Renal amyloidosis

Renal amyloid deposition is common in systemic amyloidosis. Presentation is usually with proteinuria renal impairment. With effective treatment of the underlying amyloidotic condition and good supportive care renal function can stabilize or improve but many patients still progress to end-stage renal failure.

Renal dysfunction is evident at presentation in most types of systemic amyloidosis. Renal biopsies are the single most common tissue from which a diagnosis of amyloidosis is made and account for 42% of the positive biopsies reviewed at the UK National Amyloidosis Centre. Nonetheless renal amyloidosis is not a common cause of kidney disease in general and is the major diagnosis in less than 3% of native renal biopsies (Nishi et al, 2008) with an estimated incidence of 2.1 per million (Bergesio et al, 2007). The incidence of amyloidosis seems to be increasing in renal biopsy series and this may reflect either a genuine increase in the disease or a change in practice with more renal biopsies performed in older patients. Amyloidosis is more frequent in older age groups and is the diagnosis in up to 10% of patients presenting with nephrotic syndrome after the age of 44 years (Haas, 1997).

The histological appearances of amyloidosis are very variable; at one extreme the deposits can be so subtle that the biopsy can be misdiagnosed as minimal change glomerulonephritis (in which appearances by light microscopy are near normal) and at the other extreme extensive amyloid deposits can obliterate the normal renal architecture. Deposits can be seen throughout the kidney or localized to the vessels, glomeruli, tubules or interstitium.

Renal involvement in the different types of systemic amyloidosis

AA amyloidosis

AA amyloidosis is a predominantly renal disease (Gillmore et al, 2001a; Lachmann et al, 2007), presenting with non-selective proteinuria and/or renal insufficiency in more than 95% of cases. More than 50% of patients with AA amyloidosis will have frank nephrotic syndrome at presentation and approximately 10% have reached end-stage renal failure before the diagnosis is made. Haematuria, tubular defects and diffuse renal calcification occur rarely (Luke et al, 1969). Kidney size is usually normal, but may be enlarged or, in advanced cases, reduced.

End-stage renal failure eventually develops in 40% of patients although the clinical course is variable and is frequently characterized by stepwise deterioration. Although the spleen is infiltrated in almost every case at presentation, palpable splenomegaly is relatively unusual. The adrenal glands are involved in at least 40% of cases, and the liver in one quarter but function of both organs is typically well preserved even at a late stage. Microscopic histological involvement of the heart and gut is usual and although clinical sequelae are rare, these may now be encountered more often than previously because patients with AA amyloidosis are surviving for longer with renal replacement therapy.

Factors at presentation associated with a poor prognosis include older age, reduced serum albumin concentration and end-stage renal failure. During follow up, the concentration of the amyloid fibril precursor protein, serum amyloid A protein, predicts death. Increased production of serum amyloid A protein is not only the most powerful risk factor for development of end-stage renal disease and death, but is also one that may be ameliorated through treatment of the underlying inflammatory disease.

Long-term survival is excellent in patients with sustained normalization of their acute phase response (Gillmore et al, 2001a). Amyloid regression is well recognized in patients whose inflammatory response is tightly controlled and this is frequently accompanied by improvement in renal function including remission of nephrotic syndrome. In some patients, kidney function will continue to decline despite regression of amyloid deposits, presumably from additional renal insults including drugs, sepsis, hypovolaemia and hypertension, as well as by the extent of irreversible renal damage from amyloid deposits by the time of diagnosis.

AL amyloidosis

Systemic AL amyloidosis has a much more varied phenotype than AA amyloidosis and prognosis is more closely associated with the degree of cardiac or hepatic compromise and number of organ systems involved at presentation than by the degree of renal dysfunction (Pepys, 2006). Nonetheless, more than 50% of patients will have renal AL deposits causing some degree of kidney dysfunction at presentation and the stage of chronic kidney disease at presentation predicts overall patient survival. End-stage renal disease supervenes in about 20% of those with renal involvement by amyloid at presentation after a median of ~15 months. Risk factors at presentation for progression to end-stage renal disease include absence of cardiac involvement (presumably as a result of

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prolonged patient survival), severe nephrotic syndrome and advanced chronic kidney disease. During follow up, the degree of suppression by chemotherapy of amyloidogenic monoclonal immunoglobulin free light chains, the fibril precursor protein, predicts both renal and patient survival. Analogous to AA amyloidosis, amyloid regression, which may be accompanied by improvement in proteinuria and stabilization of renal excretory function, is well recognized in patients whose underlying plasma cell dyscrasia remits with chemotherapy (Lachmann et al, 2003) although, again, renal function may continue to decline in some patients despite amyloid regression.

Hereditary amyloidosis

A number of extremely rare autosomal dominant types of amyloidosis can present with progressive renal disease. The majority of these diseases are limited to a few families but renal amyloidosis as a result of variant fibrinogen Aα chain (AFib) is very well recognized in the European and particularly UK population. AFib tends to present in the sixth decade with proteinuria and hypertension and is easily misdiagnosed as AL type (Lachmann et al, 2002; Gillmore et al, 2009). It is largely a renal disease which rarely causes clinically significant extra-renal amyloidosis and has an inexorably progressive renal course with a median time to end-stage renal disease of 4.6 years from clinical presentation. Patient survival is excellent in AFib and survival on dialysis is comparable to that with isolated non-amyloid kidney disease (Gillmore et al, 2009). The only available measure to eliminate production of the amyloidogenic variant fibrinogen at present is liver transplantation but this has never been used to try to prevent the renal decline and is reserved for selected patients undergoing simultaneous renal transplantation in order to prevent recurrence of amyloid in the renal allograft.

Localized amyloidosis

Localized amyloidosis is usually AL in type, caused by a focal clone of plasma cells within the local mucosa. Localized amyloidosis is rare but is most often diagnosed in the lower renal tract, almost certainly because bladder amyloid deposits tend to present with haematuria and this is routinely investigated by cystoscopy and biopsy. Localized amyloid deposits can occur anywhere within the urogenital tract and have been reported to cause urethral and ureteric obstruction and even to mimic renal cell carcinoma on imaging. These localized masses are almost always benign. Progression to systemic amyloidosis does not occur and treatment is local resection of symptomatic lesions.

General supportive care and organ transplantation

Organ function in amyloid is extremely brittle and acute, often irreversible kidney injury is easily precipitated, even in individuals with apparently normal organ function, by factors such as intravascular fluid depletion, intercurrent infection, general anaesthetics or nephrotoxic drugs including contrast media, analgesics and some antibiotics. In patients with systemic amyloidosis, potential renal insults should be avoided wherever possible and sepsis and volume depletion treated promptly.

Nephrotic syndrome

The oedema of nephrotic syndrome generally requires treatment with loop diuretics. These may need to be administered in high doses and resistant cases may require addition of thiazide and/or potassium-sparing diuretics. Salt and, in many cases, fluid restriction is advisable. In patients who have difficulty maintaining their intravascular volume infusions of salt-poor human albumin may be helpful, particularly in the context of achieving a diuresis. This is often the case in patients receiving high-dose corticosteroids or dexamethasone as part of their chemotherapy for AL amyloidosis since steroids significantly increase fluid and sodium retention.

There is a theoretical risk of venous thrombosis in patients with amyloidosis-induced nephrotic syndrome but in practice this is fairly rare (National Amyloidosis Centre, unpublished observations). In view of the bleeding tendency that is sometimes present in AL amyloidosis (Mumford et al, 2000), routine prophylactic anticoagulation is not recommended in patients with a large whole body amyloid burden or those who have evidence of gastrointestinal bleeding or excessive cutaneous bruising. Treatment of hypercholesterolaemia should be considered. Patients with nephrotic syndrome are vulnerable to systemic sepsis. In many patients this is exacerbated by functional hyposplenism and by treatment-related immunosuppression. Prophylactic antibiotics are often useful and are usually included in chemotherapeutic protocols. In a few patients with persistent significant hypogammaglobulinaemia intravenous immunoglobulin replacement can dramatically reduce the incidence of intercurrent infections but this is difficult to obtain and can cause renal osmotic damage so should only be used following expert advice.

Hypertension and orthostatic hypotension

Hypertension is relatively unusual at presentation but is common in patients with hereditary renal amyloidosis caused by variant fibrinogen and in patients with amyloid regression particularly in AA type. It should be treated aggressively since amyloid-infiltrated kidneys appear to tolerate hypertensive damage very poorly. There are no clear cut-offs for treatment but the authors' practice has been to borrow the guidelines used in diabetic nephropathy. Angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers are the antihypertensive agents of first choice for their anti-proteinuric effect but should be initiated with appropriate monitoring of renal function.

Orthostatic hypotension is frequently a feature of autonomic neuropathy, and it may be exacerbated by cardiac amyloidosis and hypoalbuminaemia. Adrenal amyloid deposits are common, but adrenal insufficiency is rare and can be excluded by the short Synacthen test. Many patients with apparently severe supine and orthostatic hypotension remain asymptomatic and do not require treatment. Patients should be given lifestyle advice to avoid sudden changes into an upright posture and exertion after large meals. Men may develop micturition syncope and if so should be specifically advised to pass urine seated. Support stockings may also be helpful. If necessary measures should be taken to minimize hypovolaemia including reducing diuretics and easing salt restriction.

Fludrocortisone 100–200 μg/day can be helpful in some patients, but may cause or exacerbate fluid retention and hypokalaemia. One of the most effective agents available is midodrine, starting at a dose of 2–5 mg three times daily, gradually increasing up to 15 mg three times daily. Midodrine forms an active metabolite, desglymidodrine, which is an alpha-1 agonist, and exerts its actions via activation of the alpha-adrenergic receptors of the arteriolar and venous vasculature, producing an increase in vascular tone and elevation of blood pressure. Its chief adverse effect is supine hypertension, and other pressor agents must be co-administered with caution. In some cases ephedrine can be given either orally or as a subcutaneous infusion but care must be used as it carries a serious risk of cardiac side effects. Desmopressin has been used to expand the circulating volume but can precipitate hyponatraemia so must be monitored very carefully including regular checks of serum electrolytes.

Dialysis

End-stage renal failure can be treated with dialysis and this improves survival, particularly for patients without associated cardiac involvement (Martinez-Vea et al, 1990; Gertz et al, 1992). Patients on dialysis because they have renal AL amyloidosis have been thought to have a dismal prognosis (Bergesio et al, 2008; Bollee et al, 2008) but a sustained haematological response following chemotherapy can be associated with excellent outcomes.

Although survival on dialysis is usually estimated at ~70% of that of non-diabetic age-matched dialysis-dependent patients, unpublished data from the authors' centre suggests that median survival from start of dialysis now exceeds 4 years. There is no evidence to favour either peritoneal or haemodialysis in amyloidosis. Risk factors for early mortality on dialysis include a low albumin and high N-terminal prohormone brain natriuretic peptide (NT-proBNP) (>4000 pmol/litre) at the start of dialysis. In some symptomatic cases of ongoing heavy proteinuria despite dialysis, measures to reduce urine output may be indicated.

Renal transplantation

Renal transplantation in AL amyloidosis has rarely been used, because of concerns about prognosis as a result of progressive extra-renal amyloid and possible recurrence of amyloid in transplanted kidneys. There are a few case reports and small series of renal transplantation in AL amyloidosis but there is insufficient evidence to make firm recommendations (Hartmann et al, 1992). There are descriptions of patients with long-term survival but a suggestion of relatively high early mortality as a result of infection.

Approximately 9% (22 of 249) of dialysis patients with AL amyloidosis from the authors' centre have undergone renal transplantation and outcomes have generally been good with 1- and 5-year patient survival of 91% and 77% respectively. Graft failure as a result of recurrent amyloid has not featured and death has usually been unrelated to amyloidosis although progressive extra-renal amyloid did cause two of nine deaths in this cohort. Renal transplantation needs to be considered on an individual case basis, but is generally feasible in patients with a good functional status who do not have significant extra-renal amyloid if the underlying clonal plasma cell disease has remitted following chemotherapy.

Renal transplantation in AA amyloidosis has been very successful in selected patients whose underlying inflammatory disease is suppressed. Five-year graft and patient survival among 30 patients with AA amyloidosis attending the authors' centre is 74% and 78% respectively (Lachmann et al, 2007). The role of solid organ transplantation in hereditary renal amyloidosis depends on the variant protein and the specific mutation. In general isolated renal transplantation has been successful but amyloid deposition can eventually cause graft failure.

In the commonest type of hereditary renal amyloidosis (AFib) the variant amyloidogenic protein, fibrinogen, is produced solely by the liver (Tennent et al, 2007). This raises the possibility of surgical 'gene therapy' by hepatic transplantation combined with renal transplantation (Gillmore et al, 2000). This joint transplant procedure prevents ongoing amyloid deposition but the operative risks are significantly higher than for isolated renal transplantation and as the native liver functions entirely normally in the vast majority of patients the only justification for the hepatic transplant is long-term protection of the renal allograft. Isolated renal transplants have a median survival of 7 years in AFib so any anticipated benefit of combined transplantation is likely to be deferred for at least 5–10 years (Gillmore et al, 2009). The choice between isolated renal or combined liver and kidney transplantation is exceedingly complicated and depends on patient preference, age at end-stage renal failure, time on dialysis and comorbidity.

In lysozyme amyloidosis (ALys) the precursor protein is produced ubiquitously so the role of transplantation is simply to replace a failed organ. In this extremely rare disease the outcome of isolated transplantation has been

surprisingly good with excellent intermediate graft survival despite ongoing amyloid deposition. In apolipoprotein AI amyloidosis (AApoAI) approximately 50% of the variant amyloidogenic protein is produced by the liver (Gillmore et al, 2001b). AApoAI has a very slowly progressive natural history with a median time from presentation with proteinuria to end-stage renal disease of ~8 years and among the very few patients with this disease who are known to have undergone isolated renal transplantation outcomes have been excellent with several grafts surviving >20 years (Gillmore et al, 2006). Four patients worldwide are known to have had combined liver and kidney transplantation for AApoAI amyloidosis, invariably in the context of progressive extrarenal amyloid, and all have had improvement in extrarenal symptoms and/or amyloid regression following the procedure (Gillmore et al, 2006).

Conclusions

Renal disease is the commonest single presentation of systemic amyloidosis. Nephrotic syndrome can remit following treatment of the underlying amyloidogenic disease and renal excretory function can stabilize or improve. Supportive care is vital in preserving renal function but progression to end-stage renal failure can supervene. Outcomes on dialysis are reportedly dismal, particularly in AL amyloidosis, but have improved significantly in the past decade. Renal transplantation remains unusual and experience is limited but is generally encouraging if appropriate patients are selected. **BJHM**

Conflict of interest: none.

KEY POINTS

- Renal amyloidosis usually presents as proteinuric renal impairment.
- Most patients will have significant amyloid deposition in other tissues too.
- Treatment relies on control of the underlying amyloidogenic condition combined with good supportive care.
- Survival on dialysis is improving.
- Renal transplantation is an option in carefully selected individuals.

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