

Inflammatory Bowel Disease and Systemic AA Amyloidosis

Prayman T. Sattianayagam · Julian D. Gillmore · Jennifer H. Pinney ·
Simon D. J. Gibbs · Ashutosh D. Wechalekar · Janet A. Gilbertson ·
Dorota Rowczenio · Philip N. Hawkins · Helen J. Lachmann

Received: 19 September 2012 / Accepted: 24 December 2012 / Published online: 31 January 2013
© Springer Science+Business Media New York 2013

Abstract

Background Systemic AA amyloidosis is a recognised complication of inflammatory bowel disease. AA amyloidosis is a potential cause of end-stage renal failure and mortality but little is known of the natural history of this condition in inflammatory bowel disease.

Methods We evaluated the clinical phenotype, disease progression and outcome amongst 26 patients with inflammatory bowel disease and AA amyloidosis followed prospectively at a single center between 1989 and 2010.

Results Twenty-two patients had Crohn's disease and four had ulcerative colitis. Fistulae and abscesses occurred in ten cases, all of whom had Crohn's disease. Amyloidotic proteinuric renal dysfunction occurred in all of the cases. It resolved in five patients with well-controlled inflammation, but was progressive in all of the other patients. Fifteen patients reached end-stage renal disease after a median time of 6.3 years from development of renal dysfunction (by Kaplan–Meier estimate), six of whom subsequently proceeded to renal transplantation. There were five functioning grafts at census 0.8, 3.2, 4.2, 20.1 and 24.6 years after transplantation. One graft failed 14.5 years after renal transplantation because of amyloid recurrence in a patient with sustained chronic inflammatory activity.

Conclusions AA amyloidosis remains a serious complication of both Crohn's disease and ulcerative colitis, and is characterized by proteinuric renal dysfunction that may

resolve following suppression of inflammatory activity. Patient and graft survival are excellent in patients who undergo renal transplantation.

Keywords Amyloidosis · Amyloid · Crohn's disease · Ulcerative colitis · Renal transplantation

Introduction

Amyloidosis is a multisystem disorder in which normally soluble precursor proteins adopt an abnormal fibrillary conformation and accumulate in the extracellular space disrupting tissue structure and function.

Classification of amyloidosis is based upon the fibril precursor protein. Systemic AA amyloidosis is one of the most common forms of systemic amyloidosis in the developed world. It can occur in association with many kinds of chronic inflammatory disorder, including inflammatory bowel disease (IBD). The lifetime incidence of AA amyloidosis in those with chronic inflammatory conditions is 5–17 % [1–4]. In the developed world the most frequent conditions underlying AA amyloidosis are the inflammatory arthritides, followed by chronic sepsis, IBD and the hereditary periodic fever syndromes. Six percent of patients with AA amyloidosis have no clinically overt inflammatory disease [4].

The amyloid precursor protein in AA amyloidosis is a N-terminal fragment of the acute phase reactant serum amyloid A protein (SAA), an apolipoprotein constituent of high-density lipoprotein. SAA is synthesized by hepatocytes and its gene transcription is regulated by cytokines, in particular IL-1 and IL-6 [5]. A median SAA value in healthy individuals is 3 mg/l but its concentration may rise 1,000-fold during inflammation and remain persistently

P. T. Sattianayagam · J. D. Gillmore · J. H. Pinney ·
S. D. J. Gibbs · A. D. Wechalekar · J. A. Gilbertson ·
D. Rowczenio · P. N. Hawkins · H. J. Lachmann (✉)
Department of Medicine, Centre for Amyloidosis and Acute
Phase Proteins, National Amyloidosis Centre, University
College London, Royal Free Campus, Rowland Hill Street,
London NW3 2PF, UK
e-mail: h.lachmann@ucl.ac.uk

elevated until the stimulus remits. The latency between onset of inflammation and diagnosis of amyloid can vary from months to years.

The phenotype and natural history of AA amyloidosis associated with IBD has largely been reported only in case reports and small series. This study is the largest series reported to date, with an emphasis on clinical phenotype and disease progression and their relationships to biochemical markers of inflammation. These features are also evaluated in a sub-group of patients who had renal transplants after developing end-stage renal disease (ESRD) due to renal amyloid.

Methods

Patients

The study comprised all 26 patients with IBD and AA amyloidosis followed prospectively at the UK National Amyloidosis Centre (NAC) between 1989 and 2010. Diagnosis of AA amyloidosis was confirmed in 25 patients by histology and in one patient by non-invasive means. Diagnostic criteria were amyloid deposition on SAP scintigraphy; evidence of chronic inflammation on the background of histologically confirmed IBD; no mutations in the genes encoding transthyretin, fibrinogen A- α chain, apolipoprotein AI, apolipoprotein AII, and lysozyme (to rule out hereditary forms of amyloidosis) [6]; and a negative serum free light chain assay and negative serum and urine immunofixation to rule out monoclonal light chain amyloidosis [7]. A biopsy was performed if any of these criteria were not met.

Histology and Immunohistochemistry

Sections from formalin fixed paraffin-embedded biopsies were stained for amyloid with Congo-red and viewed under cross-polarized light [8]. Immunohistochemical staining of the amyloid deposits to confirm AA type was performed using monoclonal antibodies reactive with SAA (Eurdiagnostic REU-86.2; IgG2a).

Assessment and Monitoring at the National Amyloidosis Centre

Patients attended the NAC for their initial diagnostic evaluation and were followed at regular 6 monthly to annual intervals, depending on disease activity, for evaluation of organ function and monitoring of whole body amyloid load by serial ^{123}I -SAP scintigraphy. Anterior and posterior scintigraphic imaging using an Elscint Superhelix gamma camera was undertaken 6 or 24 h after administration of ^{123}I -labeled SAP, as previously described [9]. The labelled

SAP studies were interpreted by a panel of physicians with experience of over 10,000 SAP scans. Patients underwent serial electrocardiography and echocardiography to evaluate for cardiac amyloid. Blood samples were obtained at a frequency of 1–3 monthly to assess inflammatory activity with SAA and C-reactive protein (CRP) levels with standardization based on the respective WHO International Reference Standards (WHO 1987) [10]. Listing for renal transplantation (RTx) and transplant protocols in those patients who reached ESRD was at the discretion of their local transplant centers.

Ethical Considerations

The medical care was performed with informed consent from each patient in accordance with the Declaration of Helsinki. Institutional review board approval for the study was obtained from the Royal Free Hospital Ethics committee.

Results

Baseline Characteristics of Inflammatory Bowel Disease

Baseline characteristics of IBD in the 26 patients are listed in Table 1. Of these patients, 22 (14 male) had Crohn's disease (CD) and 4 (2 male) had ulcerative colitis (UC). The median (range) age of onset of CD was 23 (9–62) years. Fourteen patients had a Crohn's colitis, ten patients had ileal CD and six patients had more extensive small intestinal disease. Fifteen patients with CD had intestinal resections; nine had large intestinal resections, four had small intestinal resections and two had both. Suppurative features occurred in ten patients with CD—a fistulae in one case, abscesses in three cases and a combination of the two in five cases. Six of eight patients with abscesses had perianal abscesses with one patient requiring a defunctioning colostomy for such. The four patients with UC were diagnosed at the ages of 23, 33, 57 and 61 years. They had no suppurative features and only one of them (patient 24; Table 1) needed surgical intervention. She had a panproctocolectomy.

Extra-intestinal manifestations of IBD occurred in 11 of the 22 patients with CD. Ocular complications (iritis, uveitis and episcleritis) occurred in three cases, erythema nodosum in four cases and oral aphthous ulceration in two cases. In four patients with small intestinal disease there was evidence of gallstone disease (three cases) and renal oxalate stones (one case). Ankylosing spondylitis occurred in three patients and another two patients had a peripheral arthropathy attributed to CD. The only extra-intestinal

Table 1 Characteristics of patients—IBD and systemic amyloidosis

Patient	Age (years) at diagnosis of IBD/CD or UC	Site of IBD	Suppurative complications	Extra-intestinal complications	Surgical treatment of IBD	Medical treatment of IBD	Age of diagnosis of amyloidosis (years)	SAP scintigraphy—extra-renal amyloid	Dead (D) or alive (A)/Age at census or of death
1	62/CD	I	IA	O		U	67	SP	A/78
2	33/CD	I, C		AS		S, A, ASA	53	SP	D/55
3	11/CD	SI, C	F-Ileorectal	G	Colectomy and ileostomy, small intestinal resections	S, A, T	31	SP/AD	A/36
4	33/CD	I		EP, G, AR	Right hemicolectomy	S, A, T	61	SP/AD	A/66
5	53/CD	I			Ileal resection	S, A, ASA	70	SP	D/71
6	47/CD	C				S, ASA	63	SP	A/69
7	16/CD	C		EN	Panproctocolectomy	A	36	SP/AD	A/47
8	30/CD	SI, C			Panproctocolectomy	U	44	SP/AD	D/44
9	19/CD	SI, I	IA, F-enteroenteric		Ileal resection	U	37	SP/AD	D/37
10	21/CD	SI	PA, F-perianal		Small intestinal resections	S, A, T	54	SP/AD/L	D/58
11	12/CD	C			Colectomy and ileorectal anastomosis	A, ASA, T	29	SP/AD	A/33
12	54/CD	SI, C				S, A	54	SP/AD	A/56
13	24/CD	C	PA, F-perianal		Panproctocolectomy	S, A	34	SP	A/38
14	22/CD	C		IR, AS		S, ASA	29	SP/AD	D/30
15	12/CD	I	PA			S, T	25	SP/AD	A/28
16	30/CD	C	PA	M	Defunctioning colostomy	A, 6-MP, T	50	SP	A/50
17	24/CD	I		AS	Small intestinal resections	S, A, ASA, M	36	SP	A/48
18	18/CD	SI, C	PA, F-perianal	G	Panproctocolectomy and ileostomy, Small intestinal resections	U	38	SP	A/49
19	18/CD	I, C	PA, F-perianal	EN	Right hemicolectomy, sigmoid colostomy	S, A, C	34	SP/AD	A/47
20	9/CD	I, C		EN	Right hemicolectomy	S, A, E	32	SP/AD	A/57
21	24/CD	C			Panproctocolectomy and ileostomy	ASA	25	SP	A/60
22	15/CD	I		EN, M		S, ASA	22	SP/L	D/39
23	61/UC	C		AS		S	77	SP	D/78
24	57/UC	C			Panproctocolectomy	–	64	SP	D/67
25	23/UC	C				S, ASA	26	SP	A/33
26	33/UC	C		AS		S, ASA	63	SP/L	A/70

I ileum, SI small intestine, C colonic, IA intra-abdominal abscess, PA perianal abscess, F fistulae, O oxalate stones, AS ankylosing spondylitis, G gallstones, AR IBD-related arthropathy, EP episcleritis, EN erythema nodosum, IR iritis, M oral ulcers, A azathioprine, ASA 5-aminosalicylates, 6-MP 6-Mercaptopurine, S steroids, M methotrexate, T anti-TNF, α agents, C cyclosporine, E elemental diet, U unknown, SP spleen, AD adrenal, L liver

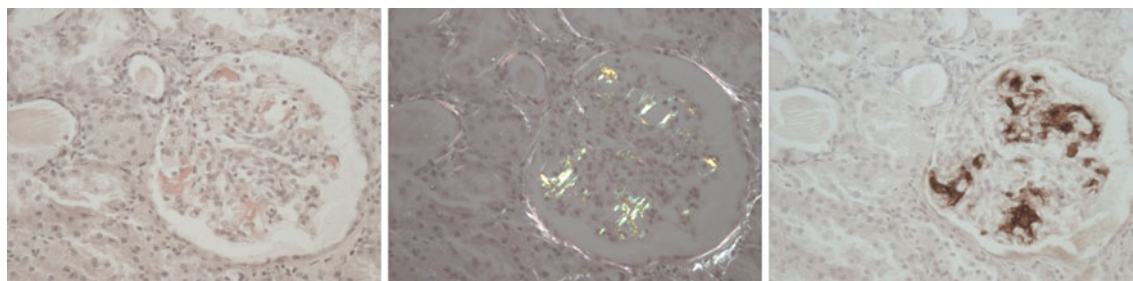


Fig. 1 Renal biopsy (glomerulus) with extensive amyloid deposition with positive Congo-red uptake (*left*), red-green birefringence when the same section is viewed under cross-polarized light (*middle*) and

immunohistochemical staining of the same biopsy with a monoclonal antibody confirming the presence of serum amyloid A protein within the deposits (*right*)

manifestation in the four patients with UC was ankylosing spondylitis, which occurred in two cases.

Baseline Characteristics of Systemic Amyloidosis

In all cases the diagnosis of IBD pre-dated the diagnosis of systemic AA amyloidosis. The histological diagnosis of amyloid was made from renal biopsies in 23 cases, an appendectomy specimen in one case and an intestinal resection specimen in one case. Immunohistochemistry with anti-SAA antibodies was positive in all cases (Fig. 1). Only one patient (patient 2; Table 1) did not have a histological diagnosis of amyloid but she had unequivocal renal and splenic amyloid on her SAP scan, proteinuric renal dysfunction, a background of chronic inflammation associated with CD, no evidence of a plasma cell dyscrasia and no genetic mutations that might encode for a hereditary form of amyloidosis.

The median (range) time from diagnosis of CD to diagnosis of systemic amyloidosis was 16.3 years (0.3–33.2). In the four patients with UC the time from diagnosis of UC to diagnosis of systemic amyloidosis was 3.1, 7.0, 16.0 and 29.9 years. All of the patients in the series had impaired renal function and/or evidence of proteinuria at the time of diagnosis. This was the presenting clinical feature in all except patient 16, who was referred to the NAC by a cardiologist with echocardiographic features of cardiac amyloid (left ventricular wall thickening with diastolic dysfunction in the absence of hypertension or aortic stenosis) when he was investigated for non-specific chest pain. At the time of his diagnosis of amyloidosis he had SAP scintigraphic evidence of renal and splenic amyloid, proteinuric renal dysfunction and AA-type amyloid on renal biopsy without evidence of a haematological clonal disorder nor a genetic mutation that might encode for a hereditary form of amyloidosis. Ten patients had already reached ESRD requiring renal replacement therapy prior to their first review at the NAC, three of whom had already undergone RTx.

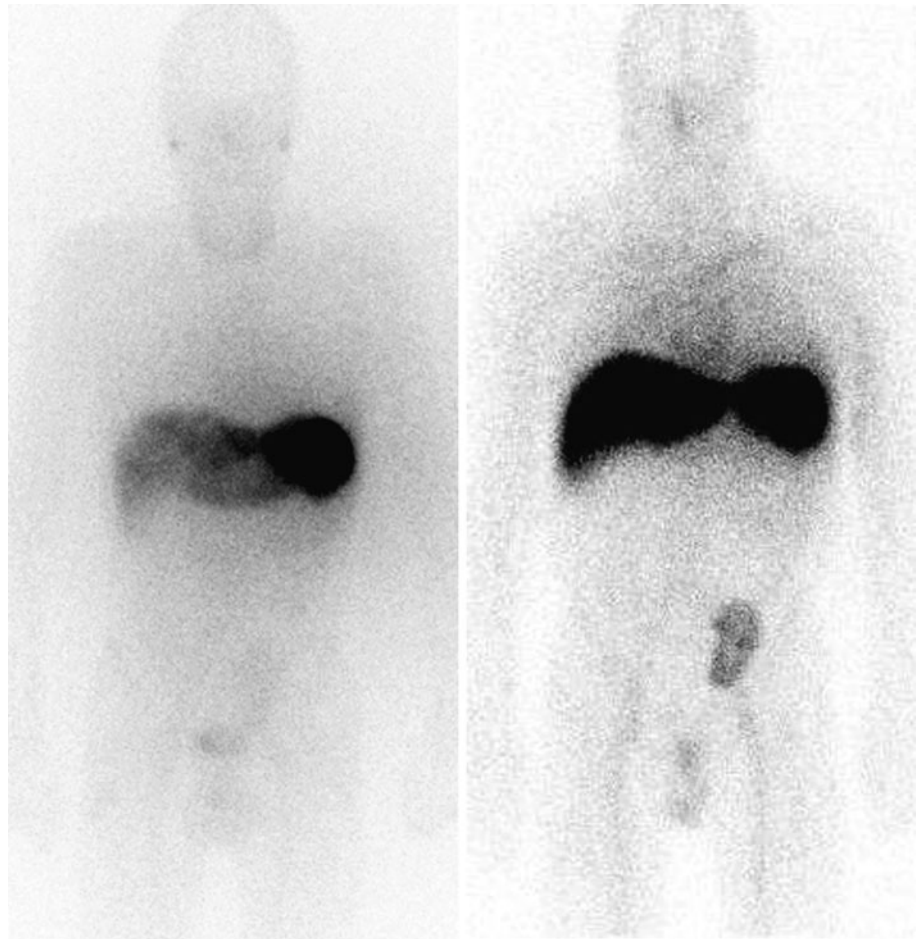
In addition to renal amyloid deposits there was evidence of splenic amyloid in all patients on SAP scintigraphy at their baseline visits (Fig. 2). In three patients there was also evidence of hepatic amyloid on SAP scintigraphy. No patients however had hepatomegaly or abnormal liver synthetic function. Clinical hypoadrenalism occurred in three cases, all of whom had received steroids previously and two of whom also had evidence of adrenal amyloid on SAP scintigraphy. Of note however were ten additional patients who had evidence of adrenal amyloid on SAP scintigraphy but without evidence of disease.

Clinical Course of Systemic Amyloidosis

The cohort of 26 patients, which included six patients with CD who had RTx, were followed for a median (range) time of 4.1 (0–20.0) years. In five patients who did not require renal replacement therapy (patients 4, 7, 11, 13 and 26; Table 1) there was improvement in proteinuric renal dysfunction with complete resolution of nephrotic-range proteinuria over 5.6, 9.0, 3.5, 4.3 and 6.6 years, respectively. They had median serial SAA values of 12, 3, 5, 10 and 7 mg/l and median CRP values of 2, 2, 2, 5 and 5 mg/l, respectively, during these follow-up periods. In keeping with their normal or very mildly elevated biochemical markers of inflammation they had well-controlled symptoms of IBD.

All of the other 21 patients had evidence of progressive renal dysfunction and/or progressive proteinuria. During follow-up, in addition to the ten patients who presented to the NAC after having reached ESRD, there were five further patients who progressed to ESRD during follow-up. The median time from detection of proteinuric renal dysfunction to ESRD by Kaplan–Meier estimate in the entire cohort was 6.3 years. Five patients (patients 3, 12, 15, 17 and 19; Table 1) who had progressive renal dysfunction had serial blood tests over >6 months [median (range) period of 62.4 (8.2–155.3) months] to assess inflammation

Fig. 2 Serial anterior whole body ^{123}I SAP scintigraphy of patient 22 after renal transplantation showing hepatic and splenic amyloid with no evidence of renal graft amyloid in the left iliac fossa 6.9 years after transplantation (*left*) and progression of hepatic amyloid and recurrence of graft amyloid 8.1 years after transplantation (*right*)



prior to ESRD or RTx. Their median SAA values were 46, 16, 25, 18 and 26 mg/l, respectively, and their median CRP values were 25, 8, 6, 1 and 13 mg/l, respectively, during their follow-up periods. The difference between these two acute phase reactants is particularly apparent in the case of patient 17 in whom serial CRP values were always 1 mg/l despite consistently elevated SAA levels.

Five patients (patients 11, 12, 13, 18 and 24; Table 1) had hypotensive/hypovolaemic episodes which precipitated rapidly progressive renal dysfunction. Patients 12, 18 and 24 rapidly progressed to ESRD after developing sepsis, which required hospitalisation. Of note patient 12 had normal renal function, despite nephrotic-range proteinuria, prior to her hospital admission. Patients 11 and 13 were diagnosed with renal amyloid after a significant and acute deterioration in renal function after surgery for their IBD. Subsequent tight inflammatory control in both cases resulted in resolution of proteinuria.

There was no evidence of a peripheral or autonomic neuropathy in any patient during follow-up. Patient 16 was the only patient who had echocardiographic evidence of cardiac amyloid during follow-up.

Outcomes of Renal Transplantation

Six patients had RTx after reaching ESRD (Table 2). Four patients had deceased-donor transplants and two patients had live-related transplants. The median (range) time from ESRD to RTx in this group of patients was 1.7 (0.2–7.8) years. Four grafts (patients 17, 18, 19 and 20; Table 2) were functioning at census 0.8, 3.2, 4.2 and 20.1 years after RTx. There was no evidence of amyloid recurrence in these grafts by serial SAP scintigraphy over the course of 0.8, 2.5, 3.2 and 19.5 years after RTx, respectively. Furthermore, there was no evidence of proteinuric renal dysfunction in any of these patients during follow-up. One graft (patient 22; Table 2) failed 14.5 years after RTx with evidence of amyloid recurrence in the graft on SAP scintigraphy more than 6 years before graft failure. Another patient (patient 21; Table 2), whose graft had survived 24.6 years, was being considered for a pre-emptive second live-related renal transplant, as he was approaching ESRD at census. There had been no evidence of recurrent graft amyloid on his serial SAP scans nor evidence of significant proteinuria after RTx to suggest ongoing amyloid

Table 2 Characteristics of patients who had renal transplants

Patient	Time from ESRD to RTx (years)	Type of graft	Median SAA/CRP (mg/l) after RTx	Recurrence of graft amyloid on SAP scan/time of recurrence after RTx (years) or time of last SAP scan with no evidence of recurrence after RTx (years)	Graft failure/time from RTx to graft failure or census (years)	Dead (D) or alive (A)/time from RTx to census or death (years)
17	2.5	L	40/5	N/0.8	N/0.8	A/0.8
18	7.3	D	4.5/1.5	N/2.5	N/3.2	A/3.2
19	7.8	D	3/3	N/3.2	N/4.2	A/4.2
20	0.2	L	7/2	N/19.5	N/20.1	A/20.1
21	1	D	5/3	N/22.2	N/24.6	A/24.6
22	0.3	D	19/8.5	Y/8.1	Y/14.5	D/16.1

ESRD end-stage renal disease, RTx renal transplantation, SAA serum amyloid A protein, CRP C-reactive protein, L live-related graft, D deceased donor graft, Y yes, N no

deposition in the graft. His progressive renal dysfunction was attributed to recurrent urolithiasis.

The median serial SAA and CRP values after RTx in the six transplant recipients are outlined in Table 2. In four patients (patients 18, 19, 20 and 21; Table 2) the median SAA and CRP values during follow-up, which of note was more than 20 years in patients 20 and 21, were in single figures and there was no evidence of graft amyloid recurrence in any of their grafts. In the two other patients (patients 17 and 22; Table 2) the median serial SAA values after RTx were 19 and 40 mg/l, respectively, and the median serial CRP values were 8.5 and 5 mg/l, respectively. The potential discrepancy in the levels of these two acute phase reactants is again highlighted here. The former patient's graft had no evidence of amyloid recurrence at census but he had only been followed for 0.8 years after RTx and the latter's graft failed because of recurrent amyloid 14.5 years after RTx.

Survival

During follow-up, which was over a median (range) period of 4.1 (0–20) years, nine patients in the cohort died at a median (range) age of 55 (30–75) years. The median survival by Kaplan–Meier estimate from diagnosis of amyloid was 16.9 years. Two patients, both of whom required renal replacement therapy, died from myocardial infarction, two died from pneumonia, one from intestinal perforation and peritonitis and one postoperatively after cardiac valve replacement. In the three remaining cases the causes of death were not known.

Discussion

The association between IBD and amyloidosis was first described in 1936 [11]. It has evolved from a post-mortem diagnosis [12] into a pre-mortem diagnosis [13]. This is

largely due to an increased appreciation of the risk of AA amyloidosis together with an improvement in diagnostic techniques for amyloid including better histological diagnosis with immunohistochemistry and SAP scintigraphy [14].

There have been several studies estimating the incidence of systemic amyloidosis associated with IBD. In the United States this incidence has been estimated at 0.9 % in CD and 0.07 % in UC [15]. In Northern Europe the incidence of systemic amyloidosis secondary to CD has been estimated at 0.8 % with a ten-fold increase in risk of developing amyloid compared to in UC [16]. These incidence studies, which are more than a decade old, may not be relevant to the present day. Results from one epidemiological study of CD from Leiden University Hospital suggested that the incidence of amyloidosis secondary to CD is falling [17]. This could be because of improved treatments, especially with the addition of biologic agents to the treatment armamentarium.

Our study is not a study of incidence but there is a very obvious discrepancy in the number of referrals of patients with CD compared to UC to the only amyloidosis center in the UK, which supports the results from previous studies [15, 16]. One possible explanation for this is the greater acute phase response seen in CD compared to UC [18], which might be explained by the higher prevalence of suppurative features in the former. In the present study ten of 23 patients had fistulae and/or abscesses. Fifteen of 22 cases of CD in the study of Greenstein et al. [15] and 13 of 18 cases in the study of Wester et al. [16] also had similar features. Another possible explanation for the apparent discrepancy in risk of development of amyloidosis between CD and UC is that whereas surgery can be a definitive treatment in UC by completely removing the inflammatory source, as occurred in patient 24 who had complete resolution of nephrotic-range proteinuria after panproctocolectomy, in CD as the entirety of the gastrointestinal tract can be affected surgery may not be as efficacious in

reducing inflammation. In addition, the extra-intestinal manifestations of IBD in isolation can lead to a significant inflammatory stimulus. Ankylosing spondylitis, which is a recognised cause of AA amyloidosis [19], may be the explanation for a substantial proportion of the AA amyloidosis seen in UC, as occurred in two of the UC patients in this series.

The fact that all patients in our cohort had proteinuric renal dysfunction highlights the fact that AA amyloidosis is a disease of the kidneys. It should be noted that there are a number of other potential causes of renal dysfunction in patients with IBD. These include interstitial nephritis secondary to 5-aminosalicylates, glomerulonephritis, renal oxalate stones and proximal tubular defects [20]. Furthermore those patients with severe IBD are at risk of sepsis and surgery, both of which may result in hypotensive episodes and hence precipitate acute tubular necrosis, which can contribute to chronic renal impairment.

Hepatic amyloid was evident in three patients in the present series but this was of no clinical significance with respect to liver synthetic function. Hepatic amyloid in the context of AA amyloidosis secondary to a variety of inflammatory conditions is known to confer a reduced survival risk [4] and probably reflects a large total body amyloid burden. Two of the three cases with hepatic amyloid in the series died four and 17 years after diagnosis of amyloid. Only one patient in the study had echocardiographic features of cardiac amyloid and was awaiting an endomyocardial biopsy at census. This feature is unusual in the context of AA amyloidosis. Only two of 374 patients in a large series of AA amyloidosis followed over 15 years till 2005 had echocardiographic evidence of cardiac amyloid [4].

Our series highlights the benefits of good inflammatory control in systemic AA amyloidosis associated with IBD. By reducing or ideally eliminating production of the amyloidogenic precursor SAA, it is possible for the balance to shift from amyloid deposition to amyloid resorption. The mechanisms by which this occurs are not known but it has been postulated that macrophages may have a role in amyloid regression. This has been highlighted with *in vivo* studies using macrophage inhibitors that reduce amyloid regression [21]. There is evidence that if serial SAA values are maintained below 10 mg/l in the inflammatory conditions underlying AA amyloidosis then one can see amyloid regression and improvement of amyloidotic organ function as well as improved survival [22]. This is highlighted in those patients our series in whom complete resolution of proteinuria was achieved when median SAA values were maintained ≤ 12 mg/l during follow-up. The case of patient 17 highlights the importance of monitoring serial SAA levels rather than CRP levels in patients with systemic AA amyloidosis. His CRP levels were consistently 1 mg/l during follow-up, which in isolation gives the impression

of good inflammatory control. His serial SAA levels (median value 18 mg/l) were however disproportionately high, indicative of ongoing inflammation, and as a result he developed progressive renal dysfunction secondary to ongoing amyloid deposition, which culminated in ESRD. The reason for a potential discrepancy between CRP and SAA levels is not known.

The benefits of inflammatory control in terms of improvement of amyloidotic organ dysfunction are not dependant on type of medical treatment administered or whether surgical resection of the inflammatory source is pursued but on how efficacious the intervention is in reducing SAA levels. However, in this series in those patients in whom complete resolution of proteinuria was achieved there were significant lengths of diseased intestine resected, resulting in removal of the inflammatory focus and hence reduction of SAA levels. Fifteen of 22 patients with CD (68 %) had some form of intestinal surgery in this series. This percentage, although representative of a small number of patients, is more than the 43 % undergoing surgery reported in a British epidemiological study of CD over a similar time period [23]. Intestinal surgery in CD is warranted with severe disease and hence is probably a surrogate marker of inflammatory risk and the risk of developing amyloidosis. It is worth highlighting that our series spans more than 20 years. Treatments have changed over this time period including availability and use of biologic therapy, which has revolutionized treatment of IBD. There have been numerous case reports showing significant improvements in amyloidotic renal dysfunction after anti-TNF α therapy [24, 25] and this may explain in part the reduced incidence of amyloidosis associated with CD [17]. Furthermore, some drugs such as 5-aminosalicylates, which were used as the mainstay of treatment in some of the patients with CD in this series, are now considered to be less effective as anti-inflammatory drugs in CD compared to UC [26].

A feature of amyloidotic kidneys, which was apparent in this cohort is the risk of functional decompensation in the face of sepsis, hypotension or other physiological stresses. This phenomenon occurred in five cases, three of whom had surgery prior to acute deterioration of renal function and three of whom progressed rapidly to ESRD. We would therefore recommend careful evaluation for proteinuric renal dysfunction with urine dipstick analysis in patients with IBD at risk of developing systemic AA amyloidosis. If systemic AA amyloidosis is confirmed we would advocate tight control of inflammation guided by serial SAA values, aggressive treatment of sepsis and careful hydration during surgery.

The graft and patient survival in all patients who had RTx after reaching ESRD in this series was excellent and appears quite comparable to RTx in other renal diseases (<http://www.uktransplant.org.uk>). There was only one graft failure,

14.5 years after RTx in patient 22, who was also the only patient in this group to die during follow-up, 16.1 years after RTx. His graft failed because of ongoing inflammation and recurrent graft amyloid, interestingly with a time lag of more than 6 years between SAP scintigraphic evidence of recurrent graft amyloid and subsequent graft failure. During follow-up, like patient 17 he had disproportionately high serial SAA levels when compared to serial CRP levels. Our own recommendation is that RTx should be considered in selected patients with IBD who have reached ESRD secondary to AA amyloidosis. There should be evidence of sustained tight control of inflammation, as assessed by serial SAA levels and this should be maintained after RTx. This recommendation is further supported from RTx experiences for ESRD on the background of other inflammatory causes of renal AA amyloid [27, 28].

Conclusion

Systemic AA amyloidosis occurs more commonly in association with CD than UC. This may be explained by the more pronounced acute phase response seen in CD, which may be related to a higher prevalence of suppurative features in CD. AA amyloidosis on the background of IBD is predominantly a disease of the kidneys characterized by progressive proteinuric renal dysfunction. In those with well-controlled inflammation, guided by serial SAA levels rather than CRP levels, one may see amyloid regression and improvement of organ function. Amyloidotic kidneys are sensitive to physiological stresses and therefore urine dipstick analysis in those who are at risk of amyloidosis, which may aid early diagnosis, is extremely important. Aggressive treatment of sepsis or hypotension in those with confirmed amyloid is therefore imperative. In those who progress to ESRD and have RTx, both graft and patient survival are excellent. To prevent graft amyloid recurrence it is important that there is tight inflammatory control, again guided by serial SAA values.

Acknowledgments We thank our many colleagues for referring and caring for the patients: T. Lane, A. Hughes, E. Pyart, D. Gopaul and D. Hutt for their technical and clinical support at the National Amyloidosis Centre. We thank J. Berkeley for expert preparation of the manuscript.

Conflict of interest None.

References

- Hawkins PN. Systemic amyloidosis. In: Weinstein WM, Hawkey CJ, Bosch J, eds. *Clinical Gastroenterology and Hepatology*. City: Elsevier Health Sciences; 2005:853–858.
- Alishiri GH, Salimzadeh A, Owlia MB, Forghanizadeh J, Set-arehshenas R, Shayanfar N. Prevalence of amyloid deposition in long standing rheumatoid arthritis in Iranian patients by abdominal subcutaneous fat biopsy and assessment of clinical and laboratory characteristics. *BMC Musculoskelet Disord*. 2006;7:43.
- Koivuniemi R, Paimela L, Suomalainen R, Tornroth T, Leirisalo-Repo M. Amyloidosis is frequently undetected in patients with rheumatoid arthritis. *Amyloid*. 2008;15:262–268.
- Lachmann HJ, Goodman HJB, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. *N Engl J Med*. 2007;356:2361–2371.
- Urieli-Shoval S, Linke RP, Matzner Y. Expression and function of serum amyloid A, a major acute-phase protein, in normal and disease states. *Curr Opin Hematol*. 2000;7:64–69.
- Lachmann HJ, Booth DR, Booth SE, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. *N Engl J Med*. 2002;346:1786–1791.
- Lachmann HJ, Gallimore R, Gillmore JD, et al. Outcome in systemic AL amyloidosis in relation to changes in concentration of circulating free immunoglobulin light chains following chemotherapy. *Br J Haematol*. 2003;122:78–84.
- Puchtler H, Sweat F, Levine M. On the binding of Congo red by amyloid. *J Histochem Cytochem*. 1962;10:355–364.
- Hawkins PN, Lavender JP, Pepys MB. Evaluation of systemic amyloidosis by scintigraphy with ¹²⁵I-labeled serum amyloid P component. *N Engl J Med*. 1990;323:508–513.
- Poole S, Walker D, Gaines Das RE, Gallimore JR, Pepys MB. The first international standard for serum amyloid A protein (SAA). Evaluation in an international collaborative study. *J Immunol Methods*. 1998;214:1–10.
- Moschkowitz E. The clinical aspects of amyloidosis. *Ann Intern Med*. 1936;10:73–89.
- Werther JL, Schapira A, Rubinstein O, Janowitz HD. Amyloidosis in regional enteritis. A report of five cases. *Am J Med*. 1960;29:416–423.
- Mir-Madjlessi SH, Brown CH, Hawk WA. Amyloidosis associated with Crohn's disease. *Am J Gastroenterol*. 1972;58:563–577.
- Lovat LB, Madhoo S, Pepys MB, Hawkins PN. Long term survival in systemic AA amyloidosis complicating Crohn's disease. *Gastroenterology*. 1997;112:1362–1365.
- Greenstein AJ, Sachar DB, Panday AK, et al. Amyloidosis and inflammatory bowel disease. A 50-year experience with 25 patients. *Medicine (Baltimore)*. 1992;71:261–270.
- Wester AL, Vatn MH, Fausa O. Secondary amyloidosis in inflammatory bowel disease: a study of 18 patients admitted to Rikshospitalet University Hospital, Oslo, from 1962 to 1998. *Inflamm Bowel Dis*. 2001;7:295–300.
- Weterman IT, Biemond I, Pena AS. Mortality and causes of death in Crohn's disease. Review of 50 years' experience in Leiden University Hospital. *Gut*. 1990;31:1387–1390.
- Saverymuttu SH, Hodgson HJF, Chadwick VS, Pepys MB. Differing acute phase responses in Crohn's disease and ulcerative colitis. *Gut*. 1986;27:809–813.
- Immonen K, Finne P, Hakala M, Kautiainen H, Pettersson T, Gronhagen-Riska C. No improvement in survival of patients with amyloidosis associated with inflammatory rheumatic diseases—data from the Finnish national registry for kidney diseases. *J Rheumatol*. 2008;35:1334–1338.
- Izzedine H, Simon J, Piette AM, et al. Primary chronic interstitial nephritis in Crohn's disease. *Gastroenterology*. 2002;123:1436–1440.
- Van Rooijen N, Sanders A. Liposome mediated depletion of macrophages: mechanism of action, preparation of liposomes and applications. *J Immunol Methods*. 1994;174:83–93.
- Gillmore JD, Lovat LB, Persey MR, Pepys MB, Hawkins PN. Amyloid load and clinical outcome in AA amyloidosis in relation

- to circulating concentration of serum amyloid A protein. *Lancet*. 2001;358:24–29.
23. Ramadas AV, Gunesh S, Thomas GA, Williams GT, Hawthorne AB. Natural history of Crohn's disease in a population-based cohort from Cardiff (1986–2003): a study of changes in medical treatment and surgical resection rates. *Gut*. 2010;59:1200–1206.
 24. Iizuka M, Sagara S, Etou T. Efficacy of scheduled infliximab maintenance therapy on systemic amyloidosis associated with Crohn's disease. *Inflamm Bowel Dis*. 2011;17:E67–E68.
 25. Fernandez-Nebro A, Urena I, Irigoyen MV, Garcia-Vicuna R. Anti-TNF-alpha for treatment of amyloidosis associated with Crohn's disease. *Gut*. 2006;55:1666–1667.
 26. Akobeng AK. Review article: the evidence base for interventions used to maintain remission in Crohn's disease. *Aliment Pharmacol Ther*. 2008;27:11–18.
 27. Lachmann HJ, Gillmore JD, Wechalekar AD, et al. Survival on dialysis and outcome after renal transplantation in AA amyloidosis. *Amyloid*. 2010;17(Suppl. 1):73.
 28. Ozdemir BH, Ozdemir FN, Sezer S, Sar A, Haberal M. Among therapy modalities of end-stage renal disease, renal transplantation improves survival in patients with amyloidosis. *Transplant Proc*. 2006;38:432–434.