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Case Report

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Bilateral nephrectomy for severe nephrotic syndrome in systemic AA amyloidosis

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Abstract

Systemic amyloid A (AA) amyloidosis is an uncommon complication of Crohn's disease. The natural history is of nephrotic syndrome and progressive renal failure. A 58-year old man with a 36-year history of Crohn's disease presented with nephrotic syndrome. A diagnosis of AA amyloidosis was established, proteinuria progressed to 54 g per day and ESKD ensued. Haemodynamic instability prevented safe dialysis. Chemical nephrectomy was attempted but adverse effects ensued. Bilateral nephrectomies were performed allowing successful dialysis and discharge. Historically renal amyloidosis has a grave prognosis, here we present bilateral nephrectomies as a life-saving strategy, with hope for future transplantation.

Introduction

Systemic amyloid A (AA) amyloidosis is an established yet uncommon complication of Crohn's disease, occurring in 0.3 – 10% of patients [1]. It carries significant mortality, as a consequence of nephrotic syndrome and renal failure. Serum amyloid A (SAA), an acute phase reactant, is produced in response to stimulation from pro-inflammatory cytokines and cleaved into fibrils. Chronic inflammation leads to persistently elevated levels of SAA and ensuing amyloid deposition. Over time there has been an epidemiological shift from chronic infections to chronic inflammatory disorders as the underlying cause; rheumatoid arthritis and Familial Mediterranean Fever account for a majority. There is a temporal relationship between onset of primary disease and development of secondary amyloidosis, on average 17 years [2].

Renal involvement is of the most significance [2]. Classically glomerular amyloid deposition results in nephrotic syndrome, with progression to renal failure. A large cohort study of 374 patients in the UK found 97% presented with some degree of renal impairment, typically proteinuria, and 67% developed ESKD [2]. Outlook is historically poor, with mean survival between 5 – 11 years [2,3]. Although Crohn's patients account for only 5% of cases, the risk of progression to ESKD is four times higher than in other disease groups [2].

Systemic amyloidosis is notoriously difficult to treat. Whilst the underlying diseases may be heterogeneous, treatment aims are universal-control primary disease activity and thus suppress production of SAA. Immunomodulators such as anti-TNF agents have demonstrated efficacy in the suppression of SAA and halting progression of amyloidosis, both in controlling the underlying disease, and postulated direct action on SAA [4]. Most data pertains to rheumatoid arthritis, however there are case series demonstrating positive effects of infliximab to reduce circulating SAA in Crohn's disease [5]. Scintographic studies have demonstrated that amyloid can regress once production of SAA is eliminated, however heavy amyloid deposition is unlikely to be fully reversible [6].

For those patients who have reached ESKD due to amyloidosis the outlook can be bleak. Renal replacement therapy can be difficult to deliver due to hypotension, and there is increased infection risk in the context of hypogammaglobulinaemia. Here, we present a case of systemic AA amyloidosis in a patient with a long history of Crohn's disease. The difficulty in managing severe nephrotic syndrome and ESKD in the context of amyloidosis is discussed, with bilateral nephrectomies required to stem the persistent and catastrophic proteinuria.

Case presentation

A 58-year old man was admitted to an Australian rural referral hospital from an endoscopy unit, unwell with active stricturing Crohn's disease, following an admission 6-weeks prior for a previous flare. A long history of Crohn's disease was present, first diagnosed aged 22 years. He had undergone 10 surgeries, with resultant ileostomy and rectal stump. Treatment comprised vedolizumab every 8 weeks. He had never received infliximab. Co-morbidities included renal amyloidosis, diagnosed on biopsy in 2004, and dyslipidaemia. Urine protein creatinine ratio (PCR) in 2008 measured 37 mg/mmol, he was since lost to renal follow up. Other medications were atorvastatin, mesalazine, enalapril and pantoprazole. There was no significant family history.

On review, he was hypotensive with pallor, blood pressure 86/60 mmHg. Temperature measured 37.5°C. Minor anasarca was present. Jugular venous pressure was not elevated. Creatinine measured 169 umol/L, with urea 5.9 mmol/L. Albumin was unrecordable at <6 g/L. There was leucocytosis with WCC 32 x 10^9/L and neutrophilia of 30 x 10^9/L. Corrected calcium was 2.78 mmol/L. Urine Albumin Creatinine Ratio (ACR) measured 1005 mg/mmol, with PCR 2200 mg/mmol. Faecal calprotectin measured 2620 ug/g. Renal tract ultrasound demonstrated kidneys 12 cm in length with increased parenchymal echogenicity and reduced corticomedullary differentiation. 24-hour urine collection confirmed 26 g/day proteinuria. Hypogammaglobulinaemia was present; IgG <1.1g/L. Total cholesterol was 6.9 mmol/L. Nephrotic syndrome secondary to renal amyloidosis was diagnosed, alongside infective flare of Crohn's disease, and the patient was admitted under the general physician.

Twice daily intravenous albumin was required to maintain serum albumin and haemodynamic stability. Intravenous steroids and antibiotics were commenced. E coli bacteraemia was isolated. MRI enterogram demonstrated a psoas abscess which was percutaneously drained. Intravenous immunoglobulin was administered. Although severe nephrotic syndrome was present, there were concerns regarding gastrointestinal bleeding risk and he was not therapeutically anticoagulated.

Renal biopsy performed demonstrated heavy deposition of eosinophilic hyaline material, positive for Congo red with apple green birefringence. Strong staining for amyloid A was present. (Figures 1a, b and c).

Hypoalbuminaemia persisted, with numerous reviews for hypotension. Repeat 24 hour urine on 6th September demonstrated 54 g/day proteinuria. Renal function deteriorated, necessitating haemodialysis; this was precluded by persistent hypotension and required inotropic support. Given ongoing torrential proteinuria, it was decided to attempt 'chemical nephrectomy'. A regimen of naproxen (with pantoprazole cover) and cyclosporin was commenced. The patient subsequently contracted influenza A and developed melaena; this strategy was abandoned.

Significant clinical deterioration had occurred over 2 months. Chemical nephrectomy was not tolerated. Bilateral renal artery embolisation was discussed but decided against in favour of bilateral surgical nephrectomies. Despite post-operative ileus, he recovered well following nephrectomies, transitioned to intermittent haemodialysis thrice weekly, with no further hypotension, and was discharged home. Treatment for Crohn's disease was recommenced with adalimumab and azathioprine, and renal transplantation is the future consideration.

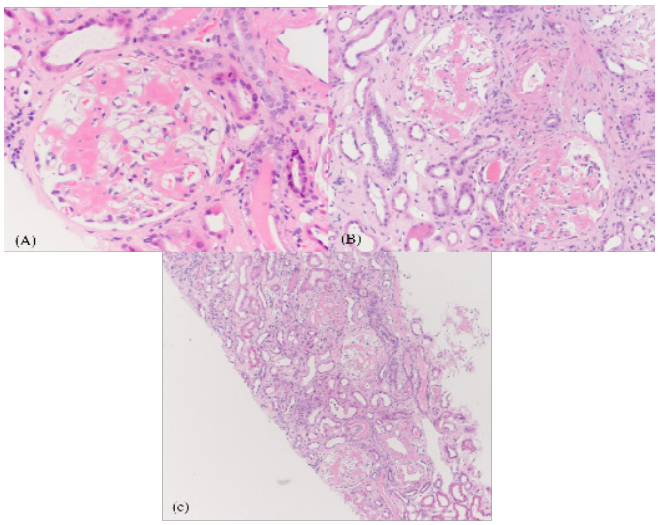

Figure 1: (A,B,C) Sections from a biopsy of left native kidney. Heavy deposition of eosinophilic hyaline material that is positive for Congo red. The amyloid deposition is seen within the glomeruli, interstitium and within the vessel wall. There is strong staining for amyloid A

Discussion

This case highlights the difficulties of managing severe nephrosis secondary to amyloidosis. Bilateral nephrectomies provided life-saving treatment for this patient, where 54 g/day proteinuria impeded safe dialysis and hospital discharge, due to ongoing hypotension and intravenous albumin requirement.

This is an established issue; an Italian cohort of amyloidosis patients, found hypotension to be the primary issue in performing dialysis, and demonstrated a 5 year survival rate of 30% - poorer than other dialysis populations; sepsis was also more prevalent [7]. By eliminating both proteinuria and immunoglobulin loss here, we hope to improve this patient's survival.

This case reflects a typical example of severe amyloidosis. The history of the primary condition is long, at 36 years, and severe, with ongoing inflammation. Interestingly he had never received anti-TNF therapy, and was receiving vedolizumab, a lumen specific agent. Infliximab has been demonstrated as effective in treating secondary amyloidosis in patients with rheumatoid arthritis and Crohn's disease [8,9], this likely relates to controlling the underlying disease. In this vein, colchicine and IL-1 inhibition with canakinumab are effective in reducing amyloid in those with Familial Mediterranean Fever, including re-

currence in transplanted patients [10,11]. It is postulated that biologic agents may also have a direct effect on SAA secretion, blocking the pro-inflammatory cytokines that lead to its production; tocilizumab is one such agent which has shown merit for this. In this particular case, the co-existence of nephrosis with sepsis, psoas abscess and hypogammaglobulinaemia, provoked concerns regarding immunosuppressing the patient. In addition, the severity of proteinuria rendered attempts to regress the amyloid obsolete. Unfortunately, this patient was lost to renal follow up for 11 years. Perhaps earlier administration of an anti-TNF agent may have halted the progression of amyloidosis.

Bilateral nephrectomies, although drastic, were ultimately life-saving. This is a management strategy well-described in patients with polycystic kidney disease, necessitating dialysis as a bridge to transplantation, however it is rarely noted in the literature regarding amyloidosis treatment [12]. Bilateral renal artery embolization has previously been used, however there is a risk of post-embolization syndrome, characterised by pain and fever [13].

Renal transplantation is the goal for this patient. Transplantation is a treatment option in advanced renal amyloidosis, and survival outcomes are superior to dialysis [14]. A control-matched study examining 45 patients with amyloidosis who underwent renal transplantation demonstrated similar graft survival at 3 years, however patient survival was reduced [15]. A control-matched study comparing living donor transplants found similar graft survival over a 10-year period [16]. Whilst graft survival may be similar, patient survival is lower, with sepsis and cardiovascular disease playing a role [17].

If the patient undergoes transplantation, how can we ensure that amyloidosis does not recur in the transplanted kidney, and how do we monitor for this? A French multi-centre study found recurrence rate of amyloidosis to be 14% over a median of 5.5 years post renal transplant [17]. It has been shown that SAA levels in Crohn's disease correlate with systemic amyloid deposition, and in the future more widespread monitoring of SAA may identify patients vulnerable to recurrence or ongoing systemic amyloidosis [18].

Transplant immunosuppression may be beneficial in reducing both recurrence of amyloidosis and suppressing Crohn's disease activity. Indeed, animal studies have suggested tacrolimus may be effective in reducing amyloidosis [19]. Patients with IBD who undergo renal transplantation have been shown to have higher mortality, with an increase in infections and hospitalisations, however disease activity may be less of an issue [20]. Regarding this patient, anephric on intermittent haemodialysis and living at home has been a superior outcome compared with futile attempts to reduce proteinuria. We hope a period of stability will allow successful renal transplantation in the future.

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