



Systemic amyloidosis in inflammatory bowel disease: Retrospective study on its prevalence, clinical presentation, and outcome

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Received 31 October 2009; received in revised form 13 November 2009; accepted 19 November 2009

KEYWORDS

Systemic amyloidosis;
IBD;
Crohn's disease

Abstract

Background: Systemic amyloidosis is a rare but life-threatening complication of inflammatory bowel disease (IBD), most cases being reported among Crohn's disease (CD) patients. The only two available retrospective studies showed a prevalence ranging from 0.9% to 3% among CD patients.

Aims: To evaluate the prevalence of secondary systemic amyloidosis in a large IBD cohort of a referral centre, and to describe its clinical characteristics and outcome.

Methods: Patients diagnosed with amyloidosis were identified among 1006 IBD patients included in the IBD database of our centre, and their medical records were carefully reviewed.

Results: 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. Two patients died after developing renal failure. Two patients were treated with anti-TNF agents, showing a clinical improvement of their amyloidosis.

Conclusions: Secondary amyloidosis occurs mainly in long-lasting, complicated, Crohn's disease and seems to be as prevalent among IBD patients as previously reported.

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1. Introduction

Amyloidosis is a clinical condition resulting from abnormal folding of human proteins, which precipitates as insoluble fibrillar polypeptide aggregates in the extracellular tissues, thereby interfering with their normal function. The beta-

sheet disposition of amyloid confers unique staining properties (such as the affinity for Congo red with resulting green birefringence) and a high resistance to denaturation. For the diagnosis of amyloidosis, the demonstration of this fibrillar deposit by a positive Congo red staining is mandatory. Amyloidosis is now considered as a heterogeneous group of diseases in which one out of more than 25 human proteins aggregates into these characteristic fibrils. Based on the biochemical nature of the protein itself, systemic amyloidosis had been historically classified as primary (AL) or secondary (AA). The commonest clinical manifestations are nephrotic syndrome, congestive heart failure, and peripheral neuropathy. AL-amyloidosis is usually considered as idiopathic or related to multiple myeloma, whereas AA-amyloidosis is associated to several chronic inflammatory conditions such as rheumatologic or intestinal diseases, familial Mediterranean fever, or chronic infectious diseases such as tuberculosis. In the latter, the so-called amyloid A protein derives from the acute phase reactant serum AA that increases in the course of inflammatory, infectious, or neoplastic disorders.^{1,2} Systemic amyloidosis among IBD patients is a rare but serious complication that may lead to death specially when renal failure occurs, and only two studies assessing its prevalence have been published to date.^{3,4} The aims of our study were to evaluate the prevalence of systemic amyloidosis in a large cohort of IBD patients, and to describe their clinical features and outcome.

2. Patients and methods

All patients diagnosed with systemic amyloidosis were identified from the IBD database of our centre. This database includes the clinical data of all IBD patients who ever attended our IBD unit from 1995 up to now. Medical records were carefully reviewed, and demographic, epidemiological and clinical data (regarding both IBD and amyloidosis) were recorded, with special attention to those related to persistent inflammatory activity (such as steroid-dependence, chronic fistulae, and abscesses), treatments, clinical presentation and outcome, and chronological relationship between the two diseases.

3. Results

Among a total of 1006 IBD patients (494 with CD, 486 with ulcerative colitis [UC], and 26 with indeterminate colitis), only 5 CD patients had been diagnosed with systemic amyloidosis. No cases of amyloidosis were identified among UC patients. Thus, the prevalence of systemic amyloidosis was 0.5% for IBD, and 1% for CD. A detailed description of each case is reported, and the main characteristics of the five cases are summarized in Table 1.

3.1. Case 1

A 65-year-old Caucasian man, active smoker, with a past history of chronic obstructive pulmonary disease and ankylosing spondylitis was referred for IBD control. He was diagnosed with ileal and pancolonic CD at the age of

51 years, and went into remission with systemic steroids followed by sulfasalazine as maintenance therapy. He remained in clinical remission for 5 years until he developed perianal disease, which required repeated surgical interventions. Two years later, the patient relapsed from his luminal disease along with worsening of his perianal disease. Because of steroid-refractoriness, the patient required proctocolectomy and a 30-cm resection of the terminal ileum, with definitive ileostomy. No maintenance therapy was prescribed. Within the next 17 years, the patient developed peri-ostomal abscesses and fistulae. Although treatment with azathioprine was attempted, it had to be discontinued because of secondary acute pancreatitis, starting mesalazine therapy. When referred to our centre, the patient was markedly disabled by the spondylitis, but he had no problems with the ileostomy. In addition, hypoalbuminemia with proteinuria of 1.5 g/24 h and microalbuminuria of 1 g/24 h were noticed, together with a rapid worsening in renal function (serum creatinine raised up to 3.4 mg/dL). Secondary amyloidosis was diagnosed by means of subcutaneous tissue aspiration biopsy. At the same time, a pulmonary mycetoma was also diagnosed. Finally, a long-lasting, mild, alteration of liver biology consisting of increased alkaline phosphatase and gamma-glutamyl transpeptidase with negative autoantibodies and a normal magnetic resonance cholangiography, was treated with ursodeoxycholic acid. The patient refused percutaneous liver biopsy as well as ileoscopy. Treatment with biological agents was rejected because of the advanced stage of his spondylitis and the occurrence of infectious complications as well. The patient died 2 years later because of community-acquired pneumonia and septic shock.

3.2. Case 2

A Caucasian male was diagnosed with ileocolonic CD at the age of 11 years. Despite an initial successful response to systemic steroids, he required ileal resection after a few months because of intestinal perforation. Six years later, a 30-cm ileal resection and right hemicolectomy were performed because of intestinal obstruction, followed by mesalazine maintenance treatment thereafter. When he was 21 years old, CD relapsed and perianal disease developed. Disease control was achieved with a new course of steroids together with oral antibiotics. Within the following 2 years, multiple episodes of intestinal occlusion occurred, and a new 24-cm intestinal resection (including the previous ileocolic anastomosis) was performed. Refractory, progressive, and disabling perianal disease led to unsuccessful attempted several therapies including cyclosporin, azathioprine, tacrolimus, hyperbaric oxygen, and infliximab.

Twelve years after CD diagnosis, while on tacrolimus treatment, the patient presented facial and leg oedema, with severe hypoalbuminemia (11 g/L) and proteinuria (10 g/L). A rectal biopsy was negative for Congo red staining, but amyloid deposit was found at renal biopsy. The subsequent clinical evolution was extremely poor: the patient had to be repeatedly hospitalised because of perianal abscesses, he developed bone marrow aplasia secondary to thiopurines, as well as adrenal insufficiency. Finally, a Hartmann colostomy was performed because of an episode

Table 1 Main clinical characteristics of patients.

	Case 1	Case 2	Case 3	Case 4	Case 5
IBD type	Crohn	Crohn	Crohn	Crohn	Crohn
Age at IBD dx	51	11	23	30	30
IBD location	Ileum, colon	Ileum, colon	Jejunum, ileum, colon	Ileum, colon	Ileum, colon
Intestinal stenosis	No	Yes	Yes	Yes	No
Enteric fistulae	Yes	No	No	Yes	Yes
Perianal disease	Yes	Yes	No	Yes	Yes
Extraintestinal manifestations	Ankylosing spondylitis	No	No	Erythema nodosum, iridocyclitis, polyarthralgia	Ankylosing spondylitis
IBD therapy	5-ASA, PDN, AZA	5-ASA, EN, PDN, AZA, CsA, Tacrolimus, IFX	5-ASA, PDN, AZA	EN, PDN, AZA, MTX, IFX, ADA	5-ASA, EN, PDN
IBD-related surgery	Proctocolectomy, ileal resection	Hemicolectomy, ileal resections, colostomy	No	Hemicolectomy, ileal resections	Hemicolectomy, ileal resection
Time from IBD to AA dx	24 years	12 years	4 years	20 years	14 years
Clinical presentation of AA	Proteinuria, hypoalbuminemia, renal function impairment	Proteinuria, hypoalbuminemia, renal function impairment	Nephrotic sd	Nephrotic sd	Renal function impairment
AA therapy	No	No (haemodialysis)	IFX + colchicine + enalapril	ADA	Colchicine (haemodialysis)
Follow-up after AA dx	2 years (death)	6 years (death)	15 years	3 years	9 years

IBD—inflammatory bowel disease; dx—diagnosis; AA—secondary systemic amyloidosis; 5-ASA—mesalazine; EN—enteral nutrition; AZA—azathioprine; PDN—prednisone; CsA—cyclosporin; IFX—infliximab; ADA—adalimumab.

of perianal sepsis. Although the patient developed postoperative progressive renal failure requiring definitive haemodialysis, perianal disease dramatically improved and, after some months, neither abscesses nor draining fistulae ever reappeared. The patient was then evaluated for a renal transplantation 3 years later; in view of the impossibility to maintain CD in remission with drug therapy, and the risk of cancer development in a long-term immunosuppressed young patient with an excluded rectum, it was decided to perform elective proctectomy with definitive colostomy before including the patient in the waiting list for transplantation. However, surgery was complicated by persistent intraoperative peritoneal and perineal bleeding, leading to multiorgan failure and the patient's death a few weeks later.

3.3. Case 3

A non-smoker man was diagnosed with CD involving sigmoid colon, ileum and jejunum, at the age of 23 years. Despite an initial response to steroids, metronidazole, and sulfasalazine, he developed steroid-dependency and azathioprine was introduced 2 years after diagnosis. Three years after thiopurine introduction, the patient presented with nephrotic syndrome, and a renal biopsy yielded a diagnosis of secondary amyloidosis. No therapy was added to azathioprine, which was discontinued 1 year later by the patient on his own decision. He moved to Chinese Medicine for the following 10 years, with no remarkable CD-related complications. At

the age of 41, he began with recurrent episodes of acute pericarditis with mild pericardial effusion at echocardiogram, and familial Mediterranean fever was diagnosed by clinical criteria together with the existence of the p.Lys695-Arg/p.K695R mutation. Low-dose colchicine and enalapril were then started. The patient also complained of long-lasting, recurrent, self-limited abdominal pain with increased stool frequency and mild increase of acute phase reactants. No CD-related active lesions were found at ileocolonoscopy but only mucosal scars in the sigmoid and ascending colon. However, both a barium meal and follow-through and magnetic resonance enterography disclosed extensive inflammatory involvement of the proximal ileum together with multiple short intestinal strictures in the jejunum. In addition, the patient persisted with ankle oedema, marked hypoalbuminemia (21 g/L) and proteinuria (6.19 g/24 hours), with normal serum creatinine values. While being evaluated, the patient presented an episode of acute, severe, abdominal pain and low-grade fever, without symptoms of intestinal obstruction that resolved in 48 h. Transabdominal ultrasonography demonstrated free peritoneal fluid. With the suspicion of an acute flare of familial Mediterranean fever in a patient with extensive, chronically active CD, and nephrotic syndrome secondary to AA-amyloidosis, treatment with enteral nutrition, azathioprine, colchicine at higher doses, and infliximab was started. This resulted in a dramatic and rapid improvement in his general well being, as well as an increase in patient's weight, reduction of oedema, and disappearance of the recurrent abdominal pain.

3.4. Case 4

A non-smoker woman was diagnosed with ileal and pancolonic CD at the age of 30 years. At disease onset, she also presented extraintestinal manifestations (polyarthralgia, erythema nodosum, and iridocyclitis). Five years later, azathioprine was introduced because of chronically active disease. Ileal resection together with right hemicolectomy had to be performed 6 years later because of ileal and colonic stenosis. Soon after surgery, an intraabdominal abscess led to the resection of the ileocolonic anastomosis and a jejunal loop. Azathioprine was maintained and the patient remained in remission for the following 10 years when she developed perianal disease and relapsed of her luminal disease involving the sigmoid colon and the neoterminal ileum. A sigmoidectomy was performed, and a duodenal-colic fistula was noticed intraoperatively. A complex duodenal-cutaneous fistula appeared postoperatively, with persistent output and recurrent abdominal right lower quadrant abscess that led to multiple hospital admissions, surgical drainages, and unsuccessful endoscopic therapeutic attempts.

One year later, ankle oedema developed and marked hypoalbuminemia (11 g/L) and proteinuria (5.6 g/24 h) were documented. Rectal biopsy was positive for Congo red staining. Combined therapy with infliximab and methotrexate was then started, with a significant improvement in proteinuria, and normalisation of serum albumin values and oedema. Nevertheless, the enterocutaneous fistula persisted and recurrent abdominal abscesses forced repeated hospitalisations. A jejunal feeding tube was then placed through a percutaneous endoscopic gastrostomy and biological therapy was changed to adalimumab. After 2 years of treatment, ileocolonoscopy did not find mucosal lesions, serum albumin remained within the normal range, and the patient did not require further hospital admissions despite persistent duodeno-cutaneous fistula by imaging techniques.

3.5. Case 5

A Caucasian non-smoker male was diagnosed with ileocolic CD at the age of 30 years. He presented a long-lasting past history of extraintestinal complications such as complicated nephrolithiasis that required even a transient nephrostomy because of obstructive uropathy, ankylosing spondylitis and chronic coxitis that required articular bilateral prosthesis placement when he was 18 years old, and perianal disease that started 14 years after the initial diagnosis of CD. A 20-cm ileal resection and right hemicolectomy were performed 5 years after CD diagnosis because of the development of an enterocutaneous fistula. The patient followed maintenance therapy with mesalazine and required repeated courses of steroids, although conventional criteria of steroid-dependency were never fulfilled. He never received immunomodulators and biologicals were not available at the time. Fourteen years after CD diagnosis, he presented a slow but progressive increase in serum creatinine levels (without proteinuria) that was initially attributed to chronic consumption of NSAIDs and obstructive nephropathy. At the age of 60, a rectal biopsy was performed showing positive Congo red staining. In spite that colchicine therapy was started, the patient required haemo-

dialysis 9 years later because of terminal renal failure and was then lost of follow-up.

4. Discussion

IBD is a chronic inflammatory disorder that most often starts clinically between the second and fourth decades of life, with a life expectancy similar to that of general population.^{5,6} In turn, chronic inflammatory activity will occur in a proportion of patients. Up to 30% of patients will develop steroid-dependence, and around 70% will present stricturing or penetrating disease-related complications within the first 10 years from CD diagnosis.^{7–10} However, AA-amyloidosis will develop in only a minority of them. Many case reports have been published since the first description in 1948 by Olsan et al.¹¹ but, to our knowledge, only two studies assessing the prevalence of AA-amyloidosis among IBD patients have been reported. Greenstein et al., found 25 cases of AA in a series of 3050 IBD patients, yielding a prevalence of 0.9% in CD, and 0.07% in UC.³ Wester et al., in a more recent study that included 500 CD patients, reported a prevalence of 3%.⁴ In a very interesting study, Lowdell et al.¹² prospectively assessed the prevalence of subclinical systemic amyloidosis in 174 IBD patients (77 CD, 97 UC) who attended regular follow-up and had long-lasting disease (at least 5 years from diagnosis). A sigmoidoscopy with rectal forceps biopsy for Congo red staining, as well as measurements of proteinuria, serum creatinine, urea, and electrolyte levels were performed, but no cases of AA-amyloidosis could be identified.¹² We found prevalence closer to that reported by Greenstein et al., with AA-amyloidosis in 1% of CD patients and nil in UC. After a search of those case reports published within the last 10 years, it becomes evident that there is still a predominance of AA-amyloidosis among CD^{13–21} over UC,^{22,23} and that AA-amyloidosis occurs mainly in patients with certain clinical characteristics, as seen in our series. First, patients are usually male,⁴ with extensive disease involving the ileum, or even with ileocolic or upper gastrointestinal tract involvement. Disease behaviour is often fistulising, and a past history of insidious perianal disease is also frequent. Finally, most patients had long-lasting CD (more than 10–15 years) at the time AA-amyloidosis was diagnosed. In summary, AA-amyloidosis develops in IBD patients with persistent, long-lasting, uncontrolled inflammatory activity, thus accounting for the low incidence of this complication in paediatric patients.²⁴ Taking into account that UC often presents as recurrent acute flares, and that colectomy is a definitive treatment for refractory-disease, it seems logical that the prevalence of AA-amyloidosis in UC was much lower than in CD. In the present series, most patients had extensive involvement, penetrating complications, perianal disease, and AA-amyloidosis was diagnosed more than 10 years from IBD diagnosis in all patients but one. Moreover, that patient also lacked fistulizing complications but was diagnosed with familial Mediterranean fever some years later. Familial Mediterranean fever has been also associated to AA-amyloidosis^{25–28} or even to certain common pathogenic mechanisms of CD.^{29–31} Clinical presentation as renal impairment with proteinuria and nephrotic syndrome accounts for 90% of cases, and the development of renal

insufficiency is the most important predictor of mortality in these patients, as it also occurred in our series.

Classically, colchicine has been the only available drug to prevent the progression of amyloidosis, but only few patients avoid haemodialysis or renal transplantation.^{32–35} As long as AA-amyloidosis develops because of the abnormal deposition of a protein that derives from an acute phase reactant, the control of the underlying inflammatory process should lead to the reduction of the precursor protein (serum AA) and, thus, it should avoid worsening of amyloidosis. In this sense, many authors reported clinical improvement of IBD-related amyloidosis after surgical resection of the involved intestinal segment.^{36–40} Moreover, in a mortality study among CD patients in Leiden (The Netherlands), Weterman et al. found that amyloidosis disappeared as a cause of death after 1973, a fact that the authors claimed to an improved surgical management of CD.⁴¹ However, a review of 14 CD patients with secondary amyloidosis who underwent resective surgery stated that postoperative mortality is increased in these patients, and amyloidosis improvement rarely occurs.⁴² In our series most patients were diagnosed with amyloidosis after intestinal resection, suggesting that surgery itself is not enough to prevent or reverse this complication and that long-term strategies to control disease inflammatory activity are warranted. In recent years, it has been reported that the use of more powerful anti-inflammatory drugs such as biological agents may improve the clinical course of AA-amyloidosis in rheumatologic and IBD patients,^{43–48} or even in patients with familial Mediterranean fever,^{49,50} as occurred in two of our patients. In this regard, recent biochemical research revealed that synthesis of serum AA is regulated by certain proinflammatory cytokines such as TNF- α .⁵¹ However, therapeutic approaches should be individualized as long as there is still scarce information on the long-term efficacy and safety of biological agents in this clinical setting. The emerging concept of mucosal healing as a therapeutic target, as well as the implementation of more intensive therapeutic strategies (such as early introduction of immunomodulators and/or biologicals), might change the prevalence and prognosis of secondary complications such as AA-amyloidosis in IBD in a near future. By now, amyloidosis should still be suspected and ruled out, especially in CD patients with long-lasting, uncontrolled inflammatory activity, whenever clinical symptoms of renal, cardiac, or neurological impairment appear.

Acknowledgements

This study was partly supported by CIBERehd (Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas) of Fondo de Investigación Sanitaria of the Instituto de Salud Carlos III, from the Spanish Ministry of Health.

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