Segmental Colitis Associated with Diverticulosis (SCAD)

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Abstract



Purpose of Review A distinctive, possibly "novel" form of a segmental inflammatory colonic disease process associated with diverticular disease (so-called SCAD or segmental-colitis-associated-diverticulosis) is reviewed.

Recent Findings Although this phenotype of inflammatory colonic disease was initially recognized decades ago, mainly in the elderly, recent evidence from long term natural history studies along with meta-analyses confirms that its clinical course is usually benign and drug-responsive. Interestingly, its appearance in some treated with monoclonal agents (eg., ipilimumab associated colitis) or infected with coronavirus-19 may have critical implications for its pathogenesis.

Summary This review further explores the implications of recognition of this pattern of colonic inflammatory disease, with relevance for physicians involved in both clinical practice and clinical trials of newer therapeutic agents.

Keywords Segmental Colitis · Diverticulosis · Crohn's Disease · Long-term Follow-up and Natural History · Diverticulitis · SCAD

Introduction

Over the past few decades, an unusual form of inflammatory colonic disease associated with diverticulosis (SCAD) has been described and increasingly appreciated by specialist physicians. Historically, clinical and pathological features of Crohn's disease of the colon were thought to be distinguishable from those of ulcerative colitis [1]. In some, however, inflammation involved the sigmoid colon alone, co-existent with diverticular disease [2]. Most, but not all, were elderly adults. In addition, most patients seemed to respond readily to treatment with a benign clinical course seen over 20 years [3–5]. Although overlap is evident, Table 1 summarizes these inflammatory disease patterns and their usual clinical behaviour for adults.

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Clinical Features and Disease Behaviour

In recent decades, SCAD has been recognized as a distinctive clinical and pathological entity, usually in males, presenting with rectal bleeding (more than 70%) and, virtually exclusively, as a disorder of the elderly, usually after age 50 years. Often, especially in this elderly age group, initial referral is made to exclude an occult colorectal malignancy. In some, but not all, diarrhea and/or constipation may be present. Extra-intestinal features associated with inflammatory bowel disease are rare with post-operative pyoderma gangrenosum recently described [6]. Fever is unusual. These clinical and epidemiological features [7] were noted to differ from the features of Crohn's disease recorded in over 1000 patients from the same hospital center having a predominately female sex distribution and younger age; in this prior study, only occasional patients were initially diagnosed with Crohn's disease after age 60 years [7, 8].

A prominent clinical feature evident in long term studies was the frequency of spontaneous resolution and remission without the need for pharmacological therapy or with limited treatment, perhaps an oral 5-aminosalicylate alone. Occasionally, however, ongoing symptomatic disease or recurrent disease was noted, necessitating use of steroids, or other immunosuppressant medications, but rarely, eventual surgical resection of a strictured sigmoid segment [5].

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	Crohn's Disease	Ulcerative Colitis	SCAD
Age/Sex	Usually < 50 years/often female > male	Usually < 50 years/male and female	Age > 50 years/usually male
Pattern	Focal/segmental, often ileo-colonic	Diffuse with involved rectal mucosa	Colonic with spared rectal mucosal
Behaviour	Inflammatory, often with stricture, fistulae and/or abcess	Often severe and chronic persistent or recurrent	Usually benign, occasional recurrence
Neoplasia	Usually in the involved intestine	Usually in the involved colon	May occur, but appears unrelated to involved area

Table 1 Patterns of Inflammatory Bowel Disease

Pathological Features

Most cases of SCAD have described non-specific inflammatory changes (usually, but not exclusively, diffuse and transmucosal in type) confined to the sigmoid colon based on evaluation of multiple colorectal endoscopic mucosal biopsies. Usually, the histopathological features are noted to be non-granulomatous, although cases with granulomas have also been described [9]. An essential component of definition of SCAD is direct visualization and histopathological confirmation of normal rectal mucosa, distal to the sigmoid inflammatory process, so-called "rectal sparing". Multiple sigmoid diverticular changes with imaging are also observed. Interestingly, immunohistochemical evaluation with an antibody to tumor necrosis factor alpha showed over-expression in SCAD, similar to the pattern in Crohn's disease and ulcerative colitis [10]. Further studies are needed to determine if this observation has relevance to the pathogenesis of SCAD or represents a type of "specificity marker" in this inflammatory process. Often, inflammatory changes are seen within the inter-diverticular mucosa, but not involving the orifices of the diverticula (some have descriptively termed the latter appearance as type A or "crescentic fold disease", the most common pattern, as well as other apparently descriptive endoscopic types B, C and D patterns thought to be similar to ulcerative colitis-like, Crohn's disease-like, and severe ulcerative colitis-like, respectively) [11, 12]. Interestingly, some biological forms of treatment, such as ipilimumab used for treatment of metastatic melanoma and other advanced malignancies, may be associated with similar endoscopic and histopathologic changes in the sigmoid colon; indeed, in one study [13], SCAD was noted in 17% of their patient series while segmental colitis without diverticulosis was seen even more commonly in 50%. Further evaluation of newer drugs may also define concomitant SCAD in treated patients.

Other Laboratory Changes

Other laboratory tests tend to be normal or negative. Leukocytosis is unusual. Routine fecal bacterial and parasitic studies to delineate an infectious agent have been negative. Serological markers, (eg., perinuclear neutrophil cytoplasmic antibodies (i.e., pANCA) and anti-*Saccheromyces cervisiae* antibodies (i.e., ASCA), often positive in other forms of inflammatory bowel disease (i.e., ulcerative colitis, Crohn's disease), are generally negative in SCAD. Fecal calprotectin may help to differentiate SCAD from healthy controls or the irritable bowel syndrome, but not differentiate from other forms of inflammatory bowel disease [14].

Treatment Options

To date, evidence for treatment of this condition has been limited largely to small non-blinded series or case report experiences, so clear and specific recommendations for treatment are not available. However, in larger long-term follow-up studies (up to over 20 years), most endoscopically and histopatholically well-defined patients (over 80%) received oral 5-aminosalicylate alone or elected to pursue no drug treatment. Prescribed use of antibiotics for treatment was not required in this cohort or other guidelines offered by national groups [15]. Of these long-term patients, most (over 80%) recovered completely within 6 months, but occasionally, symptoms persisted over more than 1 year. Most patients, non-compliant with 5-aminosalicylates, resolved their disease spontaneously, but if recurrence developed, added prednisone may have been required for remission. In rare patients with an apparent poor response, an anterior (localized sigmoid) resection for a persistent sigmoid inflammatory stricture was done. Similar results have been noted in other studies. Of course, there are some case reports of successful anecdotal treatment experiences with biological agents, including some monoclonal antibodies, i.e., infliximab and adalimumab [16, 17].

Long-term Natural History

In explorative studies of the long-term natural history of SCAD, recurrent disease has been recorded after more than a year after complete clinical and histopathological resolution. Other long-term studies with limited numbers of patients have

also been published [18, 19]. All show a similar course, mostly described as benign during long-term follow-up ranging from 5 and 7 years, respectively. A further review of 486 cases with meta-analysis also confirmed this emerging entity with a male predominance (male, 58.7%) in an elderly population (mean age 63.6 years), marked by a benign course with spontaneous resolution or response to 5-aminosalicylates or steroids [20••]. The estimated prevalence in patients with diverticulosis in their study was 0.3% to 1.3%, also with the endoscopic and histopathologic features of ulcerative colitis.

Indeed, the majority of those suffering an initial recurrence may even have a second episode of recurrence, often after up to a decade after the initial clinical illness suggesting that there may be overlap with some other forms of chronic recurring inflammatory bowel disease. Further studies focused on this potential relationship needs added study.

Complicating Neoplastic Disease

Although colonoscopic resection of isolated adenomas was recorded in some, colon cancer may also develop. In our small series, there were intriguing features. In one patient, a rectal cancer developed 4 years after SCAD had resolved. This was distal to the original site of inflammatory disease defined histopathologically with normal rectal mucosa. In a second, cancer was detected proximally in the cecum, 9 years after SCAD resolution. In this latter patient, SCAD even recurred after 5 further years and resolved within 2 months using 5-amino-salicylate therapy alone [5]. This site dissociation observed for this unusual, but localized, segmental inflammatory process and the location of colon cancer is intriguing and may provide some added pathogenetic clues to this segmental inflammatory process and its role (or lack of role) in colorectal cancer pathogenesis.

Significance of SCAD

For clinicians treating inflammatory bowel disease patients, the significance of a type that may have a benign or limited course has special importance in diagnosis and sorting through different treatment options. There is clearly overlap with changes of Crohn's disease or ulcerative colitis [21••], and, in some with these disorders, coincidental diverticulosis may be entirely possible. Some SCAD patients may respond to virtually any treatment option, or may enter remission without any form of medication. Is this an entirely separate form of inflammatory colonic disease, and if so, are there biomarkers that may confirm the clinical impression of a specific phenotype and aid in decision making? Alternatively, does this localized sigmoid inflammatory disorder simply represent an early stage of colonic Crohn's disease that may resolve with minimal treatment rather an initial presentation later in the disease course with penetrating disease complications, including fistulae and abscesses? For those involved in therapeutic trials of newer or novel agents that tend to have a shorter term, exclusion of segmental colitis (and its benign course) may be very important to permit precise evaluation of treatment efficacy in the management of a presumptive inflammatory bowel disease diagnosis (i.e., localized Crohn's colitis).

The pathogenesis of the endoscopic and histologic lesion in SCAD remains obscure, however similar findings have been described with the recent coronavirus pandemic and its known diverse effects on the intestinal tract, including the colonic mucosa [22, 23, 24 \bullet]. Perhaps, as in COVID-19 disease, changes relate to ischemic injury from either vascular disease or hypoperfusion, more likely in an elderly population. Definition of SCAD and other "new" forms or patterns of disease with a benign clinical course may be a crucial consideration in future treatment paradigm.

Declarations

Conflict of Interest The author declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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