Retrospective analysis of old-age colitis in the Dutch inflammatory bowel disease population

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Abstract

AIM: To describe the characteristics of Dutch patients with chronic inflammatory bowel disease (IBD) first diagnosed above 60 years of age-a disease also known as old-age colitis (OAC) and to highlight a condition that has a similar appearance to IBD, namely segmental colitis associated with diverticular disease (SCAD).

METHODS: A retrospective longitudinal survey of patient demographic and clinical characteristics, disease characteristics, diagnostic methods, management and course of disease was performed. The median follow-up period was 10 years.

RESULTS: Of a total of 1100 IBD patients attending the Department of Gastroenterology, 59 (5%) [median age 82 years (range 64-101); 25 male (42%)] were identified. These patients were diagnosed with ulcerative colitis (n = 37, 61%), Crohn's disease (n = 14, 24%), and indeterminate colitis (n = 8, 15%). Remission was induced in 40 (68%) patients within a median interval of 6 mo (range 1-21) and immunosuppressive therapy was well tolerated. Histological evaluation based on many biopsy samples and the course of the disease led to other diagnosis, namely SCAD instead of IBD in five (8%) patients.

CONCLUSION: OAC is not an infrequent problem for the gastroenterologist, and should be considered in the evaluation of older patients with clinical features suggestive of IBD. Extra awareness and extensive biopsy sampling are required in order to avoid an erroneous diagnosis purely based on histological mimicry of changes seen in SCAD, when diagnosing IBD in the presence of diverticulosis coli.

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INTRODUCTION

Inflammatory bowel disease (IBD), a lifelong uncontrolled inflammation of the intestinal mucosa, is broadly subdivided into ulcerative colitis, Crohn's disease, and in 10%-15% of patients, indeterminate or unclassified colitis, when a definitive diagnosis of ulcerative colitis or Crohn's disease cannot be made at colonoscopy, colon biopsy or colectomy[1,2].

The pathogenesis of IBD remains obscure. While it is clear that there are genetic, environmental, and immunological factors involved in the pathogenesis of IBD, the exact contribution of each and the sequence of events that culminates in clinically apparent IBD remains the subject of intense investigation.

Although IBD may occur at any age, the peak age of onset is 15-30 years old and approximately 10% of cases occur in individuals < 18 years old[3]. Old-age colitis (OAC) refers to patients older than 60 years, who are affected by a broad group of colonic diseases, such as infection, carcinoma, drug-induced disease, vasculitis, microscopic colitis, ischemic colitis, and IBD. Diagnosis of IBD in older patients may be difficult because it can easily be confused

with other forms of colitis commonly occuring at this age.

Earlier reports have indicated that both ulcerative colitis and Crohn's disease have a bimodal age distribution, with a second, smaller peak incidence occurring in individuals aged 50-70 years[4-7]. Two recent studies have shown that 21%-23% of ulcerative colitis occurs after the age of 50 years and 5% after 70 years[8,9]. This age group comprises around 12% (range 8%-20%) and 16% (range 7%-26%) of all newly diagnosed patients with ulcerative colitis and Crohn's disease, respectively[10].

An additional group of disorders called segmental colitis associated with diverticular disease (SCAD) has been found to masquerade as IBD on both a clinical and histological basis[11], since colonic diverticula, most often involving the sigmoid colon, commonly affect middle-aged and elderly individuals[12,13].

In this retrospective cohort, we attempted to differentiate the broad nomer OAC and to describe the characteristics of Dutch IBD patients older than 60 years. In addition, we wanted to highlight one of the conditions that is similar to IBD, namely SCAD, since an overlap of IBD and diverticular disease has long been recognized and is not infrequent in clinical practice[14].

MATERIALS AND METHODS

An IBD database review of more than 1100 patients, covering the years 1990 to the current time, provided 64 cases with OAC. The diagnosis of IBD was determined according to conventional endoscopic, radiological and histological criteria[15-17]. Medical records of each patient in this study were reviewed for the following information: sex, age, diagnosis, duration of disease, presenting symptoms, medications (including non-steroid anti-inflammatory drugs), anatomic location of disease, coexistence of diverticulosis, extraintestinal manifestations, laboratory results, radiological results, histopathological examinations, previous medical and surgical treatment strategies, remission rate and development of refractory disease, postoperative morbidity and mortality, overall outcome, and development of malignancy. Dedicated gastroenterological pathologists revised histological specimens from all subjects. Extraintestinal manifestations included erythema nodosum, pyoderma gangrenosum, peripheral arthritis, sacroiliitis/spondylitis, and episcleritis or uveitis. Refractory disease was defined as patients who were not adequately controlled with conventional therapy or immunosuppressive agents, or who required surgical intervention[18]. The diagnosis of colonic diverticular disease was established by colonoscopy, barium enema, or both. SCAD was considered when colitis was restricted to a diverticular segment of the left colon (excluding the rectum); the rectum and proximal colon were endoscopically and histologically normal; and when there was no recurrence of segmental colitis following surgical resection of the affected segment[11].

Statistical analysis

Descriptive analysis was performed and continuous data

| Table 1 General characteristic of patients with OAC	
Characteristic	**Total (*n* = 59)**
Age, median (range, yr)	82 (64-101)
Men, *n* (%)	25 (42)
Body mass index, median (range)	21 (17-29)
Patient subsets, *n* (%)	
Ulcerative colitis	37 (63)
Crohn's disease	14 (24)
Indeterminate colitis	8 (13)
Presenting symptoms, *n* (%)	
Rectal bleeding	35 (65)
Diarrhea	27 (50)
Abdominal pain	23 (42)
Weight loss	18 (33)
Constipation	7 (13)
Fever	5 (9)
Extra-intestinal symptoms, *n* (%)	9 (17)
NSAIDs, *n* (%)	13 (22)
Diverticulosis coli, *n* (%)	36 (61)
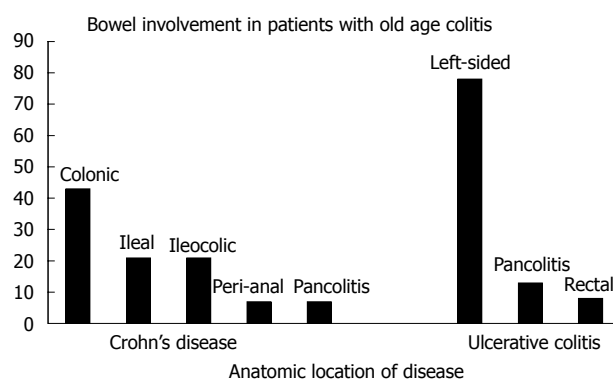
Figure 1 Bowel segment involvement in OAC.

were expressed as the median (range) and categorical data as numbers (percentage). Differences in erythrocyte sedimentation rate, serum albumin and hemoglobin were compared by using one way analysis (ANOVA). $P \leqslant 0.05$ was considered statistically significant. Sensitivity and predictive values of radiographic examinations were calculated by using 2×2 tables when the diagnosis was based on endoscopic and histological results. Statistical analysis was performed using the Statistical Software Package version 11.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients and disease characteristics

A total of 64 patients with OAC were identified. Five patients were excluded because the required histopathological studies were not available, and the remaining 59 patients were included in the analysis. Table 1 summarizes the general and disease-related characteristics and Figure 1 illustrates the bowel involvement in patients with Crohn's disease and ulcerative colitis. Colonic involvement was the rule in all eight patients with indeterminate colitis. Seven patients, including one with indeterminate colitis presented with pancolitis, and one patient had fistulous Crohn's disease. Extra-intestinal
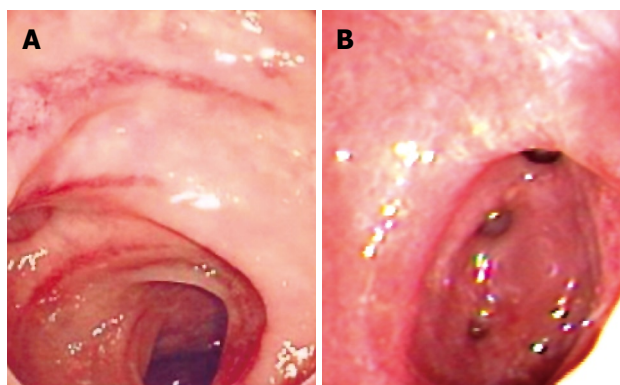
Figure 2 Endoscopic images showing signs of mucosal inflammation of sigmoid segment affected by diverticulosis coli, the inflammatory signs are stressed along the crests of the colonic folds in (**A**), and diffusely spread in (**B**).

manifestations included peripheral arthritis ($n = 5$), uveitis ($n = 2$) axial spondylitis ($n = 1$), and erythema nodosum ($n = 1$).

High erythrocyte sedimentation rate was found in 41 (69%) patients at presentation, exceeding in frequency decreased serum albumin or anemia (30% and 29%, respectively, $P < 0.001$). A total of 51 radiographic examinations were performed including barium enema ($n = 36$), small bowel follow-through ($n = 8$), and abdominal computerized tomography ($n = 7$), and depicted features suggestive of IBD in 17 (29%) patients (sensitivity 0.36 and PPV 0.79). An average of five (range 3-17) biopsies were obtained from separate segments of the colon and usually from affected and normally appearing mucosa on each endoscopical examination. Histology of surgically removed bowel segments was further evaluated in eight patients.

Infiltration of inflammatory cells was confined to the mucosa in the majority of patients [35 (95%) patients with ulcerative colitis, 10 (71%) with Crohn's disease, and seven (87%) with indeterminate colitis], and extended from the mucosa with reactive involvement of muscularis propria in the remaining patients. The inflammatory infiltrate was transmural in one patient with Crohn's disease. Crypt abscesses were identified in 26 (70%) patients with ulcerative colitis, four (29%) with Crohn's disease, and four (50%) with indeterminate colitis. Granulomas on the other hand, were recognized in three (8%) patients with ulcerative colitis, five (36%) with Crohn's disease, and four (50%) with indeterminate colitis.

Management and course of the disease

Mesalazine preparations, corticosteroids and azathioprine were administered to either induce or maintain remission in a total of 43 (73%), 23 (40%) and seven (12%) patients, respectively. No marked side effects were reported during a median follow-up period of 10 years (range 1-14). Remission was induced in 27 (73%), seven (50%) and six (75%) patients with ulcerative colitis, Crohn's disease and indeterminate colitis, respectively, within a median interval of 6 mo (range 1-21).

Eighteen (30%) patients were considered to

have refractory disease that necessitated surgical intervention, such as sigmoid resection, partial colectomy, pancolectomy, or ileal or ileocecal resection. However, postoperative recurrence was documented in two patients with Crohn's disease and postoperative morbidity and mortality was 66% and 6%, respectively. Two patients died due to terminal cholangiocarcinoma, one patient postoperatively (*Klebsiella pneumonia* sepsis), and three patients due to causes unrelated to IBD, with an overall mortality of 10%.

SCAD

Diverticulosis coli was present in 61% of patients with OAC. Five (8%) patients showed features that were suggestive of a diagnosis of SCAD. All five had endoscopic as well as histopathological features of colitis that affected the sigmoid colon, with sparing of the rectum and proximal colon. Endoscopic examinations showed either a circumferencial localization of erythema, granularity and friability, and sparing of the ostia, as shown in Figure 2A, or diffuse periosteal distribution of erythema, as shown in Figure 2B. Two patients underwent surgery and remained in remission without maintenance treatment. The other three patients were treated initially with a course of mesalazine preparations and were further maintained in remission by increasing daily fluid intake and using fiber-rich laxative preparations. These patients were retrospectively considered to have SCAD and not IBD as initially diagnosed.

DISCUSSION

This retrospective cohort study showed that 5% of IBD patients who attended our referral center were aged > 60 years old, and could be categorized as having OAC. On the other hand, 8% of patients with OAC have retrospectively non-IBD colitis that the so-called OAC implicates a broader diagnosis than IBD.

With respect to the predominance of ulcerative colitis, anatomic location in Crohn's disease, presenting symptoms, management, and postoperative morbidity and mortality, our findings were in agreement with earlier observations[10,19-21]. Unlike our findings, higher incidence rates of IBD in older patients and higher frequency rates of isolated proctitis within the ulcerative colitis subgroup have been reported[22-24]. The difference in these rates is very likely related to the retrospective nature of the studies. Noticeably, two patients developed cholangiocarcinoma and none developed colorectal carcinoma during the follow-up period. The available data disallowed further disclosure of underlying sclerosing cholangitis. The use of immunosuppressive agents in this older population appears to warrant broadened application, even if there is little objective data on which to base this practice[25]. The use of infliximab as an anti-inflammatory treatment in patients with IBD has been reported to be safe, including in those aged > 60 years old[26]. However, there appears to be a significant risk of deleterious and fatal adverse events when infliximab is used in older patients[27]. More

safety data about the use of biological agents in older populations are needed, especially when more new agents with proven efficacy are evolving.

Some attribute one-third of the small incidence peak of IBD in this age group to ischemia[28]. However, the chronic course of the disease and the emergence of refractory colitis made the diagnosis of ischemic colitis unlikely in our study, along with the histological findings that were also not supportive of a diagnosis of ischemic colitis.

A recognized pitfall in clinical practice appeared in this series; misdiagnosing SCAD as IBD in 8% of patients[29-33]. SCAD has long been recognized as an example of the overlap of IBD and diverticular disease[14,16,29,30]. The pathogenesis of this apparently distinct form of colitis is unclear[14].

Factors such as age and the high predilection of Crohn's disease for distal localization in older patients contribute to the simultaneous occurrence of both disorders in this population[34]. Differentiating between IBD and SCAD imposes a challenging task to the clinician as well as the pathologist. Clinical evaluation, laboratory tests, radiological results and endoscopic examinations (especially in diffuse type), in addition to histological studies, may be misleading. Sometimes even intestinal resection cannot provide the clinician with a definitive diagnosis. Luminal mucosal inflammation, although unusual, may occur in diverticular disease due to redundancy and mucosal prolapse[35]. When the luminal inflammation appears in what is called crescentic fold disease, a diagnosis of SCAD seems more probable[36]. A diagnosis of SCAD becomes more difficult when the inflammation affects a colon segment diffusely. The histology of SCAD may closely mimic ulcerative colitis and the hallmarks of Crohn's disease[16,37]. To complicate the issue, many cases of SCAD seem to respond post aut propter favorably to treatment with mesalazine preparations similar to that given for IBD[30]. That is why a definitive diagnosis may remain obscure for a long time, and only the course of the disease may bring to light the underlying nature of the disorder. Newly emerging instruments in the diagnostic panel such as serological markers[38-40], advanced radiological examinations such as contrast-enhanced magnetic resonance imaging[41], wireless capsule video endoscopy[42], and double-balloon small enteroscopy[43] may facilitate an early and correct definite diagnosis. These diagnostic modalities appear to be valuable for patients who have indeterminate colitis or who are failing medical therapy. The multiple harvest of biopsy specimens at each endoscopic session seems to be helpful in differentiating colitis in segmental fashion, especially SCAD that can be cured by limited resection of affected segments, although this conclusion is based on limited data from this retrospective study.

In summary, OAC is not an infrequent problem for the gastroenterologist and should be considered in the evaluation of older patients with clinical features suggestive of IBD. This entity is broader than IBD alone and therefore more challenging. Extra awareness is required in order to avoid an erroneous diagnosis purely based on histological mimicry of changes seen in SCAD when diagnosing IBD in the presence of diverticulosis coli, and taking multiple biopsies from each part of the colon is recommended.

COMMENTS

Background
Inflammatory bowel disease (IBD) is a lifelong uncontrolled inflammation of the intestinal mucosa that mainly affects the young age group but also older individuals.

Research frontiers
Diagnosis of IBD in older patients may be difficult because it can easily be confused with other forms of colitis commonly occuring in this age group, such as segmental colitis associated with diverticular disease (SCAD).

Applications
Old-age colitis (OAC) is not an infrequent problem for the gastroenterologist and should be considered in the evaluation of older patients with clinical features suggestive of IBD. Extra awareness is required in order to avoid an erroneous diagnosis.

Terminology
OAC refers to patients older than 60 years affected by a broad group of colonic diseases, such as infection, carcinoma, drug-induced disease, vasculitis, microscopic colitis, ischemic colitis, and IBD. SCAD has been found to masquerade as IBD on both a clinical and histological basis.

Peer review
The authors described the characteristics of Dutch patients with chronic IBD with a first diagnosis above 60 years of age, also known as OAC, and highlighted one of the conditions that has the appearance of IBD, namely SCAD. This is an interesting study. The authors concluded that OAC is not an infrequent problem for the gastroenterologist and should be considered in the evaluation of older patients with clinical features suggestive of IBD.

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