The clinical course of UC patients who developed acute pancreatitis was compared with that of non-pancreatitis UC patients.
RESULTS
Among 51 patients who developed acute pancreatitis, 13 (0.40%) had autoimmune, 10 (0.30%) had aminosalicylate-induced, and 13 (1.73%) had thiopurine-induced pancreatitis. All 13 patients with autoimmune pancreatitis (AIP) had type 2 AIP. Two (15.4%) patients had pre-existing AIP, and three (23.1%) patients developed AIP and UC simultaneously. Compared to non-pancreatitis patients, AIP patients had UC diagnosed at a significantly younger age (median, 22.9 years vs 36.4 years; P = 0.001). AIP and aminosalicylate-induced pancreatitis patients had more extensive UC compared to non-pancreatitis patients. All patients with pancreatitis recovered uneventfully, and there were no recurrences. Biologics were used more frequently in aminosalicylate- and thiopurine-induced pancreatitis patients compared to non-pancreatitis patients [adjusted OR (95%CI), 5.16 (1.42-18.67) and 6.90 (1.83-25.98), respectively]. Biologic utilization rate was similar among AIP and non-pancreatitis patients [OR (95%CI), 0.84 (0.11-6.66)]. Colectomy rates for autoimmune, aminosalicylate-induced, and thiopurine-induced pancreatitis, and for non-pancreatitis patients were 15.4% (2/13), 20% (2/10), 15.4% (2/13), and 7.3% (239/3256), respectively; the rates were not significantly different after adjusting for baseline disease extent.

CONCLUSION
Pancreatitis patients show a non-significant increase in colectomy, after adjusting for baseline disease extent.

Key words: Ulcerative colitis; Pancreatitis; Autoimmune; Colectomy; Clinical course

Core tip: Clinical course of ulcerative colitis (UC) patients who develop acute pancreatitis is not well known. In a large prospectively maintained inflammatory bowel disease cohort at Asan Medical Center, we found 51 cases of acute pancreatitis among 3,307 UC patients. Among these, there were 13 (0.4%) patients with autoimmune, 10 (0.3%) with aminosalicylate-induced, and 13 (1.73%) with thiopurine-induced pancreatitis, whose colectomy rates were 15.4% (2/13), 20% (2/10), and 15.4% (2/13), respectively. The colectomy rate for non-pancreatitis patients was 7.3% (239/3256), which was not significantly different from those of acute pancreatitis patients, after adjusting for baseline disease extent.

INTRODUCTION
The incidence rates of ulcerative colitis (UC) and Crohn’s disease (CD) are rising in parallel with rapid urbanization[1]. Patients with inflammatory bowel disease (IBD) seem to be at risk for developing pancreatitis[2]. Pancreatitis in IBD has several causes: it can be an extraintestinal manifestation (EIM) [3-6], or it can be drug-induced [7-10] or autoimmune-related [11]. Gallstones and alcohol abuse are also long-established risk factors for acute pancreatitis [12]. The relationship between IBD and autoimmune pancreatitis (AIP) is mainly confined to UC [13,14]. Several studies have reported positive associations between risk for acute pancreatitis and IBD severity [15-17]. To our knowledge, however, no study has evaluated the clinical course of UC patients who develop pancreatitis according to its etiology. Recently, we described the clinical course of UC in a cohort of 2802 Korean patients, and reported a cumulative colectomy rate of 14.2% during a follow-up period of 20 years [18]. In this study, we aimed to describe the clinical course of UC patients who develop acute pancreatitis in a large prospective cohort, and to compare these patients with the rest of the UC cohort. In particular, AIP and drug-induced pancreatitis were analyzed, and the clinical outcomes were compared according to the etiology.

MATERIALS AND METHODS

Patients
This study enrolled patients with UC who were managed at Asan Medical Center, a tertiary university hospital in Seoul, South Korea, between June 1989 and May 2015. All patients were diagnosed with UC between 1977 and 2015, based on composite criteria of clinical, radiological, endoscopic, and histopathological findings [19,20].

Diagnosis of acute pancreatitis
AIP was diagnosed using the International Consensus Diagnostic Criteria [21]. Drug-induced pancreatitis was clinically diagnosed after excluding other potential causes of pancreatitis. In drug-induced pancreatitis cases where causal relationship was uncertain, patients were rechallenged. Severity of acute pancreatitis was classified using the revised Atlanta classification [22].

Study design
The IBD registry of Asan Medical Center is a well-established prospectively maintained registry, and has been described previously [18,23-25]. We used the clinical data from this prospectively maintained registry to retrospectively analyze the incidence of acute pancreatitis among patients with UC and the clinical course of UC patients who developed acute pancreatitis. The information obtained from the registry included sex, date of birth, date of symptom onset, and disease course.

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onset, date of UC diagnosis, family history of IBD, smoking status, disease activity, disease extent at diagnosis and during the course, medication use, and colectomy. The extent of disease was determined on the basis of endoscopic findings. Proctitis was defined as disease < 15 cm from the anal verge, left-sided colitis as disease up to the splenic flexure, and extensive colitis as disease beyond the splenic flexure\(^\text{[20]}\). To investigate the subsequent evolution of the disease, we evaluated the rates of proximal disease extension and of colectomy.

**Treatment policy**

Our treatment strategies for UC were detailed previously\(^\text{[18,26]}\) and are based on a step-up approach that is similar to that of Western countries. To briefly summarize, topical and/or oral 5-aminosalicylates were used to induce and maintain remission in mild to moderate UC; systemic corticosteroid therapy was used for moderately to severely active disease; and thiopurines (azathioprine or 6-mercaptopurine) and, in case of failure, anti-tumour necrosis factor (TNF) agents were used for steroid-dependent or steroid-refractory patients.

Pancreatitis was managed conservatively with fasting and antibiotics after discontinuation of the causative drug if present. Patients with AIP were treated with corticosteroids (prednisone 0.6 mg/kg to 1 mg/kg) for 2 to 4 wk, with a taper of 5 mg/d every week. After induction treatment with corticosteroids, immunomodulator agents were given, unless contraindicated.

**Statistical analysis**

Continuous variables are presented as either mean with SD or median with range. Fisher’s exact test was used to compare proportions, and the Mann-Whitney U test was used to compare quantitative variables. Logistic regression with a forward variable selection was used to calculate the adjusted OR and 95%CI for colectomy. In multivariable analysis, the variables with \(P < 0.05\) on bivariate analysis were entered into the model. For drug-induced pancreatitis, clinical characteristics and disease course were compared with non-pancreatitis patients who had also been treated with the same drugs. Stata ver. 14.2 (StataCorp, College Station, TX, United States) was used for statistical analyses.

**Ethical considerations**

This study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2016-0688).

**RESULTS**

**Patient population**

A total of 3307 UC patients [1812 males (54.8%), Table 1] were included for analysis. The median age at diagnosis of UC was 36.3 (range, 9-90) years. At the time of diagnosis of UC, the disease extent was proctitis in 1387 (41.9%), left-sided colitis in 875 (26.5%), extensive colitis in 736 (22.3%), and unknown in 309 (9.3%). Overall, median follow-up time from diagnosis of UC to the last contact was 86.8 (range, 0.2-455.5) mo.

**Incidence of acute pancreatitis**

Among the 3307 study subjects, 51 (1.5%) developed acute pancreatitis. Among the acute pancreatitis patients, 23 (45.1%) had drug-induced (13 thiopurine-induced and 10 aminosalicylate-induced), 13 (25.5%) had autoimmune, 9 (17.6%) had idiopathic, and 6 (11.8%) had gallstone-induced pancreatitis.

AIP developed in 0.40% of 3307 UC patients. All cases of AIP were type 2 (four definitive, nine

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**Table 1 Baseline characteristics of ulcerative colitis patients who developed autoimmune pancreatitis and aminosalicylate-induced pancreatitis, each compared with non-pancreatitis ulcerative colitis patients \(n (%)\)**

| Variable                                      | Autoimmune pancreatitis \((n = 13)\) | \(P\) value vs no pancreatitis | Aminosalicylate-induced \((n = 10)\) | \(P\) value vs no pancreatitis | No pancreatitis \((n = 3256)\) |
|-----------------------------------------------|-------------------------------------|--------------------------------|--------------------------------------|--------------------------------|---------------------------------|
| Male gender                                   | 9 (69.2)                            | 0.223                          | 8 (80.0)                             | 0.125                          | 1788 (54.9)                     |
| Age at diagnosis of UC, years, median (range) | 22.9 (14.9-42.8)                    | 0.001                          | 31.7 (15.7-67.3)                     | 0.444                          | 36.4 (9.0-90.5)                 |
| Smoking status at diagnosis of UC             | 0.876                               |                                |                                       |                                |                                 |
| Never smoked                                  | 8 (61.5)                            |                                |                                       |                                |                                 |
| Ex-smoker                                     | 2 (15.4)                            |                                |                                       |                                |                                 |
| Current smoker                                | 3 (23.1)                            |                                |                                       |                                |                                 |
| Not documented                                | 0                                   |                                |                                       |                                |                                 |
| Disease extent at diagnosis of UC, \(n (%)\)  | 0.012                               |                                |                                       | <0.001                         |                                 |
| Proctitis                                     | 0                                   |                                |                                       |                                |                                 |
| Left-sided                                    | 6 (46.2)                            |                                |                                       |                                |                                 |
| Extensive                                     | 4 (36.4)                            |                                |                                       |                                |                                 |
| Not documented                                | 1 (7.6)                             |                                |                                       |                                |                                 |
| Follow-up duration after UC diagnosis, mo, median (range) | 48.5 (3.2-150.9)                     |                                | 97.2 (12.4-187.6)                    |                                | 87.2 (0.2-455.5)                |
| Follow-up duration after pancreatitis diagnosis, mo, median (range) | 27.8 (3.2-81.9)                     |                                | 91.6 (10.7-174.8)                   |                                |                                 |

NA: Not applicable; UC: Ulcerative colitis.
induced pancreatitis occurred after taking oral forms.

Thiopurine-induced pancreatitis developed in 1.75% of 742 UC patients who were treated with thiopurines. The median interval from the commencement of thiopurines to the development of pancreatitis was 18 (range, 0-131) d.

There was one patient with AIP whose severity was classified as moderate; all other patients had mild acute pancreatitis.

### Casework

#### Clinical course

All 13 patients with AIP showed a good response to corticosteroids, and there were no cases of recurrence during the median follow-up of 27.8 mo (range, 3.2-81.9) following diagnosis of AIP. All 23 patients with drug-induced pancreatitis recovered uneventfully after cessation of the causative agent and with conservative care. Six of ten patients with aminosalicylate-induced pancreatitis underwent aminosalicylate re-challenge, and all cases developed repeat episodes. After permanent cessation of aminosalicylate, all 10 patients showed no further recurrence of pancreatitis during the median follow-up of 91.6 (range, 10.7-174.8) mo. One of 13 patients with thiopurine-induced pancreatitis underwent thiopurine rechallenge and showed a positive response. There was no recurrence of acute pancreatitis during the median follow-up of 21.0 (range, 0.3-89) mo.

Among 13 patients with AIP, medical therapy for

**Table 2  Diagnosis of autoimmune pancreatitis**

| Patient | Imaging | IDCP | ERP | Rt | Definitive/probable |
|---------|---------|------|-----|----|---------------------|
| 1       | Typical | 1H   | +   | +  | +                   | Probable |
| 2       | Typical | 1H   | +   | +  | +                   | Definitive |
| 3       | Indeterminate | 1D | Negative | + | + | + | Probable |
| 4       | Typical | 1D   | +   | +  | +                   | Probable |
| 5       | Typical | 1D   | +   | +  | +                   | Probable |
| 6       | Typical | 1D   | +   | +  | +                   | Probable |
| 7       | Typical | 1D   | +   | +  | +                   | Probable |
| 8       | Typical | 1D   | +   | +  | +                   | Probable |
| 9       | Typical | 1D   | +   | +  | +                   | Probable |
| 10      | Indeterminate | 1D | Negative | + | + | + | Probable |
| 11      | Typical | 1D   | +   | +  | +                   | Probable |
| 12      | Indeterminate | 1D | Negative | + | + | + | Probable |
| 13      | Indeterminate | 1D | Negative | + | + | + | Probable |

D: Ductal imaging on ERP; ERP: Endoscopic retrograde pancreatography; H: Histology of the pancreas; IDCP: Idiopathic duct centric pancreatitis; Rt: Response to steroid, i.e., rapid (< 2 wk) radiologically demonstrable resolution or marked improvement in manifestations.

**Table 3  Comparison of baseline characteristics in ulcerative colitis patients who developed thiopurine-induced pancreatitis and non-pancreatitis ulcerative colitis patients n (%)**

| Variable | Thiopurine-induced pancreatitis (n = 13) | No pancreatitis (n = 704) | P value |
|----------|----------------------------------------|--------------------------|---------|
| Male gender | 4 (30.8) | 434 (61.7) | 0.040 |
| Age at diagnosis of UC, yr, median (range) | 37.9 (12.1-57.3) | 34.8 (11.4-75.9) | 0.667 |
| Smoking status at diagnosis of UC | | | |
| Never smoked | 10 (76.9) | 405 (57.6) | 0.576 |
| Ex-smoker | 2 (15.4) | 168 (23.9) | |
| Current smoker | 1 (7.7) | 125 (17.8) | |
| Not documented | 0 | 5 (0.7) | |
| Disease extent at diagnosis of UC | | | |
| Proctitis | 2 (15.4) | 167 (23.7) | 0.837 |
| Left-sided | 3 (23.1) | 167 (23.7) | |
| Extensive | 6 (46.1) | 232 (33.0) | |
| Not documented | 2 (15.4) | 138 (19.6) | |
| Follow-up duration after UC diagnosis, mo, median (range) | 42.9 (10.7-169.2) | 91.5 (0.3-356.3) | 0.008 |
| Follow-up duration after pancreatitis diagnosis, mo, median (range) | 21.0 (0.3-89) | |

1Non-pancreatitis UC patients who had taken thiopurines. NA: Not applicable; UC: Ulcerative colitis.

probable, Table 2). Two (15.4%) patients had preexisting AIP, for 16 and 30 mo prior to the diagnosis of UC, respectively. Three (23.1%) patients developed both AIP and UC simultaneously. Among the eight AIP patients who had preexisting UC, median time to development of acute pancreatitis was 1046 (range, 294-2217) d after diagnosis of UC.

Aminosalicylate-induced pancreatitis developed in 0.30% of 3307 UC patients who were treated with aminosalicylates. The median interval from the start of aminosalicylate to the development of pancreatitis was 50 (range, 0-549) d. All cases of aminosalicylate-induced pancreatitis occurred after taking oral forms.

Thiopurine-induced pancreatitis developed in 1.75% of 742 UC patients who were treated with thiopurines. The median interval from the commencement of thiopurines to the development of pancreatitis was 18 (range, 0-131) d.

There was one patient with AIP whose severity was classified as moderate; all other patients had mild acute pancreatitis.

### Demographics and clinical characteristics of UC patients with pancreatitis

Baseline demographic and clinical characteristics of UC patients with and without pancreatitis are shown in Tables 1 and 3. Median age at diagnosis of UC was significantly younger among AIP patients compared to those without pancreatitis. Patients with autoimmune and aminosalicylate-induced pancreatitis had more extensive UC compared to those without pancreatitis.

#### Clinical course

All 13 patients with AIP showed a good response to corticosteroids, and there were no cases of recurrence during the median follow-up of 27.8 mo (range, 3.2-81.9) following diagnosis of AIP. All 23 patients with drug-induced pancreatitis recovered uneventfully after cessation of the causative agent and with conservative care. Six of ten patients with aminosalicylate-induced pancreatitis underwent aminosalicylate re-challenge, and all cases developed repeat episodes. After permanent cessation of aminosalicylate, all 10 patients showed no further recurrence of pancreatitis during the median follow-up of 91.6 (range, 10.7-174.8) mo. One of 13 patients with thiopurine-induced pancreatitis underwent thiopurine rechallenge and showed a positive response. There was no recurrence of acute pancreatitis during the median follow-up of 21.0 (range, 0.3-89) mo.

Among 13 patients with AIP, medical therapy for
In this study, we analyzed the frequency and clinical course of acute pancreatitis among UC patients in a large, well-established prospective cohort. To the best of our knowledge, this is the largest single study to date to describe the frequency and clinical course of AIP.

The most common causes of acute pancreatitis in IBD patients are reported to be gallstones and drugs[27]. Thiopurines are the drugs most frequently implicated as a cause of acute pancreatitis in IBD patients, with a reported incidence of 3%-4%[28,29]. In a prospective study among IBD patients, azathioprine-induced acute pancreatitis occurred in 37 of 510 patients (7.3%)[30]. In our study, a higher rate of acute pancreatitis was observed in thiopurine-treated patients (1.75%), compared with the rates of autoimmune (0.40%) and aminosalicylate-induced cases (0.30%).

UC patients are reported to be at an increased risk of developing acute pancreatitis compared to the general population[31]. According to a study performed in 2003, the annual incidence of acute pancreatitis in South Korea was 19.4 per 100000 persons[32]. In our patients, the annual incidence of acute pancreatitis was 152.9 (95%CI: 113.4-206.1) per 100000 persons (data not shown). The incidence was higher among our patients, and further analysis using data from the general population is required to draw firm conclusions.

Ueki et al[11] reported that five (0.5%) of 961 Japanese patients with UC developed AIP during a mean follow-up period of 86 mo. This figure is comparable with the 0.4% in our study. Although AIP is uncommon among IBD patients, it is interesting to note that the reported prevalence of AIP in patients with AIP is 6% to 27%, predominantly UC[27,33-35]. AIP is subclassified into two separate entities: type 1 AIP, or lymphoplasmacytic sclerosing pancreatitis (LPSP), and type 2 AIP, or idiopathic duct centric pancreatitis (IDCP)[31,32]. Type 2 AIP is most commonly associated with IBD, with a reported frequency of 16% to 30%[37,38]. All of our patients with AIP had type 2 AIP. It is interesting that two cases of AIP occurred before the diagnosis of UC. There have been several reports of AIP occurring before the diagnosis of CD[31,32,39,40], but to the best of our knowledge, there have been no reports of AIP that preceded UC. Our results suggest that patients with repeated episodes of unexplained acute pancreatitis should be evaluated for inflammatory bowel disease.

Among the drug-induced pancreatitis patients, some cases were diagnosed only after a prolonged period since starting the drug. It is possible that objective diagnosis of pancreatitis was delayed, since symptoms of pancreatitis and UC, such as abdominal pain, can overlap. It is also possible that the patient
could have skipped the drug after experiencing the side effect, without notifying the attending physician. In previous studies, the median duration of azathioprine therapy before diagnosis of pancreatitis was 26 (range, 6-720) d\(^4\) and 25 (range, 5-30) d\(^2\)\(^9\), which was similar to that in our study [median, 18 d (range, 0-131)]. A case of pancreatitis after 18 mo of mesalamine treatment has also been reported\(^4\)\(^2\).

Patients with AIP were younger and had more extensive disease than those without acute pancreatitis. Most patients with aminosalicylate-induced pancreatitis had extensive disease, but the reason is not clear. There were significantly more females among thiopurine-induced pancreatitis patients compared to non-pancreatitis patients in our study (69.2% vs 38.3%; \(P = 0.040\)). In a prospective study of 37 patients with azathioprine-induced acute pancreatitis, 24 (64.9%) were female (\(P = 0.06\))\(^3\)\(^0\). A study on CD patients\(^2\)\(^9\) reported that females over 40 years of age had an increased risk for developing thiopurine-related adverse events, but the reasons for increased thiopurine-induced pancreatitis among females is not clear. The incidence of thiopurine-induced pancreatitis is reported to be 3%-4% among IBD patients\(^2\)\(^7\)-\(^2\)\(^9\). Among our patients, thiopurine-induced pancreatitis developed less frequently (1.75% of thiopurine users). The reason for this is not clear, but it might represent a distinct characteristic of our cohort.

In our study, there was no case of relapse of pancreatitis among AIP patients, once treated. All our AIP patients had type 2 AIP, and previous studies reported that relapse of pancreatitis is rare in type 2 AIP compared to type 1 AIP\(^4\)\(^3\)\(^4\)\(^4\). In a large multicenter study involving 978 subjects with type 1 AIP and 86 with type 2 AIP, the relapse rate was 31% with type 1 and 9% with type 2 (\(P < 0.001\))\(^4\)\(^4\). Considering the usual step-up approach for treating UC, the higher rate of anti-TNF agent use among thiopurine-induced pancreatitis cases is expected. Aminosalicylate-induced pancreatitis patients also showed a higher rate of anti-TNF agent use, presumably because a high proportion had extensive disease (90%). Although the rate of anti-TNF use was high, the colectomy rates were not significantly different in acute pancreatitis patients compared to non-pancreatitis patients. The colectomy rate in our cohort was 7.3%, which is comparable to those of previous studies\(^4\)\(^5\)-\(^4\)\(^9\).

AIP is a new diagnostic entity, only established in 2011\(^2\)\(^1\). In addition, the tendency among Korean physicians to prescribe thiouirine only showed a rising trend in recent years\(^1\)\(^8\). For these reasons, durations of follow-up for autoimmune and thiopurine-induced pancreatitis patients were shorter than those for non-pancreatitis patients. Therefore, directly comparing the colectomy rate with non-pancreatitis patients might have led to false-negative results. As physicians are becoming more aware of AIP, and as thiopurines are being used more frequently\(^1\)\(^8\), future studies using longer analysis times seem to be required.

This study has several limitations. First, since this study was conducted at a single tertiary referral center, the conclusions could have been biased. Second, we could not analyze the severity of pancreatitis in detail, due to limitations in clinically available data. Third, as mentioned above, the follow-up time of autoimmune and thiopurine-induced pancreatitis patients was relatively short, which could have led to false negative results regarding subsequent colectomy rates. Fourth, the follow-up interval was variable among patients, which could have led to the apparently low rate of thiopurine-induced pancreatitis.

In conclusion, we described the frequency and clinical course in UC patients who developed acute pancreatitis in a large, prospectively maintained cohort. Compared with non-pancreatitis UC cases, the baseline disease extent in patients with autoimmune and aminosalicylate-induced pancreatitis was greater, and age at diagnosis of UC with AIP was younger. Anti-TNF agents were used more frequently in UC patients who had developed aminosalicylate- or thiopurine-induced pancreatitis. Despite these differences, the clinical course of UC patients who developed acute pancreatitis was not significantly different. Further studies with longer follow-up are required.

**COMMENTS**

**Background**
Patients with ulcerative colitis (UC) seem to be at risk for developing acute pancreatitis, which can be an extraintestinal manifestation of the UC, drug-induced, or autoimmune-related. The clinical course of UC in patients who develop acute pancreatitis is not well known.

**Research frontiers**
Acute pancreatitis can cause a significant impact on the course of UC by requiring change in treatment or by acting as a prognostic factor itself. This study investigated the clinical course of UC in patients who developed acute pancreatitis in a large, well-established, prospectively maintained cohort. Particular focus was given to the clinical course of patients who developed autoimmune, aminosalicylate-induced and thiopurine-induced pancreatitis.

**Innovations and breakthroughs**
The results showed that UC patients who developed acute pancreatitis had a non-significantly higher colectomy rate compared with those without pancreatitis, after adjusting for disease extent of UC at baseline. The acute pancreatitis in most patients was mild. All patients with autoimmune pancreatitis (AIP) had type 2 and there was no recurrence of the pancreatitis.

**Applications**
The data in this article can be used to predict the clinical course of patients with UC who develop acute pancreatitis, which seems to be mild in most cases. There was no recurrence of AIP. Patients with aminosalicylate-induced and thiopurine-induced pancreatitis had higher rates of treatment with a biologic.

**Terminology**
AIP is a peculiar type of pancreatitis of presumed autoimmune etiology, subclassified as type 1, lymphoplasmacytic sclerosing pancreatitis, and type 2, idiopathic duct-centric pancreatitis.

**Peer-review**
This is an interesting manuscript which describes the clinical course of patients...
Probing the association of inflammatory bowel disease and autoimmune pancreatitis

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