Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: March 31, 2024

Citation: Suliman, O., et al., 2024. Endoscopic Management of Crohn's Disease Strictures. Medical Research Archives, [online] 12(3). https://doi.org/10.18103/mra.v12i3.5128

DOI: https://doi.org/10.18103/mra.v12i3.5128

ISSN: 2375-1924

RESEARCH ARTICLE

Endoscopic Management of Crohn's Disease Strictures

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ABSTRACT

Crohn's disease is a chronic, progressive inflammatory condition characterised by gastrointestinal tract inflammation and extra-intestinal manifestations.

Some patients may develop stricturing disease, which may either be of inflammatory, fibrotic or post-anastamotic aetiologies.

The management of fibrostenosis is challenging, necessitating preventative strategies and a multidisciplinary approach to its diagnosis and management once established. Although several treatment options are currently used in the management of strictures, there are currently no targeted anti-fibrotic therapies. Endoscopically, there are several modalities that can be employed in the symptomatic patient including balloon dilatation and stenting.

In this article we will briefly discuss the pathophysiology and investigations with focus centred around endoscopic management of Crohn's strictures, before suggesting a strategy to employ when approaching these cases.

Introduction

Crohn's disease is a chronic, progressive inflammatory condition characterised by gastrointestinal tract inflammation and extra-intestinal manifestations.

There are three main clinical phenotypes, with the Montreal classification providing a useful framework through which to subclassify these: inflammatory, stricturing or penetrating[1]. Even in patients who initially primarily exhibit the inflammatory phenotype, up to 70% may subsequently display the stricturing or penetrating phenotypes within 10 years of diagnosis[2-4].

Gastrointestinal strictures may be defined as areas of luminal narrowing and in Crohn's disease, may either be 'primary', that is, of inflammatory and/or fibrotic aetiologies or both[5], or 'secondary' i.e. post anastomosis. The differentiation of aetiology of primary strictures may be considered relatively arbitrary, given frequently both inflammatory and fibrotic factors are involved[6]. Mirroring Crohn's histopathology, fibrosis and strictures are transmural, with associated wall thickening[7].

While one study was suggestive some patients may be asymptomatic of their development[8], the challenge with the majority of strictures lies in their propensity to develop stenosis and ensuing acute, sub-acute or chronic enteric or colonic obstruction. The most frequent sites for strictures are the ileum and ileo-colonic regions[9], which perhaps is unsurprising given the calibre of lumen in this area of the gastrointestinal tract.

The management of fibrostenosis remains a clinical challenge, necessitating both optimised preventative strategies and a multidisciplinary approach to its diagnosis and management. Although several treatment options are currently used in the management of strictures, there are currently no targeted anti-fibrotic therapies either addressing fibrosis directly or altering the natural disease history once strictures are established[10]. We recognise a distinct lack of randomised controlled data on this area and look forward to further research in this area informing future practice.

In this article we will discuss the pathophysiology, diagnosis and management of Crohn's strictures.

Aetiology and pathophysiology

While certain factors appear implicated in the pathogenesis of stricturing Crohn's disease such as genetic and environmental factors, including dysregulation of the immune system and altered microbiota, the exact aetiology of the disease remains unknown[11].

Fibrosis in the digestive tract, similar to other organs, involves the aberrant deposition of collagen-rich extracellular matrix, which is largely driven by activated mesenchymal cells. Smooth muscle hyperplasia and hypertrophy, together with an increase in the number of myofibroblasts, contribute to the luminal narrowing that ultimately culminates in intestinal obstruction. Various pathways appear to drive fibrogenesis, including pro-fibrotic molecules and signalling pathways, such as transforming growth factor beta (TGF-β) tyrosine kinases, interleukin (IL)-11, IL-17, IL-34, reactive oxygen species (ROS) and peroxisome proliferator activator receptors, among other factors. These so-called "pro-fibrotic" molecules can directly activate a vast array of fibroblasts, myofibroblasts and

smooth muscle cells, and lead to transient or permanent expansion of these mesenchymal cells in damaged tissue. Nevertheless, chronic inflammation remains a key contributor to intestinal fibrosis, as shown by both its impact on fibrosis expression patterns, and on the evidence of fibrosis reduction through anti-inflammatory molecules[12-13].

Investigation

As yet there are no clinical, serological or radiological markers predictive specifically of GIT fibrosis and while some genetic markers appear promising, routine genetic testing of Crohn's patients is not recommended[7].

Stenosis therefore is at present only detected when already established, whether incidentally when staging the disease, or diagnostically when assessing obstructive symptoms. Strictures can be detected using various modalities, and will often be determined by patient symptoms, which prompt relevant investigation. Dictated by initial presentation, endoscopic assessment via ileocolonoscopy will often be performed, and if a patient is asymptomatic, cross-sectional imaging whether via magnetic resonance (MR), computed tomography (CT) enterography or indeed intestinal ultrasound may follow to facilitate colonic and enteric staging of disease. All three modalities carry comparable sensitivities and specificities for identifying stenosis[14], with validated MRI activity scores increasingly being used as adjunct end points in clinical trials. Thus, endoscopic and radiologic assessment of strictures need not be viewed mutually exclusive, but rather, as complementary modalities informing subsequent therapeutic therapy. Given the transmural nature of Crohn's inflammation, and indeed strictures, endoscopic evaluation alone will fail to adequately equip the clinician in their assessment of stricturing disease.

At endoscopy, severity may be determined by the ability to advance scope through and distal to the stricture. Macroscopic evaluation should always be complemented by microscopic assessment via histology not only to determine underlying aetiology but also to exclude dysplastic or neoplastic change[15]. There are a number of endoscopic scoring systems which are used regularly in clinical trials, although the two most commonly used are the Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simplified Endoscopic activity Score for Crohn's disease (SES-CD). Both utilise complete mucosal healing as clinical end-point in trials and while the CDEIS is complex to calculate, the SES-CD is a simple, reproducible and reliable endoscopic score. CDEIS entails the assessment of six endoscopic variables (presence of deep ulcers, superficial ulcers, nonulcerated stenosis, ulcerated stenosis, proportion of ulcerated surface, and proportion of surface affected by disease) in each of the five ileocolonic segments: rectum, sigmoid and left colon, transverse colon, right colon, and ileum. For each of these segments, the presence and severity of ulceration and the degree of colonic/ileal inflammation per 10 cm contribute to its calculation, with scores ranging from 0 to 44. Higher scores are indicative of more severe disease. SES-CD is simpler than CDEIS and is based on four endoscopic variables (presence and size of ulcers, proportion of surface covered by ulcers, proportion of surface affected by disease, and presence and severity of

stenosis) of the same five ileocolonic segments[16]. Although not used extensively in routine clinical practice, the SES-CD does systematise recording of features in each segment of the colon. The utility of ileocolonoscopy is hampered by its being unable to fully assess the small bowel, however, the advent of balloon enteroscopy, whether single or double, has permitted complete endoscopic staging of the disease within the gastrointestinal tract[17].

Table 1: SES-CD Scoring System. Adapted from Lamb et al [15]. The score is calculated from the sum of the grading for each segment (ileum, right colon, transverse colon, left colon and rectum).

Variable	0	1	2	3
Size of ulcers	None	Apthous ulcers (0.1-0.5cm)	Large ulcers (0.5-2cm)	Very large ulcers (>2cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected	<50%	50-75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Impassable

Video capsule enterography should be avoided in patients with suspected stricturing disease as, while it may aid small bowel assessment, its benefit it negated by the risk of capsule retention.

While there is no clear evidence of diagnostic superiority for one cross-sectional imaging modality over another for stricture diagnosis, emphasis should be placed on techniques that minimise ionising radiation exposure. Radiologically, strictures may be defined as a 25% increase in bowel wall thickness and a 50% reduction of the diameter of the lumen compared with a normal adjacent bowel loop[18]. Radiological assessment informs us regarding stricture location, length, distribution, degree of luminal occlusion, the presence of upstream dilatation and if there is an associated wall or extra-luminal mass which was not appreciated at time of luminal assessment. It also aids in the differentiation between a stricture of inflammatory versus fibrotic origin, with delayed hyperenhancement, layered wall enhancement and increased T2 mural signal intensity, features which are reflective of wall oedema and mesenteric vascularity, being more typical of inflammatory strictures[18]. Intestinal ultrasound is becoming an increasingly explored option but it remains to be seen the degree of uptake and integration into our routine clinical practice in the near future.

Management of stricturing disease

The management of stricturing Crohn's disease can be complex and requires multidisciplinary team approach from gastroenterologists, radiologists, and colorectal surgeons. An understanding of the likely underlying aetiology arms the clinician to deploy targeted therapy, whether that be medical, endoscopic or surgical. Medical management is primarily anti-inflammatory, as to date, targeted anti-fibrotic therapy is lacking. This is perhaps highlighted by the fact that the incidence of Crohn's stricturing

disease has failed to improve despite the advances in the medical, anti-inflammatory, therapy in recent decades[19-20].

Endoscopically, there are several modalities that can be employed in the symptomatic patient: balloon dilatation, stenting, stricturotomy or stricturoplasty. These are usually considered where stricturing has proven refractory to medical therapy[21]. By nature of the condition with its inherent luminal narrowing, perforation will be a risk irrespective of the endoscopic modality, however, certain factors can be employed to minimise this, for example, the use of carbon dioxide for insufflation or utilisation of a narrow calibre scope e.g. gastroscope or paediatric colonoscope.

1. ENDOSCOPIC BALLOON DILATATION

Endoscopic Balloon Dilatation is an option for strictures that are short (<5 cm), non-angulated, and presumed to be of fibrotic aetiology. The balloon is passed into the channel of the endoscope and inflated to gradually dilate the stricture to the appropriate diameter. It should not be performed in the setting of penetrating, fistulating disease or in suspected malignancy[9]. Similar success rates are found for both primary and secondary strictures[22]. Endoscopic Balloon Dilatation or EBD can be performed in upper gastrointestinal, small bowel and colonic strictures in either a retrograde or anterograde fashion via oesophagogastroduodenoscopy,ileocolonoscopy or balloon-assisted enteroscopy and. However, careful patient selection is warranted, especially taking location into consideration; duodenal strictures have been reported to be five times more likely to necessitate earlier surgery after dilation compared with strictures in the jejunum, ileum or colon[22]. A complication rate of <3% has been reported including perforation, bleeding or post-procedural inpatient admission, and perforation risk in particular can be minimised by dilating to no more than 5mm above the pre-dilatation diameter. Repeated procedures are warranted in just over half of patients [22] but success at repeated dilatations does not appear to be determined by the number of preceding procedures, and thus, the decision regarding this or surgical intervention should be guided by patient preference and symptom improvement with each EBD as much as the feasibility of the procedure[23].

Table 2 Endoscopic balloon dilatation. Considerations prior to Endoscopic Balloon Dilatation of IBD strictures. Adapted from El Quali et al.[21]

Patient Selection
Short strictures (<5cm)
Presumed fibrotic aetiology
Non-angulated
Endoscopically accessible
Contraindications
Fistulae or abscesses
Suspicion of underlying malignancy
Additional endoscopist considerations
Anterograde vs retrograde approach
Size of balloon to employ
Presence of ulceration- may hinder success
Complications (typically <3%)
Bleeding
Infection
Perforation
Unplanned, post-procedural admission

2. INTRALESIONAL THERAPY

Intralesional corticosteroids or infliximab are two modalities that have been explored in the literature, however, a recent systematic review of this technique showed no impact on outcomes[24], and thus, we do not recommend its use at present.

3. STENTS

Stent placement in structuring Crohn's disease may be efficacious[25] however this must be analysed in light of its cost, and indeed its significant complication rate in over two-thirds of patients including stent migration, fistulisation and perforation[26-27]. This renders the technique at present as not being for routine use in clinical practice, but emerging research with removable and biodegradable stents will be interesting to critically analyse in the near future.

4. STRICTUROTOMY

Endoscopic stricturotomy is a technique in which a needle knife or an insulated-tip knife is used to incise and progressively widen a narrowed lumen[28-29]. Data remains limited at present, however, it promises impressive technical, clinical and endoscopic success rates. While some studies suggest a lower risk of perforation compared with EBD (0% vs. 2.4%), this result was not statistically significant, and the significantly higher risk of bleeding (14% vs. 0%, $p < 0.001$) limits its use in clinical practice at present[30].

There is one final consideration to note. Ought we to intervene in incidental but otherwise asymptomatic Crohn's strictures? Although dilation of asymptomatic strictures could delay the development of symptomatic strictures or the need for surgery[23,29], in the absence of guidance nationally or internationally at present on this, we suggest it ought to be performed on a case-by-case basis.

So what is our approach to Crohn's strictures?

We consider the following factors in our decision-making process. Is the stricture symptomatic, e.g. are there obstructive symptoms? Is there any evidence of dilatation proximal to the stricture? Can we assess the stricture as predominantly inflammatory or fibrotic, on the basis of serum and stool inflammatory markers and radiological and endoscopic assessment? Where is the location of the stricture; is it within reach of an endoscope? What is the nature of the stricture- its length, tortuosity and number, and can malignancy be excluded?

We would consider endoscopic stricture dilation if it were symptomatic, predominantly fibrotic, within reach of an endoscope, a single stricture, of less than 5 cm in length, not malignant and not tortuous. That said, surgery is also an option and the choice of endoscopic dilatation or surgery will depend on local expertise and patient preference[26].

We would consider a stricture for mono medical therapy only if it were predominantly inflammatory. Regardless of whether a stricture is treated endoscopically or by surgery, we would provide concomitant medical therapy to reduce or prevent inflammation to reduce the risk of recurrent strictures.

Those strictures that should be considered for surgery rather than endoscopic treatment include symptomatic strictures that are tortuous, long, multiple or with subacute obstruction.

In the elective setting, the decision about management should be discussed in a multidisciplinary setting taking the patient's preferences into consideration. In the setting of an acute intestinal obstruction, surgical opinion should be sought as an emergency.

Conclusion

Stricturing Crohn's disease is a complex disease, with patient symptoms, endoscopic and radiological appearances and multidisciplinary team assessment all contributing to the decision regarding optimum modality of choice for treatment. The distinction between an inflammatory and fibrotic stricture remains challenging; both are often at play. Therapeutic endoscopy is but one tool at the gastroenterologist's disposal, but, with appropriate patient selection, can be a non-invasive, efficacious and safe treatment option.

Conflict of Interest:

TC. Tham Honoraria: Chairing, Consulting or Advisory Role: Amgen, Lilly, Bristol Myers Squibb.

Funding:

None

Acknowledgements

None

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