REVIEW

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Recent trends in diagnostic techniques for inflammatory bowel disease

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Although ileocolonoscopy is the gold standard for diagnosis of inflammatory bowel disease and is useful for assessing the disease severity in the colon and terminal ileum, several alternative diagnostic techniques have been developed recently. For ulcerative colitis (UC), magnification colonoscopy, endocytoscopy, and confocal laser endomicroscopy enable assessment of histological inflammation without the need for biopsy. Capsule endoscopy is useful for detection of small intestinal and colonic lesions in both female and male patients. For UC, capsule endoscopy may be useful for evaluating colonic inflammation in patients with a previous poor colonoscopy experience, while it should be used only in Crohn's disease (CD) patients with unexplained symptoms when other examinations are negative. Magnetic resonance enterography (MRE) is particularly useful for detecting transmural inflammation, stenosis, and extraintestinal lesions, including abscesses and fistulas. MRE is also useful when evaluating small and large intestinal lesions, even in cases with severe strictures in which full evaluation of the small bowel would be virtually impossible using other devices. Therefore, the appropriate diagnostic devices for detecting CD lesions in the small and large intestine should be used.

Keywords: Colitis, ulcerative; Crohn disease; Magnification colonoscopy; Capsule endoscopy; Magnetic resonance enterography

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel diseases (IBDs). The pathophysiology of IBD has been investigated extensively, and involves host genetic factors, immune system dysregulation, and environmental factors. UC involves primarily the colon, and the symptoms include continuous or repeated blood in the stool and diarrhea. In contrast, CD may involve the entire gastrointestinal tract including the small intestine, colon, esophagus, and stomach. Perianal lesions are frequently observed in patients with CD. A discrepancy between clinical symptoms and endoscopic severity is observed in the clinical setting. Thus, endoscopic assessment is critical for the management of IBD. The assessment of the extent and severity of the disease is also important for decision making in the medical treatment of IBD. Ileocolonoscopy is the gold standard for diagnosis of IBD and is useful for assessing disease severity in the colon and terminal ileum, but it does not allow assessment of small-intestinal lesions. Several diagnostic devices were developed during the previous decade. In this article, some recent trends in, and the usefulness of, diagnostic devices for IBD are discussed.

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ULCERATIVE COLITIS

Usefulness and clinical impact of endoscopic procedures in UC

UC is characterized by continuous colonic mucosal inflammation that typically presents in the second and third decades of life. In most cases of UC, symptoms of the disease are either continuous or clinical remission and repeated relapse. The treatment of IBD improved markedly following the development of biological agents (e.g., anti-tumor necrosis factor-α [anti-TNFα] agents) [1]. In a recent study, anti-TNFα agents showed the potential to induce endoscopic mucosal healing [2], and the concept of endoscopic healing (so-called "mucosal healing") began to receive attention after anti-TNFα agents became available because these agents can rapidly induce both clinical and endoscopic remission. Thus, endoscopic assessment is considered critical for the management of patients with UC because endoscopic healing contributes to an improved prognosis and is considered a treatment goal [3]. Mucosal healing after 1 year of treatment is predictive of reduced subsequent disease activity and a reduced need for other active treatments [4]. Mucosal healing has also been associated with a low risk of future colectomy, and the degree of mucosal healing after 8 weeks of infliximab use was correlated with improved clinical outcomes, including a reduced incidence of colectomy [5]. Mucosal healing can also result from other medical treatments, such as 5-aminosalytilates [6,7] and corticosteroids [8]. In patients with newly diagnosed UC who were treated with steroids, the rates of hospitalization, requirements for immunosuppression therapy, and rates of colectomy were significantly higher in partial responders (patients with clinical remission without mucosal healing) than in those with both clinical and endoscopic remission [8].

Conventional white-light endoscopy is undergoing development with the aim of reducing patient burden/discomfort and increasing the diagnostic accuracy and quality. The combination of high-definition TV image quality and a wide angle of view supports detailed observation and facilitates the detection of lesions. High-resolution endoscopy enables the endoscopist to obtain detailed mucosal and vascular information. The vascular pattern can be observed in detail; thus, endoscopic remission can be strictly defined, especially in patients with UC. The diameter of the endoscope may be critical for reducing patient burden. An endoscope with a relatively small diameter is sometimes difficult to insert into the proximal colon and ileum. However, endoscopes with new responsive-insertion technology with passive bending and high force transmission are easier for both patients and physicians, despite their smaller diameter.

Several scoring systems are used to assess the severity of inflammation in UC. The Mayo endoscopic score is used most frequently [9]. The Ulcerative Colitis Endoscopic Index of Severity was developed more recently, and is the first validated endoscopic scoring system for the severity of UC [10,11].

Magnification colonoscopy

A recent study indicated that the presence of basal plasmacytosis predicts clinical relapse in UC patients with complete mucosal healing [12]. Following the recent development of high-magnification colonoscopy, the relationship between the findings of high-magnification chromocolonoscopy and the histological severity of inflammation has been evaluated. The assessment of the severity of UC using high-magnification chromocolonoscopy is correlated more highly with the histological score than with the Matts endoscopic classification [13]. Furthermore, magnification imaging is significantly superior to conventional colonoscopy in terms of predicting disease extent. Another study indicated that the magnifying colonoscopic method reflected the histological inflammation status more accurately than standard colonoscopic findings [14]. The authors of this study emphasized that the findings of magnifying colonoscopic methods can differentiate remission from active disease in patients with mild endoscopic severity (Matts grade 2). Magnification chromocolonoscopy may be useful for the detection of colitis-associated neoplasia in patients with chronic UC. These results suggest magnification chromocolonoscopy to be a potential alternative to histological examination for evaluating disease severity and for the detection of colitis-associated dysplasia/cancer.

Endocytoscopy and endomicroscopy are techniques that have been developed recently. Endocytoscopy facilitates visualization of the superficial mucosal layer

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by enabling > 1,000-fold magnification of the mucosa. Endocytoscopy enables the detection of crypt and mucosal inflammatory cells. This new technique allows discrimination of the histological severity of UC in patients with mucosal healing (e.g., Mayo endoscopic score 0), even if a pathological examination is not performed. Recently, our group reported a correlation between endocytoscopy and conventional histopathology in patients with UC. We have established an endocytoscopy score (ECSS) to denote the histopathological activity index of UC [15]. A robust correlation exists between ECSSs and conventional Matts endoscopic grades and Matts histopathological grades [15]. Neumann et al. [16] also showed that endocytoscopy enables accurate *in vivo* differentiation of mucosal inflammatory cells in IBD. Endocytoscopy enables the detection and discrimination of single mucosal inflammatory cells—including neutrophilic, basophilic, and eosinophilic granulocytes and lymphocytes. It is also useful for assessing inflammatory disease activity.

Confocal laser endomicroscopy (CLE) is useful for classifying the histopathological activity of UC [17,18]. CLE is a newly developed endoscopy technique with 500- to 1,000-fold magnification. The inflammation activity assessment includes crypt architecture, cellular infiltration, and vessel architecture [17]. Li et al. [18] classified CLE findings based on crypt architecture, microvascular alteration, and fluorescein leakage into crypts. The assessment of crypt architecture and fluorescein leakage with CLE showed significant correlations with the histological results [18].

Capsule endoscopy

Capsule endoscopy is a safe and non-invasive diagnostic tool that has been used in the diagnosis of various gastrointestinal disorders [19]. Colon capsule endoscopy (CCE) was developed in 2006 and has been used mainly for colorectal cancer screening [20-23]. Recently, the feasibility of CCE for evaluating UC was evaluated by several groups [24-26]. Patients with active UC may require repeated colonic examinations. Thus, CCE may be advantageous because it reduces the patient burden and increases acceptance of the procedure. However, the applicability of CCE for the evaluation of UC remains unconfirmed [24-26].

Recently, we demonstrated that the severity of mucosal inflammation in UC scored by CCE is strongly correlated with that of conventional colonoscopy when newly developed second-generation CCE (CCE-2) is used [27,28]. We reported that the rate of total colon observation was 85%, and 15 patients (75%) excreted the CCE-2 within 8 hours. The proportion of excellent and good cleansing was approximately 60%. Although the rate of complete observation of the entire colon has not been determined, CCE may be useful for evaluating colonic inflammation in patients with a previous poor colonoscopy experience.

CROHN'S DISEASE

Usefulness and clinical impact of endoscopic procedures in CD

Similar to UC, achieving clinical remission can improve the quality of life in CD patients. Endoscopic improvement and remission have been associated with better CD outcomes [4]; therefore, achieving endoscopic remission has become a treatment goal in CD [3]. Endoscopic scores, including the CD index of severity and the simple endoscopic score for CD, are used frequently as endoscopic disease activity indices for CD [29,30]. Such scores may be useful for establishing a definition of endoscopic remission. However, unlike UC, these scores are not commonly used because they are complex and difficult to determine in clinical practice. Therefore, the development of simpler endoscopic scores for CD is warranted. Furthermore, it should be noted that the endoscopic findings do not affect the actual severity of inflammation in patients with CD because inflammation is transmural in the majority of cases. Although cross-sectional imaging does not enable detection of small lesions, as described above, it may be useful for assessing transmural inflammation.

Because inflammation in CD involves the entire gastrointestinal tract and the small intestine in particular, assessment of small intestinal lesions in CD is critical [31]. However, few diagnostic tools for the small intestine existed 20 years ago. Barium small-bowel follow-through (SBFT) is a useful technique for distinguishing CD from other IBDs and for the confirmation of fistulas or the extent of inflammation in CD. More recently, novel technologies for IBD diagnosis

have been developed, such as capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE). These technologies are now established as useful modalities for the diagnosis and assessment of disease extent and severity. Cross-sectional imaging techniques, such as computed tomography enterography (CTE) and magnetic resonance enterography (MRE), have also been reported to be useful modalities for the evaluation of luminal inflammation in, and extraintestinal complications of, CD.

Capsule endoscopy

CE has enabled the detection of small-intestinal lesions in patients with aphthoid lesions, erosions and small ulcers that were not detected during radiation examinations. CE has been shown to be an effective, noninvasive tool for the evaluation of the small intestine, particularly in cases in which ileocolonoscopy and SBFT could not diagnose CD or other diseases, but where CD remains a possibility. CE is a sensitive test for the diagnosis of mucosal inflammation [32].

The role of CE should be discussed in the setting of established CD [31]. Although CE facilitates detection of small mucosal lesions, such as aphthous erosions and small ulcerations, it cannot be used to identify transmural lesions or extraintestinal lesions with fistulas and abscesses. Extraintestinal lesions are observed in the majority of cases of CD. Thus, CE should be used only in patients with unexplained symptoms when other examinations are negative [33].

The risk of capsule retention should be considered when CE is performed. The risk of retention in patients with CD is significantly higher than that in healthy individuals [34]. A patency capsule was recently developed for the assessment of strictures in the small intestine, and it is useful for the exclusion of significant stenosis prior to CE [35]. However, the possibility of retention should be emphasized, even if the patency capsule is used. Indications for CE and the diagnostic benefit/risk should be considered before CE is performed.

Several scoring systems for the severity of inflammation detected by CE have been developed. The Lewis score (LS) and the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) have been used to assess small-bowel inflammation [36,37]. The LS is based on three endoscopic parameters: villous edema, ulcers, and stenosis/stricture [36]. The CECDAI consists of three parameters/components: an inflammation score, a disease-extent score, and a stricture score [37]. The LS was validated by assessing the interobserver correlation and the level of agreement in a clinical setting. Interobserver agreement for endoscopic severity between the investigators and the central reader was almost perfect [38].

Whether these scores are related to clinical symptoms and other biomarkers should be determined. It is also unclear whether the findings of CE are useful in managing medical treatment. A prospective study of the correlation between CE findings and clinical and laboratory parameters of inflammation has been performed [39]. No correlation was observed at aseline between the clinical and laboratory parameters (Crohn's Disease Activity Index [CDAI], C-reactive protein) and LSs. Changes in the CDAI over periods of 4 and 12 weeks after initiation of medical treatments did not correlate with the LS [39]. Another recent study reported that a change in management was recommended in 52.3% of patients based on the video capsule endoscopy findings [40].

Balloon-assisted enteroscopy

Although CE is considered to be safe, painless and well-tolerated in patients with CD, BAE is more invasive than other modalities [31]. However, BAE has the advantage of allowing direct endoscopic examination and biopsy of lesions, which may facilitate the diagnosis of active small-bowel CD. Double-balloon enteroscopy and single-balloon enteroscopy are useful modalities for the detection of small-intestinal lesions [41-43].

Few studies have evaluated the diagnostic usefulness of BAE in patients with CD. One recent study indicated that BAE could detect aphthae, erosions, and small ulcers in small intestinal lesions [44] more readily than SBFT. However, in most cases, BAE did not detect the strictures that were identified by SBFT. These results suggest that BAE may be more useful for the detection of aphthous lesions and small ulcers in the small intestine, whereas radiological examination may be more helpful for the detection of stenosis. However, the diagnostic accuracy of BAE for the detection of strictures is satisfactory compared with that of MRE [45]. This study indicated that magnetic resonance imaging is relative-

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ly less sensitive for the detection of strictures that can be identified by single-balloon assisted enteroscopy. The detection of active lesions is important for determining the appropriate pharmacological treatment for CD, and BAE is useful for detecting intestinal damage to determine whether surgical or endoscopic treatment is appropriate.

Strictures are observed in approximately one-third of patients with CD, and can cause severe abdominal symptoms. More than half of patients with CD require surgery within the first 10 years after onset of the disease, and strictures and obstructions are common indications for surgery. To improve the clinical outcome, preventing the progression of strictures as early as possible is critical. Strictures may be categorized as fibrotic or inflammatory. For inflammatory strictures, medical treatments may improve the lesions, whereas these treatments are not effective in most cases of fibrotic strictures without inflammation. Endoscopic balloon dilatation (EBD) may relieve abdominal symptoms and obviate the need for surgery in some cases of CD. Fibrosis, shorter stricture length and no/mild inflammation around stenosis are indications for EBD. Prior to performance of EBD, the number of strictures, their length and diameter, and the presence of intra-intestinal fistulas should be confirmed by small bowel follow-through or other diagnostic techniques.

Magnetic resonance enterography

MRE has been reported to be a useful modality for the evaluation of luminal inflammation and extraintestinal complications in CD [46]. Although both CTE and MRE facilitate detection of mural and transmural inflammation [47-50], MRE can be performed without radiation exposure, making it the preferred imaging technique for the evaluation of CD in children and adolescents.

MRE can detect CD lesions and the wall thickness, wall hypersignal, extravascularity, swelling of lymph nodes, ulcerations, fistulas, edema, strictures, and extraintestinal complications. MRE has been shown to have excellent sensitivity and specificity for CD lesions. The diagnostic accuracy of MRE has been assessed mostly by comparing the ileocolonoscopy findings with those by MRE. A recent systematic review showed that the sensitivity and specificity of MRE for the diagnosis of suspected CD were satisfactory [51].

The advantages of CE and BAE include direct observation of mucosal information, whereas MRE is particularly useful for detecting transmural inflammation, stenosis, and extraintestinal lesions—including abscesses and fistulas. MRE is useful when evaluating small- and large-intestinal lesions even in cases with severe strictures, when full evaluation of the small bowel would be virtually impossible using CE or even BAE. This is the advantage of MRE over ileocolonoscopy for the assessment of intestinal lesions in patients with CD [46]. Thus, these technologies appear to complement each other.

Because MRE can be repeatedly performed to confirm the effects of medical treatment, a question arises regarding its ability to predict endoscopic remission or ulcer healing. A recent study demonstrated that a magnetic resonance index of activity (MaRIA) score cutoff of 7 showed high sensitivity (85%), specificity (78%), and accuracy (83%) for the diagnosis of mucosal healing [52]. Thus, MRE could predict endoscopic remission in patients with CD. MRE is also useful for evaluating the efficacy of medical treatments. A recent study indicated that the responsiveness for medical treatments could be objectively assessed using an MRE scoring system [53,54]

CONCLUSIONS

Endoscopic assessment for both UC and CD is critical for the management of IBD patients. For UC, histological remission is a goal for medical treatments in the near future. Magnification colonoscopy, endocytoscopy, and CLE can assess histological inflammation without the need for biopsy specimens. However, it is impossible to assess the mucosa of the entire colon using magnification colonoscopy. Other diagnostic modalities, such as calprotectin, may be useful for assessing the severity of the disease and objective efficacy of medical treatments in a non-invasive manner. In CD patients, small-intestinal lesions and transmural inflammation should be evaluated. MRE enables simultaneous assessment of mural and transmural lesions of the small intestine; however, it is expensive and requires increased time for performance of all sequences

[46]. At present, the appropriate diagnostic devices for detecting CD lesions in the small and large intestine should be selected.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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