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TOPIC HIGHLIGHT

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Old-age inflammatory bowel disease onset: A different problem?

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Abstract

Inflammatory bowel disease (IBD) in patients aged > 60 accounts for 10%-15% of cases of the disease. Diganostic methods are the same as for other age groups. Care has to be taken to distinguish an IBD colitis from other forms of colitis that can mimick clinically, endoscopically and even histologically the IBD entity. The clinical pattern in ulcerative colitis (UC) is proctitis and left-sided UC, while granulomatous colitis with an inflammatory pattern is more common in Crohn's disease (CD). The treatment options are those used in younger patients, but a series of considerations related to potential pharmacological interactions and side effects of the drugs must be taken into account. The safety profile of conventional immunomodulators and biological therapy is acceptable but more data are required on the safety of use of these drugs in the elderly population. Biological therapy has risen question on the possibility of increased side effects, however this needs to be confirmed. Adherence to performing all the test prior to biologic treatment administration is very important. The overall response to treatment is similar in the different patient age groups but elderly patients have fewer recurrences. The number of hospitalizations in patients > 65 years is greater than in younger group, accounting for 25% of all admissions for IBD. Mortality is similar in UC and slightly higher in CD, but significantly increased in hospitalized patients. Failure of medical treatment continues to be the most common indication for surgery in patients aged > 60 years. Age is not considered a contraindication for performing restorative proctocolectomy with an ileal pouch-anal anastomosis. However, incontinence evaluation should be taken into account an individualized options should be considered

Key words: Inflammatory bowel diseases; Ulcerative colitis; Crohn's disease; Eldery population

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INTRODUCTION

Old-age colitis refers to patients over 60 years of age who are affected by a group of diseases of the colon, including infections, vasculitis, microscopic colitis, colorectal cancer, ischemic colitis, drug-associated colitis [particularly non-steroid anti-inflammatory drugs (NSAIDs)] and inflammatory bowel disease (IBD)[1]. Diagnosis of IBD in this age group may be difficult because it can be easily confused with other forms of colitis. Of particular relevance is so-called segmental colitis associated with diverticular disease (SCAD), which may simulate IBD both clinically, endoscopically, and histologically[1-3]. SCAD is characterized by the presence of diverticula, most often in the sigmoid colon, and affects middle and old

aged patients. A recent study in a German IBD elderly population showed that 8% of older patients diagnosed as IBD patients were in fact affected by SCAD[4]. Special precautions and attention must be taken in the diagnosis of these patients to avoid errors. New diagnostic tools, such as serological markers or advanced radiological examinations, may be useful in for a correct diagnosis.

FREQUENCY

Approximately 10% of patients at first flare of IBD are > 60 years old, with a similar distribution between ulcerative colitis (UC) and Crohn's disease (CD); 50% of them are diagnosed between 60-70 years of age[4,5]. However, it is difficult to establish the true incidence of IBD in older patients due to problems of case definition, population, and particularly because it may be confused with other clinical conditions, such as NSAID-associated colitis or ischemic colitis[1]. A bimodal age curve for IBD incidence has been suggested in epidemiological studies, with a second peak occurring at 50-70 years[5-7], but this point is currently the subject of debate, and it was not observed in the results of four population studies using strict radiological and endoscopic diagnostic criteria. A clear decrease in incidence occurs from age 40 in patients with CD and then stabilizes from age 60. Although there is a similar trend in patients with UC, the decrease is smaller in this group[8].

Thus, the incidence in patients over 60 years old represents approximately 10% of the cases of IBD; the bimodal distribution is questionable, and care should be taken to avoid including inadequately diagnosed patients.

CLINICAL MANIFESTATIONS

The clinical manifestations of the first flare of disease, both in UC and CD, are similar in the group aged > 60 years and younger age groups. It has been noted that the severity of the symptoms of UC, particularly rectal bleeding and diarrhea, may be lower in patients in this group, but it may also have atypical forms of presentation, such as constipation[9,10]. With regard to disease location, according to the Montreal classification, proctitis and left-sided UC are more common in patients > 60 years old than in younger patients. Severity of recurrence is usually higher in elderly patients (S2-S3 by the Montreal classification), with a longer duration of symptoms, which has influence on the need for steroid treatment[11-14].

In the case of Crohn's disease, the Montreal classification considers three age groups, establishing age > 40 years as the more advanced age group[11]. It has been observed that the form of disease presentation is similar between the different age groups, but that the L2 (colonic) disease location (clinical pattern) is the most common form in the older group (48% colon involvement in > 40 years group versus 28% and 20% in the groups diagnosed between 20-40 years and < 20 years, respectively)[1,15-19]. This frequency rises to 66% in patients aged > 60 years. With regard to the disease behavior, the most common is the inflammatory disease behavior (B1), the stricturing and penetrating pattern being less common than in the 18-60 years age group[1,5,19].

There are few references on the frequency of presentation of extraintestinal manifestations in this subgroup of patients. In the study by Hadithi[5], 17% of patients over 60 years of age had extraintestinal manifestations, which, in order of frequency, were: peripheral arthritis, uveitis, spondylitis, and erythema nodosum.

DIFFERENTIAL DIAGNOSIS

There are various clinical situations that may hinder diagnosis of IBD in elderly patients. IBD may be complicated by infections or by taking certain medications, such as NSAIDs and antibiotics[1,20-22]. Similarly, certain neoplasms, and specifically small bowel lymphoma, may have similar characteristics to those of IBD or be a complication of the disease itself[23-25]. The most common causes of chronic diarrhea and bowel inflammation in patients aged > 60 years are indicated in Table 1[25-31].

Segmental colitis associated with diverticular disease (SCAD) warrants special consideration[1,25-27]. Diverticulosis affects more than half of the people over 60 years of age. SCAD is clinically manifested by abdominal pain, rectal bleeding, and altered bowel habits, but only 3%-8% of patients have mucosal inflammation around the diverticula. It involves only the sigmoid colon, with sparing of the rectum and proximal colon. Endoscopic examination shows a circumferential distribution of erythema, granularity, and friability, and sparing of the diverticular ostium and cavity with a diffuse periosteal distribution of inflammation confined to the area of the diverticula[24,25]. Histopathologically, inflammation analogous to that seen in the UC and nonspecific chronic inflammation that may contain granulomas has even been reported, leading to misdiagnosis with CD. In general, SCAD may be suspected when colitis is confined to the diverticular segment of the left colon (excluding the rectum), the rectum and proximal colon are endoscopically and histologically normal, and if surgical resection of the affected segment is required, when no recurrence of segmental colitis occurs.

There are no randomized studies specifically assessing treatment of SCAD[1,5]. Overall response to oral (2.4-3 g/d) or topical (enemas 1-2 g/d) mesalazine was good, with a clinical response of 80% at six weeks and a maintenance of response in 90% of patients at six months[5,27]. The addition of fiber and antibiotics (rifaximin) during the acute phase may improve the response. If there is no improvement with this combination treatment, steroids applied topically as enemas may improve the clinical response. Exceptionally, oral prednisone has been evaluated in some cases of non-responders. These are patients who will rarely require surgery with segmental resection for SCAD.

MEDICAL TREATMENT

The principles governing medical management of IBD in patients aged > 60 years are the same as in other age groups. The location, extent, severity, and disease behavior,

Table 1 Differential diagnostic of colitis in patients older than 60 years

Disease	Clinical characteristics	Endoscopic findings
Colitis associated to diverticulosis	Rectal bleeding, abdominal pain, diarrhea	Segmentary distribution, peridiverticular, sigma affected, rectum and proximal colon are normal
Ischemic colitis	Abdominal pain rectorragia acute onset	Segmentary colitis (sigma/left colitis), majority are non-obstructive
Microscopic colitis	Watery diarrhea, no rectal bleeding, no fever, frequent cause of diarrhea in the eldery	Normal endoscopy, multiple biopsies from colon, celiac disease association
Infectious colitis	Disenteriforme diarrhea, different agents, *C.difficile* to be ruled out	Difuse effects on the colon Increased morbidity and mortality in older-aged population
NSAIDs colitis	Recurrent abdominal pain; obstruction, perforation, hemorrhage; chronic anemia	Any part of the intestine, isolated lesions, aggravate previous UC and CD

NSAIDs: Non-steroid anti-inflammatory drugs; UC: Ulcerative colitis; CD: Crohn's disease.

both in UC and CD, will determine the medical treatment options to be used[32-37]. Special precautions and the most generally used treatments in IBD old-aged patients are summarized below. In brief, depending on the kind and severity of IBD suffered by patients, we should choose the best treatment, taking special care of side effects caused by advanced age or by drugs associated with another diseases.

Mesalazine

Oral and/or topical mesalazine is the main option for medical treatment in patients with a mild to moderate flare of UC. The availability of new distal release mesalazine preparations with the MMX formulation may facilitate compliance and, therefore, adherence to treatment. It is similar in terms of efficacy to other oral preparations of mesalazine, regardless of its form of release[38]. However, in Crohn's disease, the efficacy of mesalazine is questionable and it has a limited role in the treatment of mild flares of ileal or colonic location[36,37].

Oral or topic steroids

Beclomethasone combined with mesalazine has been shown to be effective for treating moderate flares of left UC when administered orally as a single 5 mg dose for 2-4 wk, obtaining remissions in about 60% of patients[39]. Although there is no specific study by age subgroups, it remains an option to consider that may avoid the need for systemic steroids[40,41]. Nevertheless, we have to bear in mind that local or systemic steroids administered intrarectally are absorbed and therefore not free from their side effects.

Antibiotics

A detailed case history should be made in the group of patients > 60 years old, looking for symptoms suggestive of sensory neuropathy in the use of metronidazole[42].

Immunomodulators

The prevalence of corticosteroid resistance or dependence in this group of patients has not been specifically evaluated, but it is estimated at about 30%[43]. Although there is little objective data on which to base this practice, treatment was started with conventional immunomodulatory agents (azathioprine, mercaptopurine, and methotrexate) in this group of patients without evidence of differences in terms of efficacy, metabolism, and toxicity between the patients aged > 60 years and younger patients[35-37].

Biological agents

Their indications remain similar to those for patients aged < 60 years[44-46]. However, one of the most important aspects regarding the use of these agents is the safety profile, particularly that related to the risk of infections. The trend observed in the subgroup of elderly patients with rheumatoid arthritis > 65 years old to develop infections has not been confirmed in any controlled study. It is not uncommon for patients to be treated with combination therapies (corticosteroids, conventional immunomodulators, and biological agents) because of the disease's complexity. In this regard, the higher rate of infection found in the TREAT registry in patients treated with anti-TNF agents (infliximab (IFX) in this case) may have been due to the greater severity of these patients and the greater use of steroids[47]. In fact, the only independent risk factor for infections was the concomitant use of steroids (RR = 2.33, 95% CI = 1.50-3.62). However, the results of series describing the clinical experience in treatment with these drugs will best reflect what we would encounter in our clinical practice, particularly when they report observations collected over years. In this regard, the results of the Leuven group comparing adverse effects in 734 patients treated with IFX versus 664 control patients, with a follow-up of 58 to 144 mo, showed no significant differences in the risk of severe infections, mortality, and malignant conditions. No specific analysis by age subgroups was done[48].

In the Stockholm cohort study[44], it was observed that the use of infliximab in the subgroup of patients aged > 60 years was associated with an increased risk of serious side effects and higher mortality, which was also suggested in the multivariate analysis of the Lichtenstein registry[41]. However, more safety data are required on the use of biological therapies in patients aged > 60 years. In the meantime, it seems logical to use them according to recommended usage guidelines and with strict adherence to performing all tests prior to administration. It should be kept in mind that in this age group, and particularly in countries where the prevalence of tuberculosis is higher, it is more likely that an increased frequency of cases of latent TB will be observed.

Surgical indications

In older patients surgical indications are the same as in younger patients, with failure of medical treatment being the most common cause of surgery[49]. In general, the need for surgery is lower in CD patients with an age at diagnosis > 40 years and colonic disease location, and more common in the elderly. However, it is similar in ileocecal disease[49-51].

In UC, restorative proctocolectomy with ileal pouch-anal anastomosis continues to be the surgical technique of choice[52,53]. In general, results are not as good in older patients compared to younger patients, but they are both reasonably good in terms of efficacy and morbidity. Only an increased frequency of diurnal incontinence and nocturnal leakage has been reported among patients aged > 65 years. Generally, overall quality of life was good, to the extent that in the study by Delaney[52] 89% of patients over 65 years of age were satisfied with surgery and 96% would recommend it. Therefore, age is currently not considered a contraindication for performing an ileal-anal pouch.

MORTALITY

Mortality from UC is similar to that of the general population, with more controversial results in the case of CD[1,5,41,54,55]. In UC, age at diagnosis is not associated with increased mortality, whereas in CD, there appears to be a slight increase in the risk of mortality in older aged patients (> 55 years) with long-standing disease[56-58]. However, we should be cautious, because some of the results may be biased by the type of study, study population, follow-up period, *etc*.

There are a number of aspects to consider regarding possible factors that may be associated with an increased relative risk of mortality. In this regard, there were more hospitalizations in patients > 65 years than in the younger group, representing 25% of all admissions for IBD occurring in the USA (33% of hospitalizations for UC and 20% for CD)[41]. In general, the disease course of UC is more severe in elderly patients and mortality in hospitalized patients, both with UC and CD, is estimated to be 3-5 times higher than in age subgroups < 65 years. In the study by Ananthakrishnan *et al*[41], hospital mortality was higher (OR: 3.91; 95% CI: 2.50-6.11) and age was an independent risk factor in the group of IBD patients aged > 65 years; other variables significantly associated with hospital mortality were fistulizing disease, malnutrition, and need for intestinal resection for stenosing disease. Interestingly, in this study, a greater difference was observed in mortality between unoperated and operated patients, possibly because medical salvage therapies, including immunomodulatory and/or biological therapies, may increase morbidity and mortality, suggesting that "early" surgery is associated with lower mortality in older patients. However, hospital stays were longer, particularly in the group of operated patients. Although postoperative complications were similar between this age group and those younger than 60 years, the risk of cardiovascular or pulmonary complications was greater, these being aspects to be taken into account in the postoperative period of patients.

Table 2 Summary of inflammatory bowel disease onset in the elderly

Home messages
10%-15% patients with inflammatory bowel disease > 60 years
12% UC patients
16% CD patients
Differential diagnosis with colitis associated to diverticulosis, ischemic colitis, infectious colitis (*C.difficile*)
Ulcerative colitis: proctitis/left colitis is more frequent
CD: Granulomatous colitis > frequent than ileocecal
Medical treatment
Same treatment options as younger patients
Increased rate of complications with steroids
Similar response, but recurrence less frequent
Surgery: Equal indications, ileoanal reservoir is secure
More hospitalizations
Similar mortality, increased in hospitalized patients, comorbidity

UC: Ulcerative colitis; CD: Crohn's disease.

Related to the use of biological agents, there is a study[59] that points out that 3 out of 5 deaths attributable to infliximab treatment were older than 70 years. However, these patients had a longer evolution of disease (15-26 years) and they suffered from severe diseases and comorbidities.

The risk of suffering dysplasia and cancer is higher in extended Crohn's colitis patients > 45[60]. However there is an increased incidence of these complications related to disease duration (increased risk among patients with disease duration longer than 20 years). Therefore, older and long-evolution patients should be under colonoscopic surveillance, however, only being of advanced age when an IBD outcome occurs is not enough to maintain different colonoscopic surveillance compared to naïve younger patients.

Little is known about effects of age on colonoscopy risks. In a large retrospective study of safety, feasibility, and tolerability of ileonoscopy in IBD patients[61], few severe complications where detected (0.3%-0.8%) and none of them were related to the advanced age of patients or disease activity.

CONCLUSION

The main messages regarding IBD in the elderly are summarized in Table 2. The prevalence of IBD in patients aged > 60 years is difficult to determine, but accounts for 10%-15% of cases of the disease. Diagnosis may be difficult because there are a number of clinical conditions that may mimic IBD, particularly ischemic colitis or colitis associated with diverticular disease. Diagnostic methods are the same as for other age groups. The clinical pattern in UC is proctitis and left-sided UC, while granulomatous colitis is more common in CD. Its disease course is similar to that of the younger groups. The treatment options are those used in younger patients, but a series of considerations related to potential pharmacological interactions and side effects of the drugs must be taken into account.

The safety profile of conventional immunomodulators and biological therapy is acceptable, but more data are required on the safety of use of these drugs in the elderly population. The overall response to treatment is similar in the different patient age groups, but elderly patients have fewer recurrences. The number of hospitalizations in patients > 65 years is greater than in younger groups, accounting for 25% of all admissions for IBD. Mortality is similar in UC and slightly higher in CD, but significantly increased in hospitalized patients. Failure of medical treatment continues to be the most common indication for surgery in patients aged > 60 years. Age is not considered a contraindication for performing restorative proctocolectomy with an ileal pouch-anal anastomosis.

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