Advances in the diagnosis and treatment of small bowel lesions with Crohn's disease using double-balloon endoscopy

Keijiro Sunada, Hironori Yamamoto, Tomonori Yano and Kentaro Sugano

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Abstract: With the recent development of double-balloon endoscopy (DBE) and capsule endoscopy (CE), it has become possible to observe the entire small bowel endoscopically. DBE enables us to make detailed observations and at the same time takes biopsy samples. Single-balloon endoscopy (SBE), which has a balloon only at the tip of the overtube, has also been introduced. Since DBE and SBE are similar in the concept of insertion method, a general term 'balloon-assisted endoscopy' (BAE) is used when referring to these methods. Characteristic small bowel lesions observed with BAE in Crohn's disease are aphthoid ulcers, round ulcers, irregular ulcers and longitudinal ulcers. These ulcers tend to be located on the mesenteric side of the small bowel. Since BAE can determine the location (mesenteric or antimesenteric side) of the ulceration, it is useful in distinguishing Crohn's disease from other diseases that have ulcers in the small bowel. Strictures are a major clinical problem in the course of Crohn's disease. Traditionally, surgery was the main choice for small bowel strictures. In some cases, strictures located in distal ileum or proximal jejunum have been dilated using standard enteroscopes. DBE now enables balloon dilatation to be performed endoscopically even in the deep small bowel.

Keywords: Crohn's disease, double-balloon endoscopy, endoscopic-balloon dilation

Introduction

Crohn's disease was first reported by Crohn *et al.* in 1932 as 'regional ileitis' with chronic granulomatous inflammation of the terminal ileum [Chron *et al.* 2000]. Today, Crohn's disease is known to be a chronic inflammatory disease of unknown origin that can occur not only in the terminal ileum but anywhere in the gastrointestinal tract [Feagans *et al.* 2008].

Small bowel lesions occur frequently in Crohn's disease. Traditionally, diagnosis and assessment of the small bowel lesions in Crohn's disease has depended on X-ray tests, such as small bowel follow-through (SBFT) and computed tomography (CT). In recent years, however, new endoscopic modalities such as capsule endoscopy (CE) [Iddan *et al.* 2000] and balloon-assisted endoscopy (BAE) including both double-balloon endoscopy (DBE) [Monkemuller *et al.* 2007; Zhong *et al.* 2007; Heine *et al.* 2006; May and Ell, 2006; Yamamoto *et al.*, 2001] and single-balloon endoscopy (SBE) have been developed. These instruments have enabled us to obtain

clear endoscopic images of the small bowel which are useful in making more accurate diagnosis and evaluation of the small bowel lesions in Crohn's disease [Oshitani *et al.* 2006]. Endoscopic-balloon dilation (EBD) for intestinal strictures has also become possible in a broader area of the small intestine with DBE [Fukumoto *et al.* 2007; Pohl *et al.* 2007]. In this report, we will discuss the diagnosis and treatment of small bowel lesions in Crohn's disease, focusing on DBE, which was developed mainly in our hospital.

Endoscopic findings with Crohn's disease

Aphthoid ulcer

Aphthoid ulcers are seen as small, shallow depressed lesions with loss of villi. Pathologically, they are erosions or small ulcers formed in lymphoid follicles and the epithelium. They are considered the initial lesions in Crohn's disease [Hizawa *et al.* 1994]. It has been pointed out that the detection rate for noncaseating epithelioid cell granuloma is higher than that for

Correspondence to:
Hironori Yamamoto, MD
Department of Internal
Medicine, Division of
Gastroenterology, Jichi
Medical University,
Shimotsuke, Tochigi,
Japan
yamamoto@jichi.ac.jp

Keijiro Sunada
Tomonori Yano
Kentaro Sugano
Department of Internal
Medicine, Division of
Gastroenterology, Jichi
Medical University,
Shimotsuke, Tochigi,
Japan

other lesions, and biopsy targeted at these aphthoid ulcers is recommended for pathological diagnosis.

Endoscopic images show small erosions (Figure 1) or ulcers (Figure 2) surrounded by peripheral reddening. Observed from close range, this reddening is recognized to have somewhat enlarged villi (Figure 3). We speculate that peripheral reddening and enlarged villi represent vasodilation and swelling due to inflammation. The small, depressed lesions existing on Kerkring's folds have a notched configuration when observed from the side (Figure 4). Chromoendoscopy with indigo carmine spray, which has been used to evaluate celiac disease [Hadithi *et al.* 2007] and lymphoma and to detect polyps in patients with familial adenomatous polyposis (FAP) [Picasso *et al.* 2007], is also useful in the detection and detailed observation of these lesions.

Longitudinal ulcer

Crohn's disease ulcers are characteristically discrete with little inflammation in the remaining mucosa, and they tend to align longitudinally. The shape of the ulcers varies from round

Figure 3. Erosion surrounded by enlarged villi.

Figure 1. Small erosion.

Figure 4. Notched configuration.

Figure 2. Small ulcer.

Figure 5. Round shaped ulcer.

(Figure 5) to irregular (Figure 6). We speculate that these longitudinally aligned ulcers later fuse to form the typical longitudinal ulcers of Crohn's disease (Figure 7).

Cobblestone appearance

A cobblestone appearance occurs as a result of inflammatory changes and edema in the mucosa left by the irregularly oriented ulcers. This typical cobblestone appearance is seen frequently in the colon, but is less common in the small bowel except near the terminal ileum (Figure 8).

Stricture, fistula and pseudo-diverticulum

Repeated formation and healing of ulcers causes cicatricial contraction in the intestinal mucosa. With the addition of ischemic modifications, strictures form in the intestinal canal (Figure 9). A complex shape arises when multiple strictures form in a small area and are accompanied by curvature. In some cases, part of the intestine bulges out like a diverticulum (pseudo-diverticulum), or

a clover-like shape. If the stricture is severe and impairs passage, the intestine on the oral side distends. Fistulas develop not only into nearby intestine but also to the skin, bladder and vagina in some cases. Traditionally, X-ray tests were performed to obtain findings of intestinal strictures and other morphological changes objectively. With DBE, the lead balloon is inflated and forms a wedge in the intestinal canal, and contrast imaging (selective contrast imaging) can be conducted to obtain clear images (Figure 10).

Neoplastic lesions

Crohn's disease is associated with an increased incidence of small bowel adenocarcinoma [Solem *et al.* 2004]. Adenocarcinoma has been reported to develop within small bowel strictures [Barwood and Platell, 1999]. There are currently no reliable methods for distinguishing a benign *versus* a malignant small bowel stricture in Crohn's disease with radiography. The diagnosis

Figure 6. Irregular shaped ulcer.

Figure 8. Cobblestone appearance.

Figure 7. Longitudinal ulcer.

Figure 9. Severe stricture.

Figure 10. Selective contrast imaging.

could not be made until pathology review of surgically resected specimens. Using DBE, however, the pathological diagnosis can be made by biopsy sampling. It is noteworthy that the diagnosis is difficult only with endoscopic observation, so biopsy sampling should be performed before EBD in suspicious cases.

Clinical importance of the location of lesions for differential diagnosis

A characteristic of Crohn's disease ulcers is that they tend to occur on the mesenteric side of the intestine. In DBE, the endoscope is inserted deep into the small bowel forming concentric circles as it is advanced. The mesentery is extended fanlike in the circles. In this situation, if the tip of the endoscope moves centripetally, when we move the endoscope tip toward the ulcer, the ulcer can be determined on the mesenteric side [Sunada *et al.* 2007]. This localization within the intestinal lumen is useful in distinguishing Crohn's disease from other diseases that cause inflammation in the small bowel. Ulcers associated with ischemia, Behçet's disease and enteric tuberculosis are thought to occur more frequently on the antimesenteric side of the intestine [Sunada *et al.* 2007]. In our experience, NSAID-induced small intestinal ulcers are more frequently seen in the ileum than the jejunum, but no predominant tendency has been observed in terms of their occurring on the mesenteric or antimesenteric side [Hayashi *et al.* 2005]. It is important to be aware that the location is not the only measure for diagnosis. Differential diagnosis of small bowel ulcers should be based not only on endoscopic findings but also on clinical and histological findings.

Management of Crohn's disease based on findings of imaging studies

Treatment aimed at mucosal healing is considered important and is a major factor in determining later progress of Crohn's disease [Froslic *et al.* 2007]. However, the state of the intestinal mucosa does not always reflect on clinical symptoms and blood biochemical data especially for small intestinal lesions. Even among patients considered in a period of clinical remission, endoscopic examinations can reveal longitudinal ulcers and other active ulcers in a large number of cases of small intestinal Crohn's disease. Unhealed ulcers even without symptoms could progress in disease activity resulting in causing complications such as strictures and fistulas. Therefore, symptomatic remission and no alarming abnormalities on laboratory data are not sufficient to predict a good prognosis of this disease. The state of the intestinal mucosa can be most accurately evaluated through endoscopic images.

Double-balloon endoscopy

To evaluate the condition of the mucosa in Crohn's disease, it is not always necessary to observe the entire small bowel. An observation at about 100 cm from the terminal ileum is usually sufficient. The addition of selective contrast imaging from the deepest insertion location is also useful. While the region of the lower ileum is the most common site for Crohn's disease lesions, it is difficult to evaluate with traditional SBFT because of the overlap of the intestinal canal. To monitor the status of Crohn's disease, we recommend periodical observations of the colon and distal ileum using DBE, with the addition of selective contrast studies as needed. Appropriate treatment modifications can then be made based on those findings, aiming at mucosal healing.

However, it is noteworthy that further insertion of endoscope beyond deep active ulcers carries a considerable risk of perforation. Further insertion should be avoided until the ulcers are healed. Endoscopic insertion in patients with surgical reconstructions such as ileal pouch anal anastomosis, colostomy and ileostomy has also a higher risk of perforation. Therefore, extreme care with gentle maneuver is needed in such patients.

Capsule endoscopy

CE can provide optimal visualization of mucosal abnormalities of small bowel Crohn's disease. The main disadvantage of CE is its inability to localize the lesion definitively and its

contraindication in the presence of small bowel stricture. In a recent study investigating patients with Crohn's disease, capsule retention occurred in 13% of patients undergoing CE for known Crohn's disease due to unsuspected strictures compared to only 2% of patients with suspected Crohn's disease [Cheifetz *et al.* 2006]. Recently, a patency capsule has been developed, which can be used in patients with bowel strictures to predict CE retention. However, Gay *et al.* [2005] reported a case of bowel obstruction due to the blockage of the patency capsule in the long-length ileal strictures. If CE fails to pass an intestinal stricture and is retained, surgical retrieval will be required. However, in some cases it could be retrieved safely with DBE [Tanaka *et al.* 2006].

Radiological diagnostic tests for Crohn's stricture

A major problem in the clinical course of Crohn's disease is the occurrence of intestinal strictures. Intestinal strictures are suspected when there are obstructive symptoms such as recurrent abdominal pain, severe borborygmi and vomiting. Traditionally, SBFT and CT are used as gold standard radiological diagnostic tests for strictures. Recently, CT enteroclysis (CTE) and magnetic resonance enteroclysis (MRE) have been developed.

Small bowel follow-through

SBFT had been the principal tool for the diagnosis and evaluation of small intestinal lesions of Crohn's disease. However, the principle disadvantage of SBFT includes low sensitivity in detecting mucosal abnormalities, the limited indirect information on the state of the bowel wall and extramural extension of Crohn's disease. Furthermore, radiation dose administered to patients is an important factor to consider, because many patients have onset of the disease at a young age.

Stricture result in fibrosis and/or inflammatory thickening. The differentiation between fibrotic and inflammatory strictures is crucial for selecting patients for medical *versus* surgical or endoscopic treatment. Although SBFT can depict strictures of the small bowel lumen clearly, the differentiation of the stricture type is difficult with SBFT. SBFT has also problems with overlapping bowel loops especially in the lower abdominal cavity. It is sometimes difficult to obtain clear images, and the quality of images depends on the examiner's technique.

Figure 11. Coronal image of abdominal CT. Stricture is observed in the ileum between arrows.

Computed tomography

Abdominal CT is an effective tool for noninvasive diagnosis of strictures [Amitai *et al.* 2008]. In addition to regular axial sections, images of coronal and sagittal sections can be composed in a short time using recent CT equipment (Figure 11). With close reading of these composite coronal and sagittal images, abnormalities of the small bowel can be assessed. If there are clear changes in caliber, it is easy to identify the location of strictures. Moreover, CT not only indicates strictures but can also provide information on the range of intestinal inflammation, whether there is extramural inflammation or whether there are abscesses or ascites. Important information can be obtained that can help select between surgical and conservative treatment, or can show the indications for EBD and its timing.

Computed tomography enteroclysis

CTE has emerged as the preferred imaging modality for assessing the extent and severity of small bowel disease in patients with Crohn's disease. CTE utilizes both intravenous and neutral oral contrast to enhance visualization of the small

bowel lumen, wall and perienteric mesentery. CTE has also the ability to detect strictures and penetrating complications of Crohn's disease. In addition, its advantages are its accuracy and non-invasive nature. However, the disadvantages of CTE are increased exposure of ionizing radiation, lack of functional information and poor soft tissue contrast.

Magnetic resonance enteroclysis

MRE has also recently emerged and has proven to be very effective in the assessment of small bowel abnormalities. MRE is particularly capable of providing tissue-specific information on Crohn's disease at its various stages from acute inflammatory, regenerative, fistulizing and perforating disease to the fibrostenotic stage due to its excellent soft-tissue contrast [Ryan and Heaslip, 2008; Gourtsoyiannis *et al.* 2006; Maccioni *et al.* 2006]. On the other hand, MRE is of limited value in the detection of mild Crohn's disease with subtle lesions limited to the mucosa, due to low spiral resolution [Tillack *et al.* 2008; Prassopoulos *et al.* 2001].

Endoscopic-balloon dilation therapy

Crohn's disease will likely recur even if all lesions are surgically resected unless appropriate treatment is given. Repeat surgery is needed in many cases even after surgical removal of strictures or strictureplasty, but repeated surgeries can cause advanced adhesions and ultimately lead to short-bowel syndrome. EBD, in contrast, is minimally invasive and can be performed repeatedly, making it an effective treatment method from the viewpoints of patient quality of life and preservation of the intestine. EBD was conventionally performed mainly in the large intestine [Hassan *et al.* 2007; Nomura *et al.* 2006]. In the era of push enteroscopy, distal ileal and proximal jejunal strictures have also been dilated. With the introduction of DBE dilation this has also become possible in the wide range of small intestine.

Indications for endoscopic-balloon dilation

In our hospital, EBD is indicated when there are symptoms of intestinal obstruction, such as vomiting and abdominal pain, or when there is an evident caliber change on radiological images such as CT, even if symptoms are mild.

Exclusion criteria are shown in Table 1. EBD is technically difficult and its dilation effect is weakened in cases where the stricture is long or

Table 1. Indication and exclusion criteria for endoscopic balloon-dilation therapy.

Indication

- 1 Patients with obstructive symptoms
- 2 Evidence of small intestinal strictures associated with prestenotic dilatation by radiological imaging (CT, MRT and SBFT etc.)

Exclusion criteria

- 1 Extremely long strictures (>6 cm)
- 2 Sharp angulation
- 3 Active ulcers
- 4 Severe inflammation
- 5 Low nourishment condition

CT, computed tomography; MRT, magnetic resonance tomography; SBFT, small bowel follow-through.

where there is much bending. Hassan *et al.* [2007] reviewed EBD for strictures of the colon and reported that the dilation effect is significantly poorer when the stricture exceeds 4 cm compared with cases when the stricture is 4 cm or less. Moreover, in cases of active ulcers or severe inflammation in the area of the stricture, dilation therapy should be performed once the lesion has healed in order to avoid the risk of perforation. If the patient's general condition or nutritional status is poor there is high risk from surgery conducted to repair perforations. Therefore, attempts should be made to improve the nutritional status, such as total parenteral nutrition, before performing EBD. The risk of perforation is higher in patients with fistulas and in many cases surgical treatment is ultimately necessary even if it can be postponed temporarily with EBD. Therefore, the indications for EBD must be carefully considered.

Two methods for endoscopic-balloon dilation

Balloon-dilation methods can be divided into two general categories. One is the through-the-scope (TTS) method, in which a balloon dilator is inserted through the forceps channel and dilation is done under direct observation. The other is the radiologic method, in which a guidewire is inserted endoscopically. After the endoscope is withdrawn, a balloon dilator's position is aligned and dilation is done under fluoroscopy. Usually the TTS method is selected with a therapeutic scope (EN-450T5) unlike the radiologic method which is adopted when a diagnostic scope (EN-450P5) is used, since the balloon dilator does not match the diameter of the forceps channel.

Actual methods of endoscopic-balloon dilation

Insertion of the endoscope and observation

As adhesions are likely to occur in patients with Crohn's disease, the insertion of the endoscope should be done carefully. When the stricture is reached, endoscopic observations are first done to assess the extent of the stricture and to examine whether or not there is inflammation or ulcers. If there are deep ulcers, dilation therapy is suspended and treatment with the aim of healing the ulcers is given [Pohl *et al.* 2007]. Subsequently, the balloon at the endoscope tip is inflated and selective contrast study is done with gastrografin (Figure 12). In this way the stricture length, with or without curvature, and presence or absence of fistula is confirmed.

Insertion of the guidewire and the dilator

The guide wire attached to the TTS balloon is quite stiff, so there is a risk of intestinal damage when used in the convoluted small intestine. We therefore use a flexible 0.35-inch Jagwire (Boston Scientific Corp., USA). The Jagwire is inserted through the endoscopic forceps channel and passed to the stricture. After insertion for a sufficient distance beyond the stricture under fluoroscopic guidance, the TTS balloon is inserted (Figure 13). TTS balloons are designed to be able to pass through a forceps channel of 2.8 mm. However, the insertion is difficult when there is much bending in the endoscope in the deep intestine. In such cases, the insertion becomes easier if 2–3 ml of olive oil are instilled in the forceps channel.

Step up dilation

After the TTS balloon is inserted, it is positioned under endoscopic guidance so that the stricture is at the center of the balloon. The balloon is then slowly inflated while its position is confirmed under fluoroscopy (Figure 14). The TTS balloon is set so that the dilation diameter is achieved in three stages of inflation. In our hospital, we keep the pressure for 30 s followed by a 30 s interval. Pressurization is done slowly with attention to patient discomfort. We aim for an initial dilation diameter of 12 mm in cases of Crohn's disease (10 mm with severe stricture) in general, and perform dilation up to 13.5 mm to 15 mm in the second and subsequent dilations. The TTS balloon is in close contact with the tip of the endoscope, and if water is filled between the balloon and the endoscope tip, the mucosa in the area of

Figure 12. Change in caliber and be stricture can be seen in selective contrast study.

Figure 13. Through-the-scope (TTS) balloon is inserted through stricture.

Figure 14. X-ray image during dilation therapy.

Figure 15. Endoscopic view during dilation therapy.

stricture can be observed during dilation therapy (Figure 15).

After dilation

After dilation, the dilated area should be closely observed for bleeding and tears, and the presence or absence of complications should be confirmed. If the endoscope passes through the stricture, the dilation is considered adequate. Even if it does not pass through, however, clinical improvement in stricture symptoms is expected in many cases, and it is not necessary to attempt forceful insertion. If the endoscope can pass through, the next dilation can be attempted in cases of multiple strictures. In some cases, it should be remembered that, the overtube, which has a larger diameter than the endoscope, cannot pass through although the endoscope can.

Complications

Perforation

Perforation is a major complication in EBD. The intestinal strictures that occur in Crohn's disease are suspected to be caused by fibrosis, during the healing process of ulcers, or inflammation that extends to all layers. In many cases, therefore, a change is thought to affect the muscle layer in the area of stricture. EBD for intestinal stricture in Crohn's disease has a higher risk for perforation than EBD for intestinal strictures caused by inflammation of shallower layers [e.g. diaphragm-like strictures related to nonsteroidal anti-inflammatory drugs (NSAIDs) and chronic hemorrhagic ulcers of the small intestine (CHUSI)].

Surgery is always required to treat cases of perforation. This is advisable when: (1) there is high

pressure on the oral side of stricture in the intestinal canal, and leakage of intestinal fluids is predicted; (2) the tissue in the area of perforation is fragile or has become thin and natural healing is predicted to be difficult; (3) In some cases the perforation closes naturally but another balloon dilation in the same location carries a high risk.

Bleeding

In rare cases, bleeding has been seen from the stricture after dilation therapy. Usually, the bleeding stops naturally at the level of 'oozing'. However, if this continues, it can be stopped by mild pressure with the dilation balloon. In cases of arterial bleeding, clip hemostasis can be also considered.

Conclusion

We have described the diagnosis of small bowel lesions in Crohn's disease and balloon dilation of strictures using DBE. Ulcers develop in the small intestine in a variety of diseases and it is difficult, sometimes, to make a definitive diagnosis. A detailed examination of morphological characteristics is important although in some cases a diagnosis cannot be reached with morphological features alone. DBE enables determination of the location of the lesion (mesenteric or antimesenteric side) and of biopsy sampling, advantages that are unavailable with CE. These advantages can be useful to distinguish Crohn's disease from other diseases.

In addition, using DBE, EBD can now be performed deeply in the small intestine and in the colon. Crohn's disease often occurs in young people. Repeated operations can lead to intestinal adhesion and short bowel syndrome. In contrast, EBD is noninvasive and very effective from the viewpoint of intestinal preservation. In the future, it will be necessary to elucidate the long-term outcomes associated with balloon dilation by considering periods of free symptoms and surgery-free interval after balloon dilation.

Conflict of interest statement

The author, Hironori Yamamoto, has applied for a patent in Japan for the double balloon endoscopy described in this manuscript.

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