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Alimentary Tract

Serum amyloid A level correlated with endoscopic findings in patients with Crohn's disease—Possible biomarker for evaluating mucosal healing

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ABSTRACT

Background: Mucosal healing (MH) has been proposed as an essential therapeutic goal for treatment of Crohn's disease (CD) patients. The utility of serum amyloid A (SAA) for prediction of MH in CD patients is lacking.
Aims: This study was conducted to evaluate the correlation of SAA with CD-related endoscopic disease activity.
Methods: SAA levels in serum samples obtained from CD patients as well as endoscopic findings based on a simple endoscopic score for CD (SES-CD) were assessed in relation to CD activity index (CDAI). The diagnostic ability of MH in correlation with SAA level was evaluated using receiver operating characteristic (ROC) curve analysis.
Results: Fifty-five patients with CD were enrolled. Mean SAA level was significantly higher in clinical and endoscopic active phases as compared to an inactive phase. SAA level was also significantly correlated with SES-CD ($r = 0.64$, $p < 0.01$) and CDAI ($r = 0.42$, $p < 0.01$). The area under the ROC curve for SAA level was 0.77 and the optimal cut-off value for SAA to predict MH was 5.9 μg/dl. SAA level was shown to be associated with MH, with a sensitivity of 68% and specificity of 83%.
Conclusions: SAA may be a possible biomarker for evaluating MH in CD patients.

1. Introduction

Crohn's disease (CD) is a chronic idiopathic immune disorder accompanied by such symptoms as relapsing episodes of abdominal pain, diarrhea, melena, and weight loss. Current treatment regimens for affected patients are based on suppression of excess immune activation and inflammation using corticosteroids, immune-modulating drugs, and several kinds of biologics. Of those, development of anti-tumor necrosis factor (TNF) antibodies has substantially changed the clinical course of CD, by providing symptom relief as well as mucosal healing (MH) in affected patients [1–4].

MH is based on sustained clinical remission, and associated with reduced rates of hospitalization and surgical resection, thus has recently been proposed as an essential treatment goal for CD [5–7]. However, the disease is characterized by transluminal intestinal inflammation and MH is difficult to sufficiently define by endoscopic findings in affected patients. Recently, magnetic resonance enterography (MRE) and intestinal ultrasound (IUS) have been recommended for evaluating the transluminal inflammatory condition of the intestines in CD patients [8–12]. Although the concept related to such findings is very important for considering MH, those methodologies are not always performed for that purpose in clinical practice. On the other hand, endoscopy is still widely used for assessing MH in CD.

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In patients with ulcerative colitis (UC), the entire colon can be assessed by a colonoscopy examination. On the other hand, in CD patients, involved lesions can appear in both the large and small intestines. Although balloon-assisted enteroscopy (BAE) and capsule endoscopy (CE) examinations are useful for assessing mucosal lesions in the small and large intestines [13–16], it is not easy to frequently perform those procedures for all CD patients, due to the complicated methodology as well as cost. In this regard, non-invasive reliable biomarkers of CD are needed for clinical practice.

Among various acute-phase inflammatory proteins, C-reactive protein (CRP) is widely used as a serum biomarker for monitoring disease activity as well as evaluating therapeutic response in a variety of inflammatory diseases. Numerous studies have revealed that serum CRP level is up-regulated in CD patients, and its increase correlates well with clinical and endoscopic activities [17–19]. On the other hand, amyloid A protein, which is synthesized primarily in the liver under the production of inflammation-related cytokines, is also well known as an acute phase protein [17] and serum amyloid A (SAA) levels have been reported to be elevated in the active phase of various immune-related disorders including IBD and rheumatoid arthritis (RA). Although a few previous studies have shown the efficacy of SAA as a marker for evaluating clinical activity in CD patients [20,21], little is known regarding the correlation between SAA level and endoscopic findings.

In the present study, we retrospectively examined SAA levels in CD patients who underwent an endoscopic examination to determine its utility in comparison to that of CRP for assessment of ileocolonoscopy findings.

2. Materials and methods

2.1. Patients

This study retrospectively analyzed findings from patients examined between February 2013 and May 2014 at Shimane University Hospital and Matsue Seikyo General Hospital in Japan. A diagnosis of CD was based on standard clinical, endoscopic, and histological criteria. The records of patients who received ileocolonoscopy and blood examinations were enrolled. Clinical activity on the day of the ileocolonoscopy examination was assessed based on CD activity index (CDAI) [22]. Clinical remission was defined as a CDAI value <150. The protocol of this study was approved by the ethical committees of Shimane University Hospital and Matsue Seikyo General Hospital.

2.2. Blood examinations

Blood samples were taken from the patients on the day of the ileocolonoscopy examination. Levels of serum CRP and SAA were examined using routine laboratory techniques at the two hospitals.

2.3. Ileocolonoscopy examination and simple endoscopic score for CD

For bowel preparation prior to ileocolonoscopy, patients with CD received a magnesium citrate- or polyethylene glycol-based electrolyte solution. All ileocolonoscopy procedures were separately performed by 3 IBD experts (K.K., Y.T., T.Y.), who routinely performed this examination for assessment of MH in the present CD patients. Furthermore, all endoscopic findings analyzed were independently evaluated by each of those experts. When the endoscopic grading did not match among the 3 experts, the final grade was decided based on consensus. Patients who underwent an incomplete ileocolonoscopy examination were excluded from analysis. Endoscopic activity was evaluated a simple endoscopic score for CD (SES-CD), as previously reported [23]. In the present study, endoscopic remission was defined as SES-CD ≤3.

Table 1
Baseline characteristics of patients.

Number	55
Age, years	36.7 ± 8.1[a]
Sex (M/F)	39/16
Disease duration, years	12.8 ± 8.5[a]
Disease location	
Ileum (L1)	11 (20%)
Colonic (L2)	39 (71%)
Ileocolonic (L3)	5 (9%)
Previous surgery	31(56%)
Extraintestinal complication	3 (5%)
Clinical activity	
Remission (CDAI ≤ 150)	41 (75%)
Active (CDAI ≥ 151)	14 (25%)
Perianal disease	7 (13%)
Endoscopic activity	
Remission (SES-CD ≤ 3)	19 (35%)
Active (SES-CD ≥ 4)	36 (65%)
Treatment	
Elementary diet	20 (36%)
5-ASA	47 (85%)
Thiopurine	8 (15%)
Biologics	27 (49%)
Serological markers	
SAA (mean ± SD, μg/ml)	99.3 ± 270.7[a]
CRP (mean ± SD, mg/dl)	1.17 ± 2.66[a]

CDAI, Crohn's disease activity index; SES-CD, simple endoscopic score for Crohn's disease.
[a] Value shown as the mean ± SD.

2.4. Statistical analysis

Statistical analysis was performed using the SPSS statistical package (version 19.0, SPSS, Chicago, USA). A Mann–Whitney *U* test, Chi-squared test, Kruskal–Wallis test, and Spearman's rank correlation coincidence were used as appropriate to examine significant differences. Receiver operating characteristic (ROC) curve analysis was performed to determine the area under the curve (AUC), as well as optimal cut-off values for CRP and SAA to predict endoscopic remission. Values for sensitivity, specificity, predictive value, and accuracy were determined, and 95% confidence interval (CI) values were calculated based on the optimal cut-off. Cumulative relapse rates associated with SAA levels were assessed using the Kaplan–Meier method. All P-values are two-sided and $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Baseline characteristics of patients

A total of 55 CD patients (mean age 36.7 ± 8.1 years; 39 males, 16 females) who underwent a complete ileocolonoscopy examination were enrolled and their clinical characteristics are shown in Table 1. Eleven (20%) had ileal disease, and 39 (71%) ileocolonic disease, while 5 (9%) were affected by colonic disease. None of the enrolled patients were taking steroid drugs. The mean levels of SAA and CRP were 99.3 μg/ml and 1.17 mg/ml, respectively, while mean CDAI and SES-CD values were 110.9 and 7.11, respectively. Twenty patients (36%) were receiving an elemental diet (ED). Concomitant ED therapy as part of scheduled infliximab therapy has been shown to prevent loss of response in CD patients [24]. Furthermore, ED therapy is effective in those with quiescent CD [25]. For these reasons, we sometimes use ED therapy for our CD patients. On the other hand, 47 patients (85%) were prescribed mesalazine, though its efficacy for CD remains controversial [26,27]. In Japan, based on previous studies showing the efficacy of mesalazine [28,29], guide-

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