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The Incidence of Proximal Extension of Ulcerative Proctitis in Japan and Factors Related to Proximal Extension

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Abstract : The incidence of proximal extension in patients with ulcerative proctitis is reported to be 18%–46%, but recent data on the incidence in Japan is inadequate. The aim of this study was to investigate the incidence of proximal extension of ulcerative proctitis and factors associated with the extension in Japan. This is a retrospective observational study involving a cohort of 53 patients with an initial diagnosis of ulcerative proctitis. Following verification of the diagnoses, demographic and clinical data were compiled. The cumulative incidence of proximal extension was estimated as 'person-years' and cumulative probability was calculated by the Kaplan-Meyer method. Univariate and multivariate analyses were performed to identify association factors. During a mean follow-up of 6.8 years, proximal extension was observed in 14 patients (26.4%). The cumulative incidence of proximal extension was 4.22/100 person-years and the cumulative probability at 5 years was 20.1%, consistent with recent reports from Western countries and data obtained in Japan over 2 decades ago. Univariate analysis showed active smoking (P = 0.025) and corticosteroid therapy (P = 0.006) to be risk factors in proximal extension, however multivariate analysis revealed that corticosteroid therapy was the only significant factor (P = 0.005) separating patients with and without proximal extension. No patient underwent colectomy. The incidence of proximal extension in ulcerative proctitis in Japan is comparable to that in Western countries and has not changed significantly over the past two decades. Corticosteroid therapy was identified as the only significant factor in proximal extension.

Key words : ulcerative colitis, disease extension, natural course, ulcerative proctitis

Abbreviations used : IBD, inflammatory bowel disease, UC, ulcerative colitis

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Introduction

Ulcerative colitis (UC) is a chronic relapsing-remitting inflammatory bowel disease (IBD) with symptoms which impair performance and quality of life. One feature of UC is that the inflammation diffusely and continuously extends from the distal to the proximal colon and that the rectum is primarily involved, which is a hallmark of this disease[1].

Among patients with UC, proctitis has the following distinct characteristics compared to those of left-sided or extensive disease: high age of onset, minimal cancer risk, and a low frequency of the most common complications such as toxic megacolon and bleeding[2, 3]. Although the clinical impact of ulcerative proctitis is not very significant, it accounts for one-third of all UC patients[4] and the occurrence of proctitis in UC has steadily increased in the past few decades[3, 5]. In addition, it has been reported that the rate of colectomy increases once the proctitis is entirely extended[3, 6].

To make prudent therapeutic decisions in patients with active UC, it is essential to assess both the extent of anatomical involvement as well as the severity of inflammation. Thus the extent of UC has been recognized as one prognostic factor; extensive disease increases the risk of complications like bleeding and megacolon, which can lead to surgical intervention[3, 7]. Similarly, UC is a life-long disorder with an unpredictable disease course, which is an additional source of concern for patients[8]. Accordingly, knowledge of the natural course of the disease, particularly, changes in the progression of the disease over time are valuable. We reviewed the literature on the natural history of UC and the profile of inflammation, and found considerable heterogeneity; the incidence of proximal extension has been reported to be 20%–50% , while regression has also been observed[9, 10].

The natural history of ulcerative proctitis has been investigated mostly in Western countries and, as mentioned above, disease extension is estimated to be 18%–46%[9–15]. However, factors previously identified as contributing to disease extension have been challenged[3, 6, 10, 11]. In addition, there have been very few reports describing the natural course of ulcerative proctitis in Japan. Hiwatashi *et al*[14] reported that 21 of 76 ulcerative proctitis patients experienced disease extension, with half of those patients developing the extension within 3 years of onset, bearing in mind that the patients in the study were recruited from 1954 to 1987. In addition, the prevalence of UC has steadily increased during the past two decades[16]; the current incidence of UC in Japan is estimated to be more than 4 times the level when Hiwatashi and colleagues carried out their study[14]. Therefore, it is important to know if the natural course of this disorder has changed since 1987. Hence, the objective in this study was to investigate the current incidence of disease extension in ulcerative proctitis in Japan, and examine factors associated with this disease extension.

Materials and Methods

Patients and study design

This was a retrospective observational investigation conducted at three tertiary care institutions in Japan. The study population comprised a cohort of 53 patients with a previous diagnosis of ulcerative proctitis between 1997 and 2008. The patients were followed-up for at least 3 years by a second colonoscopy. The colonoscopy was performed on the basis of clinical needs and not regularly scheduled. The end of the observation period in patients without disease extension was the final clinical or endoscopic follow-up. Observations ceased when disease extension was documented.

Diagnosis of ulcerative proctitis

Diagnosis of ulcerative proctitis was based on the following 4 criteria. 1) Patients had experienced chronic diarrhea, bloody stool, or pus in the stool. 2) Colonoscopy revealed at least one macroscopic finding, including absence of vascular patterns, friability, granularity or erosions, which was confined to the rectosigmoid junction. The severity of the endoscopic findings was determined according to Matt's score[17]. 3) Histopathological findings demonstrated diffuse infiltration of inflammatory cells, and presence of either cryptitis or a crypt abscess. Depletion of goblet cells, distortion of glands, and basal plasmacytosis were not essential. We did not determine the histological severity because of the lack of a validated scoring system. 4) Infectious disease was ruled out. The diagnoses of all cases were verified retrospectively by review of colonoscopy photographs and medical records.

Definition of proximal extension

Definition of proximal extension was the presence of macroscopic inflammation extending beyond the rectosigmoid junction judged by any follow-up colonoscopy. Time to proximal extension was defined as the period between the onset of symptoms and the time of colonoscopy when the extension was documented.

Demographic data

Demographic data included age at onset, gender, family history, smoking habits, corticosteroid therapy, clinical course, appendiceal involvement, and the use of aminosalicylates (mesalamine or sulphasalazine). Family history was defined as positive if there was any UC or Crohn's disease in a relative irrespective of family closeness (parent, child, sibling, grandparent, aunt, uncle, or cousin). Patients were defined as active smokers if they were regularly smoking at the time of diagnosis of proximal extension. The number of cigarettes and how long they had been smoking did not matter. Doses of mesalamine or sulphasalazine used for treatment were mostly 2.25 g or 3 g, respectively. Corticosteroid was given orally or topically ; 0.6 mg/kg of oral predonisolone or 1 mg of betamethasone. The clinical

course was classified as one attack, flare up-remission, or chronic active. Definition of chronic active was symptoms continuing for more than 6 months.

Statistical analysis

Continuous values are expressed as median or mean values with ranges, while categorical data are expressed as frequency and percentages. Cumulative rates of proximal extension were calculated by the Kaplan-Meier method and cumulative incidence was estimated to be 100 'person-years.' For comparison between patients with and without disease extension, the chi-square test or Fisher exact test was applied, while the Mann-Whitney *U* test was applied for descriptive and numerical data. To determine an associated factor for disease extension, univariate analysis for individual factors was applied and the significance level was based on the signed log-rank test. For this analysis, age at onset was converted to dichotomous by splitting with the median, and the three categories of clinical course were also converted to a dichotomous variable ; flare up-remission and chronic active were categorized as active disease. Factors significant in the univariate analysis were used in the Cox proportional hazards model with a stepwise procedure to adjust for potential confounders. For all analyses, a two-tailed *P*-value $<$ 0.05 was considered statistically significant. The software used for statistical analyses was SPSS for Windows.

Ethical Considerations

The protocol of this investigation was reviewed and approved by the Ethics Committees at all three participating institutions.

Results

Clinical outcomes

Among the 53 patients in the study, 15 were males and 38 were females. The median age at onset was 33 years, range 18 to 73 years (Table 1). Positive family history and active smoking was present in 3 (5%) and 7 patients (13%), respectively. At the time of the first diagnosis, 21 patients (40%) presented with appendiceal involvement. During the clinical course of the disease, 28 patients (53%) experienced flare-ups and 9 patients (17%) presented with chronic active disease. One patient did not receive any medication in the follow-up period, but all other patients were taking either mesalamine or sulphasalazine. Corticosteroid was taken was by 17 patients (32%). The mean follow-up time was 6.8 years, ranging from 3 to 20 years. No patient underwent colectomy during the follow-up period. Only corticosteroid therapy was significantly different between patients with and without proximal extension (P = 0.005). The significance levels for active smoking and clinical course were P = 0.06 and P = 0.07, respectively (ns). Colonoscopy at the time of diagnoses revealed a Matt's score of 1 in all patients and no specific features predictive of proximal extension were noted.

Table 1. Baseline demography of the patients with and without proximal extension

	disease extension (+) N=14	disease extension (−) N=39	*P* value
male (%)	29	28	NS
age of onset (median, range)	33 (24-55)	33 (18-73)	NS
family history	1 (7%)	2 (5%)	NS
active smoking	4 (29%)	3 (8%)	NS
appendiceal involvement	7 (50%)	14 (39%)	NS
corticosteroid requirement	9 (64%)	8 (21%)	0.005
clinical course			
one attack	2 (14%)	14 (36%)	
flare-remission	11 (79%)	17 (44%)	NS
chronic active	1 (7%)	8 (20%)	
aminosalicylates			
mesalamine	8 (57%)	16 (42%)	NS
sufasalazine	6 (43%)	22 (58%)	

ns = statistically not

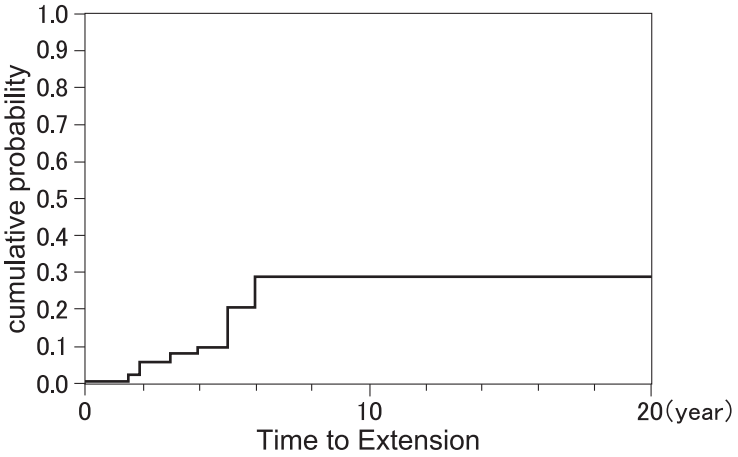

Fig. 1. Cumulative probability of proximal extension in ulcerative proctitis.

Proximal extension

During our investigation period, proximal extension was observed in 14 of 53 patients (26%). In 7 of these 14 patients, the inflammation did not extend beyond the splenic flexure. Extensive colitis along the ascending colon and the caecum developed in the remaining 7 patients. All cases presented with disease extension within 6 years of the onset of ulcerative proctitis. The cumulative incidence of proximal extension was 4.22/100 person-years and the cumulative probability at 5 and 10 years was 20.1% and 28.0%, respectively (Fig. 1).

Table 2. Univariate analyses of overall risk for proximal extension

	P value
male (%)	0.659
age of onset	0.643
family history	0.349
active smoking	0.022
appendiceal involvement	0.379
corticosteroid requirement	0.009
clinical course	0.230
aminosalicylates	0.370

By Log rank test

Association factors

In univariate analyses, active smoking and corticosteroid therapy were found to be statistically significant risk factors (Table 2). In a multivariate analysis, corticosteroid therapy was still a significant risk factor with a hazard ratio of 3.813 (95% confidence interval, 1.247–11.659).

Discussion

In this investigation, we found that proximal extension developed in 14 of 53 patients (26%) with ulcerative proctitis, with a cumulative incidence of 4.22/100 person-years. Corticosteroid therapy was found to be significantly associated with proximal extension. However, a population-based study may be more useful for generally understanding the clinical course of these diseases because such an approach should minimize selection bias. Although our study was hospital-based, we made maximum effort to avoid selection bias and therefore, our results should represent population-based data. It is appropriate to mention here that based on the unique health delivery system in Japan, patients are allowed to visit any medical institution at their own discretion. Referrals are not required to visit even a tertiary care centre. Indeed, approximately 40% of the patients in this study were not referred by primary care physicians. Additionally, by the introduction of guidelines, the medical therapy of patients with UC has been standardized nationwide.

Previous studies have reported various rates of disease extension in ulcerative proctitis, ranging from 18% to 46% (Table 3)[9–15]. This level of inconsistency may be due to different clinical settings, observation periods, geographical or racial differences, health delivery systems, or methods for evaluating the extent of the disease. However, more recent studies consistently show that disease extension in ulcerative proctitis occurs in 18% to 28% of cases[2, 12, 13, 15]. The incidence of proximal extension in this investigation is very similar to those in the latter studies, suggesting that the rate of proximal extension in ulcerative proctitis may be universal and is not as high as some reports have previously suggested.

Table 3. Previous reports examining the incidence of proximal extension of ulcerative proctitis

	observation period (months)	Number of patients	incidence of extension (%)
Western countries			
Langholtz *et al*[10]	144	61	25
IBSEN study[2]	60	127	28
Meucci *et al*[11]	64	273	27
Park *et al*[12]	62.5	134	33 (at 5 years)
Moum *et al*[9]	12	130	22
Farmer *et al*[3]	144	516	46
Chatzicostas *et al*[13]	132	62	18 (at 5 years)
Ayres *et al*[6]	132	145	27 (at 5 years)
Japan			
Hiwatashi *et al*[14]	106	76	27

The proximal extension in this study occurred over time. Langholz *et al*[10] reported that the median interval of extension was 1.3 years, while Moum and colleagues[9] also reported that 22% of cases with an initial diagnosis of ulcerative proctitis presented with an increased distribution of inflammation within a median follow-up time of 14 months, suggesting early occurrence of proximal extension. However, most other studies appear to show a gradual increase of the extension and in our investigation, early extension was not prominent. Prospective studies involving large cohorts of patients may be needed to better understand this issue.

In this study, no patient underwent colectomy during the observation period. Our findings are in agreement with the recent report of a very low rate of colectomy in Japanese proctitis patients[18]. These authors found that among 1000 UC patients who required surgery, the initial diagnosis of proctitis was only made in 2 cases[18]. According to previous reports from Western countries, the cumulative colectomy rate for UC was 7% to 32% at 5 years[3, 6, 10]. However, it should be noted that in more recent reports from Norway and Greece, the colectomy rate was very low at zero to 2 %[2, 13]. Development of novel medications may reflect the current decrease in the rate of colectomy. Interestingly, Stewenius *et al* reported that the period from the onset of symptoms to the diagnosis decreased over time[5], indicating that medical intervention has become faster as well. Thus, the rate of colectomy in proctitis patients may be low and not as high as has been reported even in Western countries.

One explanation for the absence of colectomies in this study might be a better adherence to medical care because all patients, except one, were on medical therapy (at least an aminosalicylate) during the follow-up period and aminosalicylates have been shown to reduce the risk of proximal extension[15]. In contrast, Henriksen *et al* reported that 65% of UC patients with an initial diagnosis of proctitis were free from medication after 5 years of fol-

low-up[2]. Another factor could be the favorable natural course of UC in Asians, compared to Westerners[19]. For example, Probert *et al*[20] found that migrant South Asian patients with UC had a lower risk of colectomy compared to European patients[20]. A recent study in Korea supports this notion, with only 2 of 134 proctitis patients undergoing a colectomy within a median follow-up time of 62.5 months[12]. Different genetic predispositions or environmental factors might be responsible for such racial differences. Interestingly, Pierik *et al*[21] found that Toll-like receptor 1, 2, and 6 polymorphisms influence disease extension in patients with IBD. Additionally, Western foods are suspected to promote IBD[22].

In Japan, studies examining the natural course of ulcerative proctitis are rare. Hiwatashi *et al*[14] reported the rate of disease extension in ulcerative proctitis patients was 27% within a mean follow-up time of 9.6 years and the cumulative probability after 5 years was 15% to 20%. The rate of colectomy was very low, at 3.3% or 1 in 55 cases. The data in that study were obtained in a single, but very large hospital. However, this was over 20 years ago. Given the recent availability of new medications and changes in application strategies, such as oral and rectal formulations of mesalamine, and rectal formulations of prednisolone, together with a dramatic increase in the number of UC patients during the past two decades in Japan, it is important to compare changes in the natural course of the disease over time. Surprisingly, with all these new developments, our results detailing proximal extension in patients with ulcerative proctitis are very similar to those of Hiwatashi's group[14], suggesting that the natural course of ulcerative proctitis has not changed in the 20 years since these authors published their findings.

Several studies have attempted to identify risk factors for proximal extension but the data are conflicting. Farmer *et al*[3] found early disease onset, disease severity, and extra-intestinal manifestations to be prognostic factors. Langholz *et al*[10] showed that symptomatic manifestations such as pain and diarrhea, at the time of diagnosis but not at the time of onset of the disease, were associated with proximal extension. Meucci *et al*[11] showed that more refractory disease requiring corticosteroid therapy, non-smoking, and frequent relapses were independent prognostic factors. Chatzicostas *et al*[13] also suggested that non-smoking was a risk for disease progression, while Pica and colleagues[15] reported that a more prolonged oral mesalamine treatment period was protective against proximal spread. More recently, Etchevers *et al*[23] found that a younger age at diagnosis and the presence of sclerosing cholangitis were independent predictive factors for disease extension.

To identify associated factors, we looked at the clinical and demographic data, taking into account the aforementioned reports and our clinical experience. In a univariate analysis, current smoking was associated with disease extension (albeit with a very small sample size). In general though, cigarette smoking seems to have a protective effect in UC[24]. Although positive family history has been reported to be a significant risk factor in the development of UC[12, 25], we found no association. Similarly, our finding of no association between appendiceal lesions and proximal extension is in line with the report by Byeon

and colleagues[26]. We also compared the effect of mesalamine with sulphasalazine because mesalamine is reported to have a protective effect on disease extension[15] and mucosal concentrations of total 5-aminosalicylate are much higher in patients taking sulphasalazine than mesalamine[27]. However, it should be noted that this study was not appropriately designed to directly compare the efficacy of the aminosalicylates. Our multivariate analysis showed that a requirement for corticosteroid therapy was the only factor associated with disease extension, consistent with the reports by Meucci *et al* and Pica *et al*[11, 15]. Patients who require corticosteroids may have a more severe or refractory UC and therefore, need more frequent check-ups. Indeed, most of the patients with proximal extension needed more aggressive immunosuppressive therapy after proximal extension was diagnosed.

The limitations of this study should be mentioned. First, our sample size was small, and this might have contributed to low statistical power. Most of the studies examining the natural course of UC include a few hundred cases. Second, there could be inter-observer differences in the diagnosis of ulcerative proctitis. Baron *et al*[28] reported difficulties in describing mucosal appearance particularly when clearly defined features such as bleeding were absent. However, we think that this can be minimized by reviewing endoscopic photographs taken at colonoscopy. Third, as this study was endoscopybased, we could not exclude the presence of microscopic inflammation in the proximal site in spite of the diagnosis of ulcerative proctitis. Moum *et al*[9] reported that the upper extent of inflammation at endoscopy did not completely correlate with histological inflammation. Fourth, self-limiting proctitis could not be ruled out, which may cause underestimation of the true rate of proximal extension. Likewise, colonoscopy was not scheduled which could also underestimate the rate. Nonetheless, this is the most up to date report on the natural course of ulcerative proctitis in Japan.

In conclusion, this investigation found the incidence of proximal extension in ulcerative proctitis in Japan to be 26%. Similarly, the cumulative incidence of proximal extension was 4.22/100 person-years and the cumulative probability was 20.1% at 5 years. The colectomy rate was zero. These outcomes are consistent with reports published over two decades ago, indicating that the natural course of ulcerative proctitis in Japan has not changed in recent years. Corticosteroid therapy was associated with proximal extension therefore diligent follow-up should benefit this subgroup.

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