

## R E V I E W

## Amyloidosis and inflammatory bowel disease: fact or myth?

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**Summary.** Inflammatory Bowel Disease (IBD), which includes both Crohn's Disease (CD) and Ulcerative Colitis (UC), is a chronic idiopathic inflammatory disorder affecting the gastrointestinal tract. Extraintestinal manifestations (EIMs) are common in patients with IBD, and occur in 6%-47% of patients with CD or UC. EIMs can involve organs other than the gastrointestinal tract such as skin, eyes, joints, biliary tract, and kidneys. Renal and urinary involvement particularly occurs in 4-23% of patients with IBD. Among the renal complications of IBD, secondary amyloidosis (AA-type, AAA) is a rare but serious complication. Renal amyloidosis has been proven to be the most common lethal manifestation of IBD-associated amyloidosis, since renal involvement rapidly leads to end-stage renal failure. A few studies suggest that AAA is more prevalent in CD than in UC, mainly occurring in male patients with an extensive, long-lasting, and penetrating disease pattern. The therapeutic approaches of IBD-associated AAA are based both on control of the chronic inflammatory process that causes the production and storage of serum amyloid A (SAA), which is a precursor of the amyloid, as well as on destabilizing amyloid fibrils so that they can no longer maintain their  $\beta$ -pleated sheet configuration; however, in patients with end-stage renal disease, the only therapeutic options still available are hemodialysis and renal transplantation. Whether effective treatment exists for AAA remains controversial.

**Key words:** amyloidosis, crohn's disease, ulcerative colitis, inflammatory bowel disease (IBD)

### Introduction

Inflammatory Bowel Disease (IBD), which includes both Crohn's Disease (CD) and Ulcerative Colitis (UC), is a chronic idiopathic inflammatory disorder affecting the gastrointestinal tract. (1). CD and UC af-

fect more than 1 million people in the United States, with thousands of new diagnoses annually (2,3). The natural history of CD and UC is characterized by repeated episodes of inflammation and ulceration of the bowel. This results in complications implying a worse quality of life and significant healthcare costs, due to

hospitalization, surgery and an escalation of therapy (4-7). Extraintestinal manifestations (EIMs) are common in patients with IBD, and occur in 6-47% of patients with CD or UC (8). EIMs can involve organs other than the gastrointestinal tract such as skin, eyes, joints, biliary tract, and kidneys (9). Renal and urinary involvement particularly occurs in 4-23% of patients with IBD (10). Several factors may be responsible for renal involvement.

Primary systemic affection by the disease itself or secondary complications such as chronic inflammation, malnutrition, and side effects of therapeutic agents may trigger the emergence of renal dysfunction. In general, renal manifestations, like other EIMs, tend to follow the clinical course of IBD and may have a high impact on quality of life, morbidity, and even mortality of patients (9).

Among the renal complications of IBD, secondary amyloidosis (AA-type, AAA) is a rare but serious complication. Renal amyloidosis has been proven to be the most common lethal manifestation of IBD-associated amyloidosis, since renal involvement rapidly leads to end-stage renal failure (11).

In this article the authors review the available data on secondary amyloidosis and IBD, focusing on prevalence, risk factors, clinical presentation and therapeutic measures.

### **Prevalence of amyloidosis in inflammatory bowel disease**

Amyloidosis is a term applied to a heterogeneous group of rare diseases characterized by extracellular deposition of amyloid, causing target-organ dysfunction and a wide range of clinical symptoms (12). All forms of amyloidosis are characterized by the deposition of extracellular fibrils in various tissues.

These fibrils are the result of the misfolding of a protein from its normal  $\alpha$ -helical configuration into a  $\beta$ -pleated sheet. The structure of the  $\beta$ -pleated sheet allows the binding of Congo red stain, which emits a characteristic apple-green birefringence under polarized light.

The symptoms of the disease depend on the organ involved, and include nephritic syndrome, hepa-

tosplenomegaly, congestive heart failure, carpal tunnel syndrome, gastrointestinal (GI) symptoms and macroglossia (13). Amyloidosis is clinically classified into several types depending on the precursor of the amyloid fibril. The disease involves amyloid fibrils formed *in vivo* by 27 different types of protein (14). In immunoglobulin-light-chain-related (AL) amyloidosis (also called primary amyloidosis), an underlying monoclonal plasma-cell disorder produces the constituents of the deposits, which are the variable regions of the immunoglobulin light chains. In AAA, by contrast, the amyloidogenic precursor is a normal acute-phase reactant called serum amyloid A (SAA), which is produced as the result of chronic infection or inflammation. In this connection, AAA is the representative systemic condition that develops in patients with chronic inflammatory diseases such as rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, IBD, familial periodic fever syndrome, and chronic infections (15-18). Epidemiological data for AAA, extrapolated from autopsy records in Western nations, have indicated that the prevalence varies from about 0.5% to 0.86% according to environmental risk factors and geographical clustering (19,20).

Little is known about the prevalence of AAA in patients with IBD.

In the first study, performed by Greenstein and coworkers (18), the authors evaluated the prevalence of AAA in 3050 patients with IBD (1709 with CD, and 1341 with UC), enrolled at the Mount Sinai Hospital, between 1960 and 1985. The study showed that 0.9% (n=15) of CD patients and 0.07% (n=1) of UC patients were affected by AA Amyloidosis (in total, 16 patients).

Eleven of the patients with CD who had amyloidosis also had ileocolitis, 2 colitis, and 2 ileitis; these figures represent a frequency within each group of 1.6%, 0.6%, and 0.3%, respectively. AAA was thus associated 4.4 times more often with CD of the colon than with pure small bowel disease. In this study the authors added to this group of 15 patients the 5 cases of CD that were originally reported by Werther and coworkers in 1960 (21), plus another 4 (2 with UC and 2 with CD) who have been seen since 1985, making a total of 25 patients in this series (22 with CD and 3 with UC). There was a striking male preponderance (16 of 22) among patients with CD, although 2 of the

3 patients with UC were females. AAA was diagnosed at a mean age of 40 years, about 15 years after the onset of CD. Nephrotic syndrome developed in 15 patients with CD and was accompanied by renal failure, the major contributor to mortality, in 10 of the 13 patients who died. AAA may be associated with suppurative or other EIMs of IBD.

Wester and coworkers (22), successively described 18 patients with IBD and AAA, with special emphasis on clinicopathological features and site relationships. Fifteen of the 18 patients had CD, 1 had UC, 1 had UC preceding CD, and 1 had indeterminate colitis. There was a male preponderance of 13:5 = 2.6. Five of the patients had AAA at the time of diagnosis of IBD. Median time from diagnosis of IBD to AAA was 4 years, whereas AAA was diagnosed within 5 years of onset of IBD in 11 patients. Thirteen of the patients had suppurative complications, and 12 had extraintestinal manifestations. Interestingly, ten patients had been treated by renal transplantation. After 15 years of follow-up, the survival rate was 60%. These results highlighted the previous impression of an approximately 3-fold increased preponderance in males, with at least a 10-fold increased frequency in CD compared with UC, and with a possible relationship to suppurative complications and extraintestinal manifestations, as well as an increased risk of having bowel resection.

More recently, Serra and coworkers (23) evaluated the prevalence of AAA in a large IBD cohort at a referral centre, describing its clinical characteristics and outcome. In this study patients diagnosed with AAA were identified among 1006 IBD patients included in the IBD database of the centre, and among a total of 1006 IBD patients, 5 cases of amyloidosis were identified, all of them with CD, resulting in a prevalence of 0.5% for IBD and 1% for CD. With regard to the outcome of the disease, two patients died after developing renal failure, but interestingly two patients were treated with anti-TNF agents, showing a clinical improvement of their AAA.

Furthermore, another Spanish study enrolling 4018 IBD patients found that 17 patients developed AAA, with a prevalence of 0.63% in CD, 1% in indeterminate colitis, and 0.06% in UC (24).

In summary, the available data from the literature show that the prevalence of AAA is about 0.5%

in IBD patients (with the sole exception of Wester's cohort). In most cases, AAA involves CD patients, whose prevalence accounts for about 0.7-1%.

However, the aforementioned studies present several methodological limitations: firstly, all the studies mentioned are retrospective; furthermore, all the available studies are based on selected cohorts from tertiary referral centers (thus showing a selection bias). Only Lowdell and coworkers (25) prospectively evaluated the incidence of AAA in a cohort of IBD patients (77 with CD, 97 with UC), through rectal biopsy and the study of renal function, but no new diagnosis of AAA was reported.

### Clinical presentation

Historically, the diagnosis of AAA in IBD patients has mainly been autptic (26), as reported firstly by Werther and coworkers (21). However, since the early 1980s the diagnosis of AAA has also been reported in living patients with active IBD (18,22-24).

With regard to the clinical presentation of AAA, it depends on the amount of amyloid deposits in the affected organs. At the beginning of the disease, the symptoms are unspecific, with the onset of weakness, weight loss, headache or syncope; however, in the advanced stages of the disease, organ-specific symptoms occur. The most common clinical manifestation of AAA in IBD patients is renal disease, often appearing as nephritic proteinuria; however, in the end-stage disease glomerular involvement may cause the onset of renal failure and uremia. A particular feature of renal AAA is maintenance of the regular size of the kidneys, together with the occurrence of hypotension instead of more common hypertension. In the aforementioned studies (18, 22-24) the occurrence of proteinuria and/or renal failure was reported in about 86% of the patients.

GI involvement represents the second most common clinical presentation of AAA in IBD patients, in order of frequency, as reported in the aforementioned studies. However, these studies show that only about 6% of IBD patients presented with gastrointestinal complaints, and these patients could be totally asymptomatic or present with severe malabsorption (27).

**Table 1.** Clinical studies evaluating prevalence and features related to IBD-associated amyloidosis

Study (authors, reference)	Patients (n)	Male/Female ratio (%)	Cases of Amyloidosis (n) and prevalence (%)	Localization (%)	Median follow-up (Years)	Abdominal complication (%)	Extraintestinal (%)
Greenstein and coworkers (18)	3050	73% vs. 27%	16 (0,05%); 15 with CD; 1 with UC	64% ileocolic (14% with upper CD)	15	68%	54%
Wester and coworkers (22)	500	81% vs. 19%	18 (3%); 16 with CD; 1 with UC; 1 with IC	62% ileocólica (31% with upper CD)	4	69%	66%
Serra and coworkers (23)	1006	80% vs. 20%	5 (0,5%), all with CD	100% ileocolic	15	80%	60%
Pérez – Martínez and coworkers (24)	4018	70% vs. 30%	17 (0,4%); 15 with CD, 1 with UC, 1 with IC	60% (13% with upper CD)	9	53%	47%

*Abbreviations: IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's Disease; IC: indeterminate colitis*

Myocardial involvement, although rare, represents, in order of frequency, the third most common clinical presentation of AAA in IBD patients, thus provoking the insidious onset of congestive heart failure, conduction disorders and arrhythmias (27).

Macroglossia is usually infrequent in AAA in IBD patients, because it is a peculiar clinical manifestation of primary amyloidosis. Furthermore, the liver, spleen and thyroid may also be involved in AAA in IBD patients (27).

The suspicious of the onset of AAA in IBD patients should be raised in all patients presenting with proteinuria and renal failure, or in patients with abnormal malabsorption not attributable to underlying IBD. Diagnostic confirmation of AAA should be obtained through demonstration of amyloid deposits in the affected tissues. Liver and renal biopsy presents present? an optimal diagnostic yield, but may lead to several complications. Therefore the diagnostic choice of biopsy of abdominal fat (sensitivity 60-80%) or rectal mucosa (sensitivity 50-70%) (28) seems to be more reliable; however, in the latter cases, if the samples obtained present a negative result, biopsy should be performed in the target organ.

### **Risk factors for the development of AA Amyloidosis in IBD patients**

On the basis of the reported data (18,22-24), CD appears to be more frequently associated with AAA than UC. In this connection, considering that AAA arises from storage of an acute phase reactant like serum amyloid A (SAA), it seems reasonable to think that this disease will develop in patients with long-standing disease and with poor control of the inflammation. This phenomenon seems to be more frequent in CD, since the clinical course of CD appears to be more indolent and insidious, as patients with severe endoscopic lesions are often asymptomatic, whereas UC usually presents with severe acute flares, although the reason of this discrepancy in the incidence of AA Amyloidosis in both the disease is not yet clear. Furthermore, another possible explanation of this discrepancy may be the fact that severe UC often resolves with proctocolectomy, whereas surgery often not eliminate the inflammatory process occurring in CD (27).

Further specific features of AAA in IBD patients are male preponderance, with a sex ratio of 3:1, and the presence of an extensive underlying IBD (18,22-24).

With specific regard to CD-associated AAA, more than two-thirds of the reported cases of CD-associated AAA presented with both colonic (and often pancolonic) and ileocolonic disease, and interestingly with an upper GI involvement in almost 15% of cases. Furthermore, the pattern of the CD associated-AAA was prevalently a penetrating one, with the concomitant occurrence of intra-abdominal or perianal abscesses and/or fistulae in 70-80% of patients (27).

The occurrence of further EIMs during the course of the disease in IBD patients with AAA was slightly higher than usual: onset of EIMs in this subset of patients was about 50-60%.

Finally, AAA usually appears in the context of a longstanding IBD; indeed, the onset of IBD-associated AAA was found to occur almost ten years after the onset of underlying IBD, and this phenomenon could be related to the longstanding inflammatory process of the disease (27).

Interestingly, further inflammatory chronic diseases associated with AAA may coexist with AAA-associated IBD, like rheumatoid arthritis, juvenile idiopathic arthritis, familial periodic fever syndrome, etc. Therefore it is an important diagnostic challenge to exclude the occurrence of these diseases when AAA-associated IBD is suspected (18,22,23).

In summary, AAA is more frequent in male CD patients, with longstanding, penetrating and extensive disease, often associated with EIM, although clear evidences about this AAA-associated risk factor are not yet available. However, the emerging concept of mucosal healing as a therapeutic target in IBD patients, using immunosuppressive and biological (e.g. anti-Tumor Necrosis Factor alpha, anti-TNF) drugs, could lead to a dramatic change in the prevalence and prognosis of IBD complications, such as AAA (27).

## Prognosis

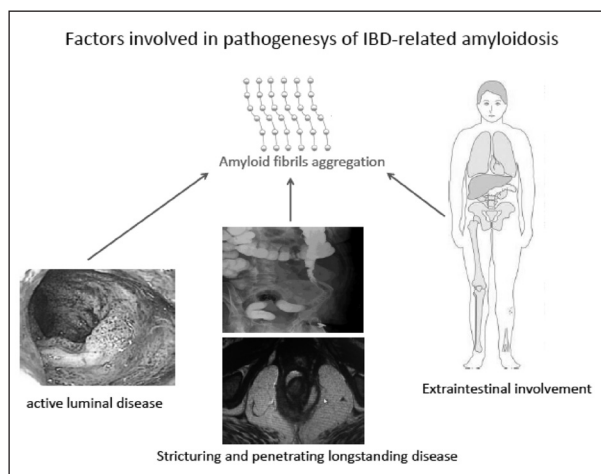
As previously highlighted, during the last few decades it has been observed that prognosis of IBD-associated AAA has dramatically changed, considering that AAA, initially mainly reported through autoptic diagnosis, successively became a real nosographic entity in IBD patients (27).

This could be due to the current optimal management (both medical and surgical) of IBD, the high index of clinical suspicion of AAA since the first epidemiological studies on AAA (22), and increased attention to knowledge of the natural history of IBD, with particular attention to the nutritional status of IBD patients, early diagnosis and prevention of IBD-associated complication and better awareness of IBD-associated drug adverse events (27).

Interestingly, a study performed by Weterman and coworkers showed that AAA has disappeared as a leading cause of mortality in CD patients; this could be due to the better medical and surgical management of these patients (29).

The best related prognostic factor of survival in IBD-associated AAA proved to be serum creatinine, as an expression of the level of renal failure (30). In the case of end-stage renal failure related to AAA, renal transplantation may be considered the best therapeutic option, thus dramatically reducing the mortality rate (31). However, patients with IBD-associated AAA present a higher mortality rate than patients without AAA, and severe infections and hemorrhage are reported to be the most frequent causes of mortality after end-stage renal failure (18,29,32).

With regard to the survival rate in this subset of patients, few data are available. It has been estimated that the median survival rates proves to be approximately 89% at five years, and 60% at fifteen years of follow-up (22).



**Figure 1.** Etiologic disease-related factors involved in pathogenesis of IBD-associated amyloidosis

## Therapy

The therapeutic approach of IBD-associated AAA is primarily based on control of the inflammatory process that causes production and storage of the SAA, which is a precursor of amyloid (27).

In this context, the role of surgery appears controversial. Even if clinical improvement of the disease is observed in some patients after bowel resection, the fact that AAA has been diagnosed after surgery does mean that the latter by itself is decisive for prevention or resolution of AAA (33-36). Furthermore, several authors have observed a higher mortality of IBD patients with AAA after surgery, without a clinical improvement in AAA, considering that such patients present a higher surgical risk, due to the occurrence of renal failure, hemorrhage or severe infections (18,37). Based on these considerations, it seems reasonable to consider the surgical option as a secondary therapeutic option in selected cases, e.g. after the failure of medical therapies, or in the case of penetrating and stricturing disease (18,25,36-38).

On the other hand, the use of drugs acting directly against the process of development of amyloidosis has been shown to be helpful. In this context, colchicine has proved to be the most effective drugs. In this connection, the effectiveness of this drug in other types of secondary amyloidosis (for example, amyloidosis associated with familial Mediterranean fever) has been demonstrated by a reduction in proteinuria, normalization of renal function, and improvement in the survival rate of affected patients (38-41).

We recommend the early use of colchicine, before the onset of renal failure. Another drug commonly used in AAA is dimethylsulfoxide, also used in other types of secondary amyloidosis; it has appeared to be helpful in maintenance of normalization of the serum creatinine and in reduction of proteinuria, after one year of treatment (42).

More recently, anti-TNF alpha drugs have also proved effective in the treatment of AAA, through reduction in proteinuria and normalization of the renal function. Several studies have shown the capacity of this drug to reduce SAA levels, probably because production and storage of SAA are enhanced by pro-inflammatory cytokines, such as TNF-alpha; therefore,

considering the efficacy of these drugs in the treatment of both IBD and AAA, anti-TNF alpha agents may play a pivotal role in elective treatment of IBD-associated AAA. Encouraging results regarding the use of anti-TNF alpha agents in AAA treatment associated with chronic inflammatory disease come from several studies carried out in the setting of rheumatic disease (43-56). Interestingly, in a recent report, tocilizumab was found to be effective in amyloidosis-associated kidney disease secondary to IBD (57).

Further therapeutic approaches target amyloid deposits directly, by destabilizing amyloid fibrils so that they can no longer maintain their  $\beta$ -pleated sheet configuration. Studies on compounds that bind serum amyloid P component (SAP), an essential constituent of all forms of amyloid deposits that constitute 5 to 10% of their weight, suggest the possibility not only of depleting SAP from the fibril but also of causing regression of amyloid deposits (58,59)

Dember and colleagues followed a similar approach, aiming to destabilize the glycosaminoglycan backbone of amyloid deposits. Eprodisate binds to glycosaminoglycan-binding sites on amyloid fibrils and in principle can destabilize them in tissues, thereby causing regression of amyloidosis; in addition, it has the potential to prevent the formation of new amyloid deposits.

The risk of worsening renal function and the rate of decline in creatinine clearance were shown to be lower in patients who received eprodisate than in those who received placebos. However, no effect was seen on the progression to end-stage renal disease or death (60).

Finally, in patients with end-stage renal disease, the only therapeutic options still available are hemodialysis and renal transplantation (27).

## Conclusion and recommendations

AAA is a clinical challenge for clinicians managing IBD patients. A few studies suggest that AAA is more prevalent in CD than in UC, mainly occurring in male patients with an extensive, long-lasting, and penetrating disease pattern. The therapeutic approaches of IBD-associated AAA are both based on control of the

chronic inflammatory process that causes production and storage of SAA, which is a precursor of amyloid, as well as on destabilizing amyloid fibrils so that they can no longer maintain their  $\beta$ -pleated sheet configuration; however, in patients with end-stage renal disease, the only therapeutic options still available are hemodialysis and renal transplantation. Whether effective treatment exists for AAA remains controversial.

There are reports suggesting that AAA improves after surgical treatment, while other reports show significant morbidity and even mortality after surgery; colchicine and dimethylsulfoxide have been used, showing significant efficacy in reducing the rate of amyloid deposition by preventing the progression of the inflammatory process at the neutrophil level. More recent reports have suggested the efficacy of TNF inhibitors in treating CD-associated AAA; in particular, treatment of renal AAA with infliximab has shown improvement in renal function and proteinuria and a decrease in SAA levels. Although infliximab has proven its efficacy in the treatment of CD, its consecutive administration in CD-associated renal AAA cannot restore the previous damage, but targets the deterioration of further damage in the kidneys and the delay of renal injury (61). Finally, further studies could evaluate the role of eprodisate, which destabilizes the glycosaminoglycan backbone of amyloid deposits, in this subset of patients.

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