Review Article

Renal replacement therapy in multiple myeloma and systemic amyloidosis

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Introduction

Multiple myeloma and systemic amyloidosis form part of a disease spectrum in which renal involvement is common. Renal failure occurs in approximately 50% of patients with myeloma¹ while in systemic amyloidosis the nephrotic syndrome affects 40–50% of patients, and renal insufficiency 25–50%.^{2,3} Renal failure also contributes to the cause of death in a significant proportion of patients with both multiple myeloma and amyloidosis.^{1,4}

Over the last decade renal replacement therapy (RRT) programmes have expanded and now offer dialysis to higher risk patients including those with coexisting medical conditions. Patients with multiple myeloma and systemic amyloidosis who develop renal failure, fall within this category of higher risk for RRT. Although there are distinct clinical differences between these disorders, we will consider them together as they are both associated with plasma cell dyscrasia and the renal deposition of abnormal immunologically derived protein.

This review examines the renal histopathology, the clinical aspects including specific management problems that may occur, the comparative outcome and the overall role of RRT in the treatment of patients with multiple myeloma, and systemic amyloidosis.

Renal histopathology

There are several histological manifestations that may result in end-stage renal failure. Multiple myeloma (defined as greater than 10% plasma cells on bone marrow examination and either radiological lytic lesions or serum/urine paraprotein) can cause renal lesions including AL amyloidosis, cast nephropathy (precipitation of light chains within the tubules with an accompanying inflam-

matory reaction and fibrosis), light chain deposition disease (LCDD), fibrillary glomerulonephritis, immunotactoid glomerulonephritis, hyperuricaemic nephropathy and acute tubular necrosis, particularly when sepsis supervenes (see Table I). These appearances may occur several years before the appearance of overt myeloma (see above).

In AL amyloidosis, electron microscopy of kidney tissue shows amyloid fibrils of 8–12 nm in thickness, arranged in beta-pleated sheets and staining positively for Congo Red and thioflavin T.⁵ The fibrils consist largely of lambda light chains and may be deposited in glomeruli, vessel walls and interstitium.⁶ The two major forms of renal amyloidosis – AL and AA, formerly known as primary and secondary amyloidosis – can be distinguished by the biochemical composition of the amyloid fibrils; AL amyloidosis has fibrils derived from immunoglobulin light chains whereas the fibrils of AA amyloidosis, which includes familial Mediterranean fever, are derived from serum amyloid A protein. Both forms stain positively with Congo Red but only the AL form remains positive after treatment with potassium permanganate.⁷

Two other rare variants of the renal manifestations of plasma cell dyscrasia – fibrillary glomerulonephritis and immunotactoid glomerulonephritis – are characterized by glomerular infiltration with a fibrillary material that resembles amyloid but that does not stain with either Congo Red or thioflavin T.^{8–12} Immunofluorescent staining is positive for immunoglobulin in both but there are ultrastructural differences. In fibrillary glomerulonephritis the deposited fibrils are 18–22 nm in thickness and are usually found in the mesangium and glomerular basement membrane;^{8–10} however, in immunotactoid glomerulonephritis the fibrils are 32–50 nm in thickness, often arranged in parallel arrays and are deposited in the mesangium and the glomerular basement membranes.^{11,12} There is debate as to whether

Table I Features of histopathological variants of renal lesions

Lesion	Light microscopy	Congo Red	Immuno-fluorescence	Electron microscopy	Light chain
Cast nephropathy	Intratubular casts, lamellated; crystals, giant cell reaction, proximal tubular atrophy	– ve	Casts + ve for light chain	Elongated crystals, granular crystals	Kappa/lambda
Amyloidosis	Nodular/diffuse mesangial deposits, vascular and interstitial deposits	+ ve	Variable	8–12 nm fibrils, beta-pleated	Lambda
Fibrillary glomerulo-nephritis	Cap wall thickening, matrix expansion, hypercellularity	– ve	+ ve IgG mesangium and capillary wall IgG4 predominates	18–22 nm fibrils, randomly arranged	Kappa and lambda
Immunotactoid glomerulo-nephritis	Diffuse cellular proliferation, thickened BM	– ve	IgG, IgM capillary walls	32–50 nm fibrils parallel arrays	Kappa and lambda
Light chain deposition disease	Mesangial nodules, glomerulosclerosis, TBM thickening	– ve	+ ve single light chain	Mesangial, GBM and TBM deposits	Kappa predominates

– ve = negative; + ve = positive; BM = basement membrane; TBM = tubular basement membrane; GBM = glomerular basement membrane.

these latter two appearances represent different lesions.^{10,12}

Kappa light chains predominate (85%) in LCDD, sometimes in association with immunoglobulin heavy chains, and are laid down in the glomerular and tubular basement membranes, the renal microvasculature and the mesangium, resulting in a granular rather than a fibrillary appearance with linear or nodular, Congo Red negative, deposits.^{6,13,14} This nodular glomerulosclerosis is very similar to the Kimmelstein Wilson lesion seen in diabetic nephropathy.

Several factors – isoelectric point, molecular weight, kappa or lambda isotype – have been proposed to explain why these different histological patterns occur, but none adequately explains the variation. Using a mouse model, Solomon *et al.* demonstrated that certain characteristics of the Bence Jones protein produced were important determinants of the type of renal lesion.¹⁵

Clinical aspects

General

The commonest presentation of both conditions is with non-specific symptoms such as fatigue, weakness, anorexia and weight loss. Oedema, purpura, or pain from peripheral neuropathy or

carpal tunnel syndrome may be the presenting features of systemic amyloidosis. Bone pain may be an early symptom in 40–60% of patients with myeloma.^{1,16} Sixty per cent of myeloma patients may be anaemic at presentation. In the absence of significant renal impairment anaemia is seen in only 10–15% of patients with amyloidosis. A paraprotein is detected in the serum of at least 40% of amyloid patients and light chains in the urine of over 70%.

Renal manifestations

Up to 80% of patients with cell dyscrasias excrete Bence Jones protein in the urine¹⁷ though this may not necessarily be accompanied by albuminuria or the nephrotic syndrome.⁶ As immunoglobulin light chains in the urine are not detected by dipstick analysis, Bence Jones proteinuria must be identified by a direct method such as the sulphosalicyclic acid precipitation test or by urine immunopheresis.¹⁸ Direct tubular toxicity of Bence Jones proteins can cause a Fanconi syndrome with renal tubular acidosis, glycosuria, amino aciduria, hypophosphataemia and hypouricaemia.¹⁷ Such patients may present with osteomalacia characterized by myopathy and bone pain, requiring treatment with vitamin D analogues, phosphate supplements and sodium bicarbonate.

Hypercalcaemia may accompany myeloma and

cause a variety of renal lesions – calculi, nephrocalcinosis, nephrogenic diabetes insipidus and hypovolaemic acute renal failure. Urinary tract infection is more common in patients with myeloma as a result of treatment-related immunosuppression, the renal lesion itself, or neurogenic bladder secondary to spinal cord compression following vertebral collapse. Plasma cell dyscrasias with severe hyperglobulinaemia can cause a hyperviscosity syndrome which may impair renal haemodynamics and induce acute renal failure.

Rare presentations of renal amyloidosis include haematuria, nephrogenic diabetes insipidus and hypertension.

Cardiac involvement

Clinically overt amyloid cardiomyopathy is associated with a significantly reduced patient survival.^{2,4} Forty to 60 per cent of patients with systemic amyloidosis have cardiac involvement which may only be clinically manifest in two-thirds of subjects.² The transformation from subclinical to overt cardiac disease can significantly influence patient tolerance of RRT.

The detection of clinically silent amyloid cardiomyopathy remains problematical. Echocardiography will only detect a proportion of such individuals but is probably superior to technetium-99m pyrophosphate scintigraphy which is strongly positive in cases of overt cardiomyopathy but does not detect subclinical deposits.^{19,20} The use of ¹²³I-labelled serum amyloid P component as a noninvasive means of detecting amyloid deposits may prove to be a useful technique.²¹ With the test, positive imaging has been noted in organs that were 'biopsy-negative' but which at subsequent post-mortem examination were found to contain amyloid deposits. However, myocardial images obtained by this technique are not as clear as those of other organs.²¹ Endomyocardial biopsy is probably the best method available to identify non-clinically apparent amyloid deposits in the heart, but this technique is invasive, not always readily available in all centres, and subject to sampling error.

Adrenal involvement

Histological adrenal involvement is a common postmortem finding⁴ and may be functionally important in over 40% of cases.^{22,23} It is possible that adrenal dysfunction contributes to the postural hypotension frequently seen in patients with systemic amyloidosis,^{22,23} although other possible causes include cardiomyopathy, autonomic neuropathy, or hypoproteinaemia with associated contraction of intravascular volume. Amyloid deposits

in the adrenal gland can be detected by serum amyloid P component scintigraphy,²¹ but as a screening investigation it is more appropriate to perform an ACTH adrenal stimulation test. A functionally significant but clinically silent hypo-adrenal state may contribute to the early mortality following renal transplantation.

Other extra-renal manifestations

Several other organ systems can be involved in amyloidosis: nervous system – peripheral or autonomic neuropathy, carpal tunnel syndrome; gastrointestinal – macroglossia, hepatomegaly, splenomegaly, pseudo-obstruction, malabsorption, diarrhoea; respiratory, skin and muscle. Cardiac and adrenal involvement are both common and can have significant clinical consequences for patients with renal disease.

Prevention and reversibility of renal failure

General principles

There are often reversible aspects to renal failure observed at the time of presentation in patients with myeloma (see Table II). Hypercalcaemia, dehydration secondary to polyuria associated with renal tubular dysfunction, or to vomiting and diarrhoea, drug adverse effects (non-steroidals, diuretics, aminoglycosides, intravenous radiocontrast media), and superadded bacterial infections can all cause acute reversible deterioration in renal function. In myeloma patients, where the renal lesion is amyloidosis, renal vein thrombosis may occur with consequent worsening of renal function. Attempts should always therefore be made to detect and treat such factors in myeloma patients who present with renal failure.

It has also been shown that precipitation of immunoglobulin light chains with Tamm Horsfall protein is more likely to occur in an acid urine, as Bence Jones proteins with an isoelectric point (pI) > 5.5 become positively charged.^{24,25} Alkalinization of the urine with sodium bicarbonate and the maintenance of a good diuresis has therefore been advocated to decrease light chain polymerization and deposition, and thereby possibly improve renal function.^{25,26}

The general management strategy of patients with multiple myeloma should therefore encompass prevention of renal failure by ensuring appropriate fluid and electrolyte balance, alkalinization of urine, prompt and aggressive treatment of infection and hyperuricaemia, avoidance of nephrotoxic drugs and intravenous contrast media, and

Table II Strategy for prevention of renal failure

<i>Avoidable or reversible factors</i>	<i>Action</i>
Dehydration – polyuria, vomiting and diarrhoea	Appropriate fluid replacement, cautious use of diuretics
Hypercalcaemia	i.v. saline/loop diuretic, chemotherapy/diphosphonates
Infection	Aseptic techniques/care of i.v. lines
Drugs – non-steroidals, diuretics, aminoglycosides, i.v. contrast	Flag chart as patient at risk of drug/contrast toxicity
Renal vein thrombosis	Warfarin
Post-chemotherapy – hypercatabolism, hyperuricaemia	Maintain hydration
Light chain polymerization in acid urine	Oral sodium bicarbonate
Hyperviscosity syndrome	Plasma exchange

finally consideration of oral anticoagulation to prevent renal vein thrombosis.

Specific treatment of myeloma and amyloidosis

Chemotherapy may also improve renal function by reducing tumour load, although dialysis may be temporarily required during the catabolic phase immediately following chemotherapy. Severe hyperuricaemia induced by chemotherapy is another preventable/reversible cause of renal failure.

There are differences in response rate to cytotoxic therapy between multiple myeloma and systemic amyloidosis. Where myeloma often responds well^{27,28} there have been only a few reports describing small numbers of patients with AL amyloidosis who have responded to a combination of colchicine, melphalan and prednisolone,^{29–31} and some controlled trials have failed to show significant benefit.³² Similarly, the use of chemotherapy in LCDD, fibrillary and immunotactoid glomerulonephritis has shown mixed results.^{6,10,12–14} The role of cytotoxic therapy in amyloidosis therefore remains unclear at present and must be balanced against the risk of leukaemia from prolonged therapy with alkylating agents.³³ Other forms of treatments with D-penicillamine and dimethyl sulphoxide have provided occasional benefit in amyloidosis but have been hampered by poor drug tolerance.⁴ Theoretically continuous ambulatory peritoneal dialysis (CAPD) should enhance the treatment of plasma cell dyscrasias by removing immunoglobulin light chains³⁴ but the reported experience is disappointing.^{4,35,36}

In patients with AA amyloidosis, it is important to treat the underlying causative disorder where possible. In cases of familial Mediterranean fever the development of amyloidosis can be prevented

by regular long-term colchicine therapy.³⁷ The continuation of colchicine post-transplantation can prevent the recurrence of amyloidosis in the allograft.³⁸

Specific management problems

Amyloid patients with nephrotic syndrome are prone to thrombotic complications, particularly renal vein thrombosis.³⁹ The development of loin pain and/or sudden deterioration in renal function warrants urgent renal venography using anionic contrast and with attention to patient hydration (Doppler ultrasound may in some cases make the diagnosis and avoid the use of contrast). A lung scan should be performed in patients developing pleuritic pain or unexplained dyspnoea. Prophylactic warfarin therapy should be considered in patients with severe nephrotic syndrome or previous history of deep venous thrombosis.

Plasma exchange may be beneficial in hyperviscosity syndromes and also has been advocated for certain patients with rapidly progressive renal failure,⁴⁰ possibly increasing the number of patients regaining dialysis-independent renal function.⁴¹

The prevention of osteomalacia associated with Fanconi's syndrome, or other tubular abnormality, can be achieved by use of sodium bicarbonate, phosphate supplements, calcium supplements, and vitamin D analogues. Careful monitoring is necessary as hypercalcaemia can readily develop in myeloma.

It is important to make a histological diagnosis which may identify reversible causes of renal impairment, aid prognosis and also planning of chemotherapy. Unless contraindicated, a renal biopsy should be performed in patients with plasma cell dyscrasia and evidence of renal impair-

ment or nephrotic syndrome. A therapeutic dilemma exists in patients with early amyloid disease and minimal symptoms. It may reasonably be expected that chemotherapy is most likely to succeed if given before advanced disease with deterioration in general condition occurs, but can the side effects be justified when patients feel reasonably well?

We feel that patients, who have multiple myeloma or amyloidosis with renal involvement, are best managed in a tertiary referral centre where there is familiarity with the above management problems, availability of dialysis and expertise in the use of complex chemotherapy regimes.

Dialysis treatment and survival

Renal involvement in multiple myeloma used to be regarded as implying a poor prognosis and was associated with a median survival of 1–3 months.^{42,43} However, more recent reports now indicate one year survival rates of 45–60%.^{27,36,44–47} In the fourth Medical Research Council myeloma trial a 46% one year survival for patients with renal involvement and an overall one year survival of 73% were observed.²⁷ In interpreting these reports it is important to distinguish between patients with acute reversible renal failure and those with established end-stage renal failure. Patients with acute renal failure in earlier studies may not have received supportive dialysis until renal function recovered, a policy that now would be recommended.⁴⁸ Although renal involvement is common, renal failure is an uncommon cause of death amongst patients with multiple myeloma.¹⁶

It has been proposed that maintenance dialysis should be restricted to patients whose myeloma has responded to chemotherapy,^{48–50} however, as the effect of chemotherapy is variable, use of maintenance dialysis in some selected patients only partially responding to treatment may enhance quality of life. Chemotherapeutic regimens may significantly reduce tumour load but are often complicated by recurrent sepsis, particularly when central venous dialysis catheters have been in use. Ideally all patients who are to receive chemotherapy should have an arterio-venous fistula constructed at an early date.

The mortality following RRT in patients with amyloidosis and myeloma is greater than that of the general dialysis population.^{35,44} It has therefore been suggested that RRT is inappropriate in these patients not only because of the high morbidity and mortality, but also the substantial cost.^{48,50} Recent studies, including our own experience, tend to contradict this view as they show that survival rates have improved sufficiently to justify the use of RRT.^{35,36,45,47} The one- and two-year survival rates

for our patients who received dialysis were 51% and 46%, respectively.⁴⁷ Iggo *et al.* have reported a 45% one-year and 38% two-year survival rate for their group of 23 patients with myeloma, who were divided equally between CAPD and haemodialysis.⁴⁵ Korzets *et al.* reported a 60% one-year survival and a 20% two-year survival rate on CAPD for 10 patients with myeloma.³⁶

Gertz and Kyle reported a 20% five-year survival for patients with AL amyloidosis with a median survival of 20 months;² this contrasted with an earlier study from the same centre in which the median survival was only 12 months for all patients, and 17 months for those patients presenting with the nephrotic syndrome.⁷ Browning *et al.* reported a two-year survival rate of less than 5% for their patients with AL amyloidosis compared to 45% for those with AA amyloidosis.⁴ Martinez-Vea *et al.* dialysed 48 patients with amyloidosis and reported a 72% one-year and a 62% two-year survival rate.³⁵ A large American multicentre survey reported a 66% one-year survival on RRT for patients with systemic amyloidosis and a 54% one-year survival for those with myeloma.⁴⁴

Persistent hypotension, particularly during dialysis, and recurrent sepsis, especially CAPD peritonitis and central venous cannula-related septicæmia, are the most frequent complications of maintenance dialysis therapy.^{35,36,45,47} Despite best efforts at prevention the nature of the underlying disease may make these problems inevitable. It is therefore important to be able to change between modes of dialysis therapy as required. Minimum use of central venous catheters and attention to detail in the prevention of CAPD peritonitis are of fundamental importance.

Renal transplantation

Successful transplantation of myeloma patients has generally been restricted to those in remission. The limited reports available indicate considerable early mortality from sepsis, progression of disease and recurrence of the disease in the graft.^{45,46,51,52} We consider the risk that progression of myeloma might be accelerated by immunosuppressive drugs too great and therefore do not consider any patient with myeloma for transplantation.

There is limited reported experience of renal transplantation in systemic amyloidosis. Cohen *et al.* described two cases performed over 20 years ago, one of which survived 2 years, the other dying within 5 months.⁵³ Pasternack *et al.* reviewed the outcome of 45 cases (3 AL, 42 AA) and reported a 57% one-year and a 45% two-year survival.⁵⁴ However, they also reported a high early mortality rate, 17 patients (nine with functioning grafts)

dying within 6 months of transplantation.⁵⁴ The most frequent causes of death were cardiovascular disease and infection. One-year graft survival rates of 73–79% have been reported elsewhere for groups containing mainly patients with AA amyloidosis.^{55,56}

We have transplanted seven patients with amyloidosis (5AA, 2AL).⁴⁷ Three (all AA) are still alive with excellent graft function at 8, 6 and 3 years respectively. Three patients died with a functioning graft, one after 6 years and one after 2 months both as a result of the combination of cardiac amyloidosis and sepsis, the other from meningococcal septicaemia one month post-transplantation. The seventh died from a myocardial infarction 6 months post-transplantation having returned to dialysis.

A worrying feature of all these series is the high early mortality rate, 25–30% of patients dying within the first 3 months. Splenic involvement by amyloidosis is common¹¹ and often induces hyposplenism⁵⁷ which may attenuate the response to infection. It may therefore be prudent to use less aggressive immunosuppressive regimens and exercise increased vigilance for signs of opportunist infections in these patients. Previously undiagnosed cardiac amyloidosis also appears to contribute to this early mortality, a disturbing fact given the difficulties in diagnosing subclinical

amyloid cardiomyopathy. Nevertheless, in a carefully chosen subgroup of patients with amyloidosis, renal transplantation is probably the mode of RRT that provides the greatest quality of life.

In conclusion we advocate:

1. The general management strategy of myeloma and amyloidosis patients should aim to minimize the incidence of avoidable renal failure.
2. Myeloma and amyloidosis patients who present with renal failure should have detailed assessment to detect and correct potentially reversible factors.
3. Chronic dialysis therapy should be employed in patients with irreversible renal failure unless the severity of the underlying condition is such to render dialysis treatment inappropriate.
4. Special care should be exercised in the selection of patients for renal transplantation in view of the high early mortality, and pre-transplant assessment should include a systematic search for subclinical cardiac, adrenal or other organ involvement.

Further research is necessary to understand the pathogenesis of this group of renal diseases better and to establish more effective forms of specific therapy.

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