Techniques in Gastrointestinal Endoscopy 18 (2016) 136–144

Contents lists available at ScienceDirect

Techniques in Gastrointestinal Endoscopy

journal homepage: www.techgiendoscopy.com/locate/tgie

Crohn's disease stricture evaluation and management

Sara Keihanian, MD*, Alan C. Moss, MD

Division of Gastroenterology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

ARTICLE INFO

Article history:
Received 25 May 2016
Accepted 19 August 2016

Keywords:
Crohn's disease
Stricture
Endoscopic balloon dilation
Therapeutic endoscopy
Stenosis

ABSTRACT

Crohn's disease (CD) is chronic inflammatory disease of the intestinal tract. Majority of Crohn's disease patients would go on to develop a complicated disease course over time including stricturing and penetrating disease. Stricturing CD requires a multidisciplinary approach between the surgical and medical team for comprehensive management. Despite significant advances in the therapeutic armamentarium for CD, there is no approved medical therapy and none on the horizon that can reverse fibrostenotic disease. Therefore, stricturing CD remains a therapeutic challenge and is associated with considerable morbidity and cost. Recent imaging technique such as MR enterography helps to better delineate stricturing disease. The therapeutic options for fibrostenotic CD comprise of endoscopic balloon dilation and surgical measures. Endoscopic balloon dilation delays the need for surgery, reduces the risk of short bowel syndrome, and has lower complication rate than surgery. The goal of this review is to present a comprehensive overview of the current knowledge, identification, and management of strictures in patient with CD, with a focus on the role of endoscopic therapy.

1. Introduction

Crohn's disease (CD) is a chronic, relapsing-remitting inflammatory disease of the intestinal tract that is classified into the following 3 distinct phenotypes: inflammatory (B1), stricturing (B2), or penetrating phenotype (B3) [1]. At the time of the diagnosis, strictures may already be present within the gastrointestinal tract in approximately 5% of patients [2]. In addition, up to one-third of those who are diagnosed with inflammatory disease go on to develop penetrating or stricturing complications by 5 years, often leading to repeated surgeries and disability [3].

Stricturing CD requires a multidisciplinary approach between the surgical and medical team for comprehensive management. There is, as of now, no approved medical therapy that can reverse fibrotic strictures, and none on the horizon for CD. In fact, patients with predominantly stricturing CD are routinely excluded from randomized controlled trials for biologics [4-8] As a consequence, strictures require mechanical interventions to correct them, either endoscopic balloon dilatation or surgical procedures, such as stricturoplasty. The goal of this review is to present a comprehensive overview of the current knowledge, identification, and management of strictures in patient with CD, with a focus on the role of endoscopic therapy.

2. Epidemiology

Strictures in CD can appear at any site of chronic inflammation in the intestinal tract. The most common locations of primary strictures are the ileum and the ileocolonic region, presumably owing to the smaller diameter of the ileum relative to colon [9,10] The actuarial prevalence of stricturing CD after 20 years of diagnosis was 20% in a retrospective study of 2002 patients by Cosnes et al [11]. Another study reported the cumulative risk for developing stricture in CD to be 22% at 1 year, 34% at 5 years, and 51% at 20 years after diagnosis [12]. The development of a stricture is one of the main indications for surgery in CD, and population-based cohort studies describe a cumulative risk of requiring surgery for CD complications between 40% and 71% within 10 years after diagnosis [13-19].

In a review by Rieder et al, the predictors of fibrostenosing CD included age less than 40, perianal disease at diagnosis, need for steroids during the first flare, small bowel disease location, smoking, deep mucosal ulceration on endoscopy, and genetic factors (NOD2/CARD15,5T5T in the MMP3 gene, rs 1363670) [2]. *NOD2*/CARD15 remains the most established genetic factor associated with complicated CD, though it has yet to be tested as a risk predictor to select patients for earlier use of anti-TNF therapy [20]. Location of inflammation in the small bowel, rather than the colon, has also been identified as predictor of disease progression to stricturing phenotype and has been associated with higher rate of surgery for associated complications [21].

* Corresponding author.
E-mail address: skeihanian@yahoo.com (S. Keihanian).

http://dx.doi.org/10.1016/j.tgie.2016.08.004
0049-0172/

3. Pathogenesis

The pathologic lesions of stricturing CD are well described, but the reasons for their presence in some patient populations and not others are incompletely understood. In CD, fibrosis can develop in the entire bowel wall of the GI tract including the mucosa, submucosa, muscularis mucosa, muscularis propria, and serosa layers [2,22]. In the presence of intestinal injury mesenchymal cells, mainly fibroblasts, accumulate and produce extracellular matrix in the tissue, with collagens and fibronectins being the major components. These can ultimately lead to development of intestinal strictures and obstruction [23-26]. The stimuli for these mesenchymal cells are inflammatory mediators released by lamina propria cells during chronic inflammation [2]. Some of the suggested profibrotic mediators include cytokines (IL-1, IL-4, IL-6, IL-13, IL-22, IL-33, TNF [tumor necrosis factor], MCP-19 [monocyte chemoattractant protein]), growth factors (TGF [transforming growth factor] β1, bFGF [basic fibroblast growth factor], PDGF [platelet-derived growth factor], IGF-I and II [insulin-like growth factor], and CTGF [connective-tissue growth factor]) [27-34]. Fibronectin has been shown to colocalize with aggregations of fibroblasts [2,22]. Within any given stricture, a mix of activated inflammatory cells and fibroblasts coexist to varying degrees [2]. Although the stimuli for fibrogenesis are ubiquitous in CD lesions, accumulation of collagen bands by fibroblasts is variable. An imbalance of tissue degradation through matrix metalloproteinases or cathepsins, and tissue inhibitors of metalloproteinases are likely to be involved [22,35-38]. Novel concepts emerging from in vivo and in vitro experimental models suggest that fibrogenic mechanisms can be distinct and, to some degree, independent of those regulating inflammation [39].

In addition to the inflammatory process of CD, other factors may contribute to the development of stricture in patients with CD, including medications (eg, nonsteroidal anti-inflammatory drugs), surgery-related ischemia, or even the healing process after anti-TNF therapy [40-44]. Although TNF inhibition could, in theory, promote fibrogenesis through TGFb, an increase in stricturing disease has not been noted in the anti-TNF era [45-47]. Because fibrosis is a downstream consequence of many inflammatory pathways, and also occurs as part of the normal healing process, how to specifically reverse intestinal fibrosis from CD remains an area of unmet need in drug development.

4. Classification

Although various studies report some endoscopic description of CD strictures, there is no general consensus on stricture classification in CD. In a study by Van Assche et al [48], a “short stricture” was arbitrarily defined as one having a maximal length of 5 cm. In a technical review by Paine et al, a proposed classification of strictures in CD was based on etiology (primary vs secondary [anastomotic] or benign vs malignant), shape (web-like vs spindle shapes or circumferential vs asymmetric), length (short vs long) and anatomical location (esophagus, pylorus, small bowel, ileocecal valve anastomosis, colon, rectum, and anus) [49]. Neither of these classifications is currently widely used, but would be helpful to categorize strictures for intervention trials.

5. Diagnosis of strictures

5.1. Clinical presentation

Strictures narrow the intestinal lumen, and eventually lead to episodes of partial or complete obstruction. Typical triggers are partially or undigested foods, such as popcorn, seeds, nuts, and raw vegetables. Symptoms of acute obstruction typically include postprandial abdominal pain, vomiting, and obstipation. These episodes usually resolve within 24 hours with intravenous fluids and gastric decompression [50]. Patients with chronic partial strictures often experience postprandial abdominal pain, 2-4 hours after meals, and gradually adjust their diets to reduce the frequency of these episodes. On examination, patients obstructed owing to strictures have abdominal distension, and may have high-pitched bowel sounds on auscultation [51-54].

5.2. Imaging

Several imaging modalities are available for accurate assessment of the anatomy of strictures as this is the key for a tailored treatment strategy. Most imaging studies in patients with CD include patients with small bowel rather than colonic disease. In addition, not all studies describe disease location, activity, and severity [84].

In recent years, there have been dramatic strides in small bowel imaging, along with major progress in existing imaging techniques [55]. Diagnostic accuracy of imaging modalities in stricturing CD is summarized in Table 1.

Traditionally, contrast radiography (barium small bowel enterography or enteroclysis) was used to detect small bowel stenosis, but these tests have the limitation of being unable to evaluate transmural and extramural extension of the disease. In single study, on 2 occasions, 4 independent observers retrospectively assessed examination findings in 78 patients with documented sigmoid strictures (43 benign and 35 malignant). The reported sensitivity of barium enema for the diagnosis of benign sigmoid strictures was 88% and 86% for the first and second assessments, respectively [56]. They can, however, determine the extent and severity of narrowing, which are important for surgical planning [57]. Among the disadvantages of these tests are the high dose of radiation exposure, and their contraindication in the setting of high-grade obstruction or perforation. Cross-sectional imaging with CT or MRI have instead become the gold standard for imaging CD in recent years. CTE (CT enterography) has high sensitivity to identify strictures, is readily available, and relatively easy to perform [44]. The reported sensitivity of CTE is 85%-95% for detection of small bowel strictures, with a specificity of 100% [58-60]. CTE imaging can delineate the location, number, length, and any associated fistula or abscess [44]. Although the presence of a single stricture was correctly determined in 100% of patients by CTE, the accuracy for the number of strictures was only 83% [61]. Unfortunately, CTE cannot differentiate inflammatory strictures from fibrostenotic ones in most cases [44]. In a study by Adler et al [62], CTE findings were compared with histology from surgically resected specimens; hyperenhancement, mesenteric hypervascularity and mesenteric inflammatory fat stranding were positively associated with a tendency toward greater tissue fibrosis. Interestingly, absence of CTE signs of inflammation in the involved

Table 1
Diagnostic accuracy of imaging modalities of stricturing CD.

Imaging modality	Sensitivity, %	Specificity, %
Ultrasound [76,82–84] [a]	74-100	89-93
CTE [58–60,84]	85-95	100
MRE [60,65–67,84] [a]	75-100	91-100
PET and PET/CT [84,85]	81-88	84-90
MR enteroclysis [84,86]	86-100	93-100

[a] Accuracy equal in both small bowel and colonic CD. The remaining data are only relevant in small bowel CD. Based on the high accuracy of CT for detecting small bowel stenosis, it is plausible that CT may be useful for similar colonic lesions.