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Diagnostic evaluation of appendiceal orifice inflammation in ulcerative colitis

BOWEL

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Original Article

ABSTRACT

Background/Aims: To evaluate the diagnostic significance of appendiceal orifice inflammation (AOI) in ulcerative colitis (UC) patients.

Materials and Methods: We retrospectively examined data from patients with colitis from May 2010 to January 2014 and assigned them to two groups: UC cases and specific colitis cases. First, we clarified the difference in the AOI+ rate between the two groups. Thereafter, imaging findings of all the patients with colitis were re-examined. Features of AOI alone or in combination with proctitis (referred to as "combination features") were considered as the two separate diagnostic criteria for diagnosing UC. By comparing the current diagnoses with the previous diagnoses, evaluation indexes were obtained.

Results: A total of 3582 colitis cases (UC cases: 427; specific colitis cases: 3155) were examined. The mean AOI+ rates in UC and specific colitis cases were 26.2% and 0.7%, respectively; a Chi-squared test indicated that the difference between these rates was statistically significant ($x^2=6.81$; $p<0.001$, OR=50.99). When the AOI features alone were used to diagnose UC, the sensitivity was 26.2% [95% confidence interval (CI), 22.3%–30.6%], agreement rate was 90.6%, and specificity was 99.3% (95% CI, 98.9%–99.5%). When the combination features were used to diagnose UC, the sensitivity was 26.2% (95% CI, 22.3%–30.6%), agreement rate was 91.1%, and specificity was 99.9% (95% CI, 99.7%–100%).

Conclusion: Combining AOI features and proctitis may lead to a more effective UC diagnosis and enable physicians to identify this condition more promptly among miscellaneous diseases.

Keywords: Ulcerative colitis, appendiceal orifice inflammation, specificity, sensitivity, diagnosis

INTRODUCTION

Ulcerative colitis (UC) is usually diagnosed based on patient history and clinical, radiological, endoscopic, and histological features. The most important aspect of its diagnosis is the exclusion of other similar conditions. Hence, the identification of a specific diagnostic feature for UC is important. With the increased use of endoscopic techniques for diagnosing UC, the frequency of identifying appendiceal orifice inflammation [AOI; also called "peri-appendiceal red patch" or "cecal patch" (1)] has also increased. For example, over the last 13 years, the number of UC-AOI cases has increased upto 27% in all UC cases in our endoscopic center.

However, the relationship between AOI and UC is unclear, although it has been evaluated in several studies. AOI has been considered to be a "skip lesion" in UC (1), and it histologically resembles colonic features rather than acute appendicitis, as confirmed by evidence showing that, in the same patient with AOI, AOI shows crypt architectural distortion, crypt branching, and crypt atrophy on low-power views of the appendix. Additionally, the inflammation is confined to the mucosa. Furthermore, a high-power view of the same slide shows a diffuse chronic inflammatory cell infiltrate with cryptitis and crypt abscess. Compared with acute appendicitis, ulcerative colitis appendices are more

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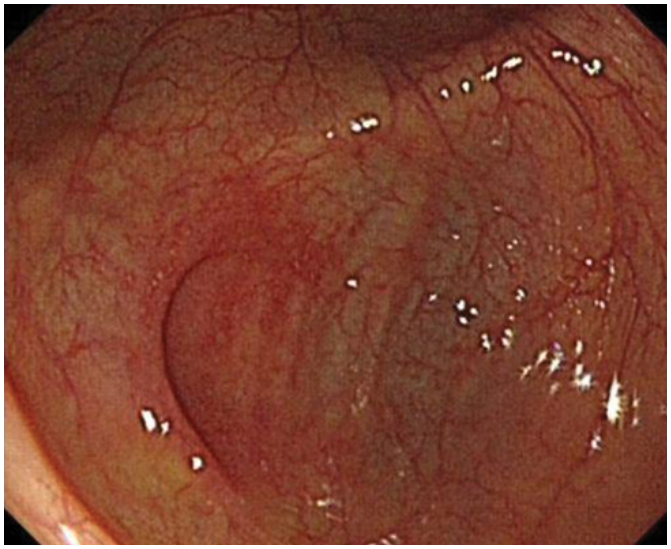

Figure 1. Congestion of the appendiceal orifice

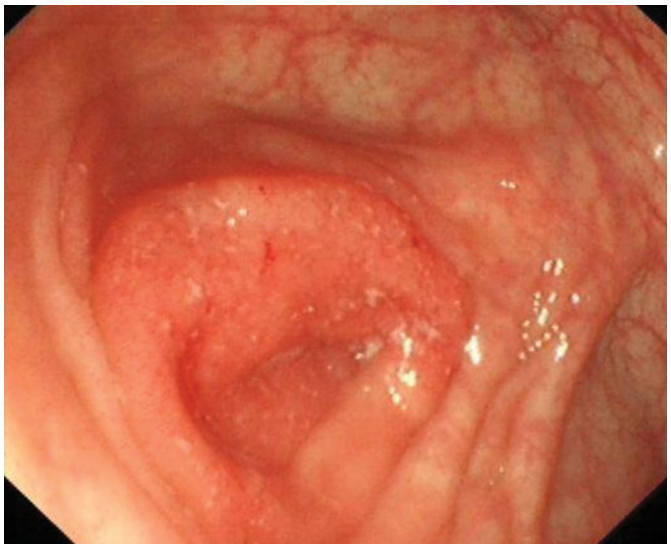

Figure 2. Erosion of the appendiceal orifice

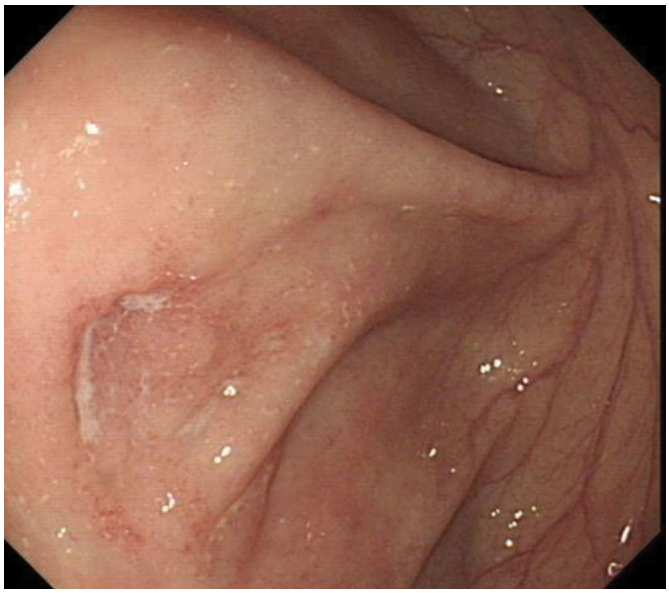

Figure 3. Ulceration of the appendiceal orifice

likely to have crypt abscesses, gland branching and shortening, and Paneth cell metaplasia and less likely to show muscularis propria infiltration by neutrophils (2). In some reports (3-5), endoscopists have identified AOI macroscopically based on the presence of mucosal erythema, congestion/erosion/ulceration, and friability (Figure 1-3). Moreover, some other investigators have indicated that AOI may be involved in the development or pathogenesis of UC (4,6,7). These evidences suggest that there is a close relationship between UC and AOI, but it remains unclear whether AOI develops only by chance. If AOI and UC are closely related, AOI could be used for diagnosing UC. In the present study, we aimed to evaluate the diagnostic significance of AOI in UC patients.

MATERIALS AND METHODS

Patient characteristics

Medical records from a total of 3582 cases were collected from the database of our endoscopy center, including 427 from patients diagnosed with UC and the remaining from patients diagnosed with specific colitis. Patients diagnosed with UC were enrolled if they met the following criterion: a diagnosis of UC according to the European and Chinese guidelines (8,9), which are based on clinical manifestations, laboratory examinations, endoscopic manifestations, pathologic examination findings, and the exclusion of other diseases. In some reports, endoscopists identified AOI macroscopically based on the presence of mucosal erythema, congestion/erosion/ulceration, and friability (Figure 1-3). Patients diagnosed with specific colitis included those with intestinal infectious colitis, ischemic colitis, radiation colitis, and intestinal ulcers. Patients were excluded if the entire colon was not completely examined, the appendiceal orifice was not observed, the colonoscopy images were not clear, incomplete information was available, or if the patient had appendicitis. Although we rarely encounter cases of Crohn's disease, Behcet's disease, and other non-specific colitis conditions at our endoscopy center, we excluded them from the present study. This study was reviewed and approved by the Institutional Research Ethics Committee.

Parameter comparisons

We first assessed the difference in the AOI^+ rates between the UC and specific colitis groups. Thereafter, we re-examined the imaging findings from all the colitis patients, whereby we examined whether or not the patient had AOI and proctitis. We chose four experienced attending physicians (split between the two groups) to distinguish AOI, and three chief physicians to serve as supervisors to resolve any disagreements between the two attending physicians in each group. They were all blinded to the original diagnosis and were not allowed to review the cases on which they were the first observers. Cases were excluded if an agreement was not reached among the five physicians. AOI features alone or in combination with proctitis were used as the two separate diagnostic criteria for UC diagnosis. By comparing the current diagnoses with the origi-

nal diagnoses, evaluation indexes were obtained. Moreover, we analyzed the clinical characteristics of UC among the patients with AOI.

Statistical analysis

All the statistical analyses were performed using SPSS 16.0 software for Windows (SPSS Inc.; Chicago, IL, USA). Comparisons between the study groups were performed with the Chi-squared test. As comparisons among ≥3 groups were not performed, the difference was considered statistically significant when $p<0.05$. Excel software (Microsoft Corp.; Redmond, WA, USA) was used to examine the relationship between the AOI$^+$ rate and the patient age. Several valuation indexes were applied for diagnostic testing, such as the sensitivity, specificity, positive predictive value, negative predictive value, and agreement rate index. Moreover, the sensitivity and specificity of the confidence interval (CI) were calculated using Wilson's method.

RESULTS

After excluding a total of 32 patients who met the exclusion criteria, the total number of patients included in the study was 3582, including 427 diagnosed with UC (234 men and 193 women) and 3155 diagnosed with specific colitis. Table 1 shows that there were 112 patients with AOI (66 men and 46 women, giving a ratio of 1.4:1), accounting for 26.2% of the total number of UC patients. When these patients were divided into the two subgroups (UC-AOI$^+$ cases and UC-AOI$^-$ cases), the average age of the UC-AOI$^+$ cases was younger than that of the UC-AOI$^-$ cases ($t=3.46$; $p<0.001$). The AOI$^+$ rates did not significantly differ between men and women (28.2% and 23.9%, respectively, Chi-squared test: $\chi^2=2.36$; $p>0.05$).

Figure 4 shows the relationship between patient age and the AOI$^+$ rate in the UC patients. We noted that older age was associated with a lower AOI$^+$ rate. In particular, UC patients aged <40 years were more likely to present AOI features.

Table 2 shows the relationship between lesion extent and the AOI$^+$ rate among the UC patients. These data appear to represent unidirectional ordinal information, and no significant difference was noted between lesion extent and the AOI$^+$ rate according to the Chi-squared test ($\chi^2=0.26$; $p>0.05$).

Moreover, a total of 112 UC patients were concurrently assessed for concomitant AOI. The AOI$^+$ rate in the UC patients was 26.2%, which was markedly higher than that in the specific colitis patients (0.70%). The difference between these values was statistically significant ($\chi^2=6.81$; $p<0.001$, OR=50.99). In particular, the AOI$^+$ rate of UC was 37.6 times that of specific colitis (Table 3).

To assess the diagnostic results in all the colitis patients, we re-examined the endoscopic images of all the patients diagnosed with colitis (427 with UC and 3155 with specific colitis). AOI features alone or in combination with proctitis were considered as two separate diagnostic criteria for the diagnosis of UC. We noted that a total of 134 patients exhibited AOI features alone

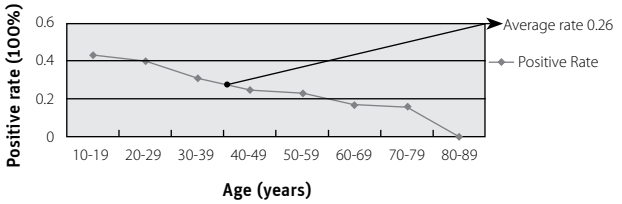

Figure 4. Relationship between patient age and the appendiceal orifice inflammation-positive rate in ulcerative colitis patients

Table 1. The main clinical features in 427 cases of UC patients with and without AOI

Group	UC-AOI+ (No.)	UC-AOI– (No.)	Statistical value
Age (years)			
10–19	4	4	
20–29	17	25	
30–39	30	66	
40–49	26	79	
50–59	20	68	
60–69	11	50	
70–79	4	22	
80–89	0	1	F=0.05 (p>0.05)
Average age (years)	43.0±14.3	48.5±14.4	t=3.46 (p<0.001)
Sex			
Men	66	234	
Women	46	193	$\chi^2=2.36$; p>0.05

UC-AOI+: ulcerative colitis with appendiceal orifice inflammation; UC-AOI–: ulcerative colitis without appendiceal orifice inflammation

Table 2. Relationship between lesion extent and the AOI+ rate among UC patients

Lesion extent	With AOI (No.)	Without AOI (No.)	Total (No.)
Rectum	40	119	159
Left side of the colon	28	72	100
Widely spread along the colon	44	124	168
Total	112	315	427

AOI: appendiceal orifice inflammation; UC: ulcerative colitis

Table 3. Relationship between lesion extent and the AOI+ rate among UC patients

Group	AOI+ (No.)	AOI- (No.)	Total (No.)
UC	112	315	427
Specific colitis	22	3133	3155
Total	134	3448	3582

AOI: appendiceal orifice inflammation; UC: ulcerative colitis

Table 4. Accuracy of UC diagnosis based on AOI features alone or in combination with proctitis

Category	Sensitivity	Specificity	PV (+)	PV (–)	Agreement rate
AOI alone	26.2 (22.3–30.6)	99.3 (98.9–99.5)	83.6	90.9	90.6
AOI with proctitis	26.2 (22.3–30.6)	99.9 (99.7–100)	96.6	90.9	91.1

All data are expressed as percentages. Sensitivity and specificity data include 95% confidence intervals.
AOI: appendiceal orifice inflammation; PV (+): positive predictive value; PV (–): negative predictive value; UC: ulcerative colitis

(112 with UC and 22 with specific colitis), while 116 patients had a combination of AOI features and proctitis (112 with UC and 4 with specific colitis). The results related to the accuracy of diagnosing UC by using AOI features alone or in combination with proctitis are presented in Table 4.

In addition, we followed several cases with complete information for the following 3 months to 5 years. Mucus in eight UC-AOI cases completely healed during that time. Three UC cases showed AOI just before their recrudescence.

DISCUSSION

Ulcerative colitis is known to be a sub-type of inflammatory bowel disease and is characterized by continuous mucosal inflammation that first develops in the rectum and then spreads proximally. The etiology of this condition remains unclear. It is clinically divided into the initial and chronic types, and the chronic type of UC is more commonly encountered. Although early diagnosis and treatment of this condition can reduce recurrence, there are no specific diagnostic indicators for this disease. At present, a combination of clinical, endoscopic, histological, and imaging features, as well as the exclusion of other diseases, is used to diagnose this condition (8,9). Moreover, most UC patients have a chronic disease course, which manifests as alternating attack stages and remission stages. Prompt diagnosis and timely treatment can relieve the patient's pain and reduce the burden of medical resources. Therefore, it is essential to identify a specific diagnostic indicator for this condition.

In our clinical practice, we found that patients with UC often also present with AOI on endoscopic examination. For instance, over the last 13 years, the number of UC-AOI cases has increased to 27% of all UC cases in our endoscopic center. Based on this finding, we hypothesized that these two features may be related; this hypothesis has been supported by other researchers. The appendix is currently considered to be part of the immune system, rather than a vestigial remnant (10,11), and its orifice is exposed to the intestinal environment. We were unsure whether there was any difference in the occurrence of inflammation between UC and specific colitis. According to our data, the AOI$^+$ rate in patients with UC was significantly higher than that in patients with specific colitis, consistent with the results of D'Haens et al. (12). In particular, the AOI$^+$ rate of patients with UC was 37.6 times that of patients with specific colitis, and patients with UC comprised 83.6% of all patients with AOI. Hence, we believe that AOI does not occur in cases of UC by chance. However, the types of UC patients who would be more likely to present with AOI are unclear.

In 1958, Lumb and Protheror (13) first described a skip lesion of the appendiceal orifice region in a UC patient. The condition was first named "ulcerative appendicitis" by Cohen et al. (14) in 1974. Since then, physicians have given more attention to AOI. After 1990, several endoscopic studies reported the incidence of AOI in UC patients, which ranged from 7.9% to 27.4% of all UC patients (5,15-17) and from 9.4% to 75% in patients with only distal UC (12,18-20). In the present study, we noted that the AOI$^+$ rate in UC was 26.2%, and this rate did not differ between patients with proctitis, left-sided colitis, and extensive colitis. Hence, the findings indicate that there is a certain probability of the occurrence of AOI in UC patients, which is unaffected by UC extent. Hence, AOI may serve as a reactive activity sign in the involved extent types of UC, in addition to distal UC (12,20). In particular, examination of the clinical characteristics of AOI in UC patients indicated that the AOI$^+$ rate was not related to patient sex or lesion involvement, although the AOI$^+$ rate in patients aged <40 years was higher than the average rate (26.2%). However, the relationship between these two factors is unclear.

In 1998, Scott et al. (2) suggested that the histological features of AOI were more typically representative of UC than of acute appendicitis. Although the pathogenesis of UC remains unclear, clinical evidence suggests that appendectomy may protect against the onset and severity of UC (21,22), suggesting that the appendix may be a priming site for UC (4). Hence, the role of the appendix in the pathogenesis of UC should be clarified, as reported by Matsushita et al. (23). However, the relationship between the inflammation of the appendiceal opening and UC has not been carefully considered; hence, the value of AOI in the diagnosis of UC is also unclear. In a recent review of the relationship between AOI and UC, it was proposed that AOI may be involved in the development of UC and may serve as an important feature in the diagnosis of some UC cases.

In the present study, we aimed to assess the diagnostic value of AOI in UC. One limitation of the diagnosis of UC is the lack of a gold standard. Hence, diagnoses were made in the current

study by re-examining the imaging findings of all the patients with colitis. We used the presence of AOI features alone or in combination with proctitis as two separate diagnostic criteria for the diagnosis of UC. Thereafter, comparing the original diagnoses with the current diagnoses enabled evaluation indexes to be obtained**.**

As mentioned above, we re-examined endoscopic images from all colitis patients, including 427 UC patients and 3155 specific colitis patients. A total of 134 patients (112 with UC and 22 with specific colitis) exhibited AOI, whereas AOI was accompanied by proctitis in 116 patients (112 with UC and 4 with specific colitis). Moreover, we noted that the sensitivity of the AO-positive index for the diagnosis of UC was not very high, but that the specificity and the agreement rate were impressive; moreover, the positive predictive value and negative predictive value were high as well. When a combination of AOI features and proctitis was used for diagnosis, the sensitivity and negative predictive values were similar to those for the previous diagnostic criterion, but the other indexes were higher than those for the previous diagnostic criterion. In particular, diagnostic specificity can reach 99.9% (95% CI, 99.7–100%). These data suggest that AOI is a highly specific indicator for the diagnosis of UC; furthermore, when AOI features are combined with proctitis, the diagnostic values are higher. Hence, patients can be mostly diagnosed with UC based on the occurrence of these two signs. Based on the information gained during the follow-up in this study, AOI can disappear along with the inflammation of UC after treatment, and it may also be a signal for the recrudescence of UC.

The main limitation of the current study is the lack of a generally accepted gold standard for UC diagnosis. For that reason, we enrolled previously diagnosed UC cases in the present study. Moreover, we did not have sufficient data regarding the presence of AOI in other kinds of non-specific colitis. As a retrospective observational study, the current analysis aimed to determine the diagnostic value of AOI in UC rather than to clarify the value of AOI in several diseases. Nevertheless, we believe that another study may help obtain more information regarding the status of AOI in other non-specific colitis diseases. Among the recruited cases, we noted that only 18 patients (0.5% of colitis cases) had AOI; the next step is to determine whether these cases have a high risk of developing UC.

In conclusion, based on the current findings, we believe that the orifice of the appendix should be carefully observed during colonoscopy. Although the sensitivity of AOI in the diagnosis of UC is not high, it has a perfect specificity and agreement rate for diagnosing UC. In particular, when AOI features combined with proctitis are noted, patients can largely be diagnosed with UC. Hence, the identification of this diagnostic indication may help physicians identify UC more easily among difficult miscellaneous diseases.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Tumor Hospital of Shanxi Province and the Affiliated People's Hospital of Shanxi Medical University.

Informed Consent: Written informed consent was obtained from patients and the patients' guardians who participated in this study.

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