Chapter 2
Epidemiology and Natural History of Fibrostenosing Inflammatory Bowel Disease

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Abstract Crohn's disease (CD) and ulcerative colitis (UC) are chronic, relapsing inflammatory gastrointestinal diseases. CD frequently results in transmural inflammation and is more commonly associated with stricturing diseases compared with UC. Inflammation in UC is usually only limited to the mucosa and stricture formation in the colon occurs rarely. Strictures in IBD can be secondary to either inflammation or fibrosis and it is important to determine the aetiology to provide definitive treatment. Once strictures occur, they can be challenging to manage. Despite the advent of multiple new therapeutic agents for IBD, there has been no significant impact on the incidence and morbidity of strictures.

Keywords Crohn's disease · Ulcerative colitis · Inflammatory bowel disease · Strictures · Inflammation · Fibrosis · Fibrostenosing

2.1 Introduction

Inflammatory bowel disease (IBD) consists of Crohn's disease (CD) and ulcerative colitis (UC). CD is characterized by transmural inflammation which frequently leads to the formation of strictures. The risk of developing strictures has been shown to progress over time. Strictures often develop a fibrotic component that is refractory to medical therapy resulting in the need for endoscopic or surgical intervention. This chapter highlights the incidence, prevalence and natural history of stricturing CD and UC and discusses potential pitfalls in depicting the true incidence and their natural history and recommendations on how to overcome them.

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2.2 Epidemiology of Fibrostenosing Inflammatory Bowel Disease

The incidence of inflammatory bowel disease (IBD) is the highest in the West with reported annual rates as high as 29.3 per 100,000 persons for CD and 24.3 per 100,000 persons for UC [1, 2]. The incidence of IBD is increasing with time in many regions around the world, especially in newly urbanized regions. Certain highly urbanized regions in the West have started to demonstrate a plateauing effect in the incidence of IBD [3]. Asia has a lower incidence and prevalence of IBD, however the incidence is rising rapidly in parallel with urbanization [4]. East Asia has the highest IBD incidence in the region, especially in China, Korea and Japan, with highest reported incidence rate of 3.4 per 100,000 persons [5].

IBD is a chronic disease that commonly affect young individuals with low mortality rates. The stable or increasing incidence of IBD accompanied by better healthcare delivery have resulted in an exponential increase in the global prevalence of IBD. This epidemiological phenomenon known as compounding prevalence, will result in a rapid increase in the global IBD prevalence [3]. Approximately 0.7% of the population in Canada has IBD, equating to more than one in every 150 Canadians, which is twice as common as multiple sclerosis or Parkinson's disease [6].

2.2.1 Crohn's Disease

Intestinal fibrosis is common in patients with CD, and clinically significant stricturing disease affects at least 30% of patients 10 years after diagnosis [7, 8]. In a population based cohort study, the cumulative probability of stricturing CD after long term follow up was 4.8% at 90 days, 7.2% at 1 year, 12.4% at 5 years, 15.2% at 10 years and 21.6% at 20 years [9]. A retrospective study from several European countries reported that 48.2% of patients with CD presented with a stricturing behaviour [10]. A prospective population-based study from eight Asian regions (China, Hong Kong, Indonesia, Macau, Malaysia, Singapore, Sri Lanka and Thailand) reported that 14–33% of patients had stricturing disease, with similar frequency to the CD patients in Australia [5]. Stricturing disease has also been observed in 39.9% of CD patients in Japan [11], 33.6% in Taiwan [12] and 20.1% in Korea [13].

2.2.2 Ulcerative Colitis

Fibrostenosis is less common in patients with UC when compared with patients with CD. However, reports on the prevalence of strictures in UC are generally limited. Most studies on the prevalence of strictures in UC included both benign and malignant strictures. A retrospective study from New York reported the prevalence

of strictures (detected radiologically, endoscopically or surgically) amongst UC patients as 5.1% [14]. Colonic stricture in UC should always raise a concern for malignancy, however the majority (71–100%) of strictures detected in UC are benign [14–16]. The prevalence of benign strictures in UC varies widely from 1 to 11.2% [14, 15, 17–20]. The disparity in the reported prevalence of strictures is likely attributed to the heterogeneous definitions used across different studies. This will be discussed further in this chapter.

2.3 Natural History of Fibrostenosing Inflammatory Bowel Disease

2.3.1 Risk and Prognostic Factors Associated with Fibrostenosis in Crohn's Disease

Several genetic mutations have been associated with the development of fibrostenosing disease in CD. Nucleotide oligomerization domain 2 (*NOD2*) variants is one of the most important mutations in Caucasian population and is an independent predictive factor for ileal disease (OR = 1.9), stenosis (OR = 1.82) and penetrating disease (OR = 1.25). NOD2 is also the strongest risk factor associated with a complicated CD disease course (OR = 2.96) [10]. Patients with biallelic *NOD2* or caspase-recruitment domain 15 (*CARD15*) mutations have a ten times higher risk of developing strictures, when compared to patients carrying only a single mutation [21–23]. Janus-associated kinase 2 (*JAK2*) has also been associated with the development of bowel stenosis in patients with CD. Genetic predispositions vary in different ethnicities [4, 24]. For instance, the presence of tumour necrosis factor superfamily 15 (*TNFSF15*) and serological marker anti-*Saccharomyces cerevisiae* (ASCA) IgA are associated with stenosis or penetrating phenotype in Asian patients with CD [25].

Clinical factors associated with intestinal strictures include the age of diagnosis of less than 40 years, perianal disease and the need for steroids during the first flare [9]. In addition, smoking is an important reversible risk factor for complicated disease course and progression from CD to initial stricture formation. A history of appendicectomy and the presence of antimicrobial antibodies have also been reported to be associated with stricture formation [21, 26]. Endoscopic feature of small bowel deep mucosal ulcerations is predictive of developing strictures in CD [26].

2.3.2 Clinical Manifestations and Disease Progression of Fibrostenosis in Crohn's Disease

CD can potentially affect any segment of the gastrointestinal tract, with a predominant involvement of the ileum and colon. In CD population in the West, ileal, colonic and ileocolonic involvement are commonly found in equal frequencies. In contrast

to the West whereby ileal disease is more common, Ileocolonic disease appears to be the most common CD phenotype in East Asian CD population, ranging from 50.5 to 71% [27–30]. The locations of CD involvement usually remain relatively stable, with only 10–15% demonstrating a change in disease location 10 years after diagnosis [7, 8, 31].

The inflammatory form of CD usually predominates in the initial years of disease with a subsequent development of penetrating or stricturing disease. The disease course generally follows a sequence of flares and remissions, with 20% of subjects having a chronic, active, continuous course. The initial disease location may determine the time and type of complication. Complications with abscesses, fistulae and stricture formation are more common if there is small bowel involvement. On the contrary, colonic involvement tends to remain inflammatory in nature and uncomplicated for many years. There seems to be no direct relationship between symptoms and disease progression, as most strictures and fistulae are subclinical and may have little or no symptoms for many years [7]. Small bowel disease usually remains latent for many years, whereas colonic disease tends to presents early [1, 32]. Of importance, half of the CD population adopts a progressive and aggressive course with high rates of complications, relapse, admissions and surgery. Fortunately, the other half remains minimally progressive and adopts a milder disease course [33–35].

Progression of the disease may take weeks to years and may be slowed or halted with medical therapy. Current medical therapy with immunosuppressive drugs mostly relieve inflammatory symptoms, but have limited effects on fibrostenosis disease [36–42], with 64% of patients with strictures requiring surgery within 1 year of diagnosis [43]. It is therefore important to identify high risk patients who will be susceptible to complications, for aggressive initial treatment before severe irreversible fibrosis sets in.

2.3.3 Risk and Prognostic Factors Associated with Fibrostenosis in Ulcerative Colitis

Fibrostenosis is less common in UC compared to CD. Factors associated with fibrostenosis in UC include a longer disease duration and more severe colitis with larger ulcers and deep ulcerations [44–47]. Strictures detected within 10 years of disease onset are usually benign. However, the risk of malignant strictures increases thereafter with a longer duration of UC [14, 15]. This is also in keeping with the observation that colonic malignancies are usually only detected in patients with more than 10 years history of UC. It has been reported in a series [14] that the following factors have been observed to be associated with a higher risk of malignant strictures:

1. The appearance of strictures late in the disease course (61% probability of malignancy in strictures diagnosed after 20 years of UC, 0% probability of those diagnosed before 10 years)

2. The location of stricture is proximal to the splenic flexure (86% probability of malignancy in strictures proximal to the splenic flexure, 47% probability in the sigmoid colon and 10% probability in the rectum)
3. Symptomatic large bowel obstruction (100% probability of malignancy, 14% probability in the absence of obstruction or constipation)

It is important to note that the percentages above served only as a guide, because in this series of 1156 UC patients, only 59 patients had developed strictures.

2.3.4 Clinical Manifestations and Disease Progression of Fibrostenosis in Ulcerative Colitis

UC classically involves the rectum and extends proximally in a continuous manner with about 30–35% presenting with proctitis, 30–45% left sided colitis and 20–25% pancolitis [1, 32]. Backwash ileitis is more commonly seen in patients with pancolitis. The diagnosis of UC may be revised to CD in 5–10% of the adult patients [1, 32]. Mucosal inflammation is usually diffuse and superficial, but deep ulcerations may occur in patients with more severe UC. Disease activity tends to decrease over time, with one third of the patients exhibiting persistently active disease [48].

Fibrostenosing disease in UC is related to the severity of inflammation, with strictures more commonly observed in patients with extensive colitis (17%), compared to those with left sided colitis (11%). There is a significant variation in the severity of fibrostenosis in UC. Reported stricture lengths may vary from as short as 2–3 cm, to as long as 30 cm [15], with an average stricture lumen diameter of 1.1 cm [18]. With chronic inflammation, it will result in marked shortening [49, 50] and rigidity of the colon, with eventual formation of clinically significant colonic strictures.

2.4 Pitfalls in Depicting Incidence and Natural History of Fibrostenosis Disease

Information on the incidence and natural history of any disease is dependent on the availability of good quality reports. Insufficient data or biased reports may significantly affect the accuracy of the data especially for uncommon illnesses. In addition, most fibrostenotic diseases are subclinical during their initial years. This has resulted in significant underestimation of the true prevalence of fibrostenotic disease in IBD patients, because only clinically apparent cases are reported. Differing definition of strictures between clinicians, radiologists and pathologists may affect the rate of the detection of fibrostenosis, resulting in a disparate incidence. To circumvent these limitations, improved clinician awareness of fibrostenotic diseases in IBD, especially in UC, which was once thought to be uncommonly associated with

strictures, will be an integral first step to timely identification. Standardized definition of strictures together with routine screening protocols for stricturing diseases will be helpful in early detection, especially for CD patients, who tend to have a higher incidence of strictures.

In summary, fibrostenosing IBD is most commonly seen in CD patients, with risks increasing with the duration of inflammation. Fibrostenosis commonly remains subclinical for many years before diagnosis, which results in significant under reporting of its prevalence. Increase clinician awareness and screening will be integral to early detection.

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