# Paraprotein-related renal disease

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## Abstract

Paraprotein-related renal disease encompasses a group of rare diseases characterized by distinct renal injury caused by the direct or indirect effects of a nephrotoxic paraprotein. Individuals can present with proteinuric renal impairment or, more rarely, tubular dysfunction. Diagnosis is often challenging because of the wide range of disease manifestations, difficulties with detection of the pathogenic clone and the common finding of an incidental paraprotein in elderly individuals. The combination of a renal biopsy along with a full haematological work-up is required to link a paraprotein to kidney disease. Chemotherapy directed at the plasma cell clone can halt the production of the paraprotein, which can in turn benefit renal function. Early diagnosis and the use of rapidly effective chemotherapy agents have improved patient and renal outcomes for these disorders.

**Keywords** Amyloid; cast; chronic lymphocytic lymphoma; fibril; glomerulonephritis; monoclonal gammopathy of renal significance; myeloma; paraprotein; plasma cell; serum free light chain

## Key points

- Patients with unexplained proteinuria or renal dysfunction should be screened for monoclonal protein, including with serum protein electrophoresis and immunofixation and serum and urinary free light chain assays
- Renal disease associated with a monoclonal gammopathy can occur irrespective of the concentration of paraprotein in the serum
- Paraprotein-related renal diseases can present as acute kidney injury (AKI), progressive proteinuric renal disease and/or Fanconi syndrome
- Prompt commencement of chemotherapy is crucial in multiple myeloma and AKI in order to minimize long-term damage to the kidneys
- Patients with monoclonal gammopathy of renal significance require chemotherapy to prevent progression to end-stage renal failure or disease recurrence in a kidney transplant

## Introduction

A paraprotein is a monoclonal immunoglobulin (MIg) or its components (light or heavy chain) produced by the clonal proliferation of plasma cells or other cells of B cell lineage. Although most individuals who are found to have a paraprotein have no associated end-organ damage (defined as having a monoclonal gammopathy of undetermined significance (MGUS)), the spectrum of potentially associated disease is wide, ranging from overt malignancy such as multiple myeloma (MM) to indirect immune system effects or direct organ toxicity from light or heavy chains.

MGUS is a relatively common finding in elderly individuals, with an estimated prevalence of 3% in those >50 years old, and carries a 1% per year risk of progression. In most individuals with kidney disease and a monoclonal gammopathy, the paraprotein is incidental to the renal pathology.

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Monoclonal gammopathy of renal significance (MGRS) is rare and refers to kidney diseases caused by a nephrotoxic paraprotein. The underlying clonal disorder is usually low grade; this may previously have been wrongly labelled as MGUS. Although the underlying clone does not usually cause tumour complications or meet current haematological criteria for treatment, specific therapy aimed at the clone can prevent further renal damage or slow the progression to end-stage renal failure (ESRF).[1]

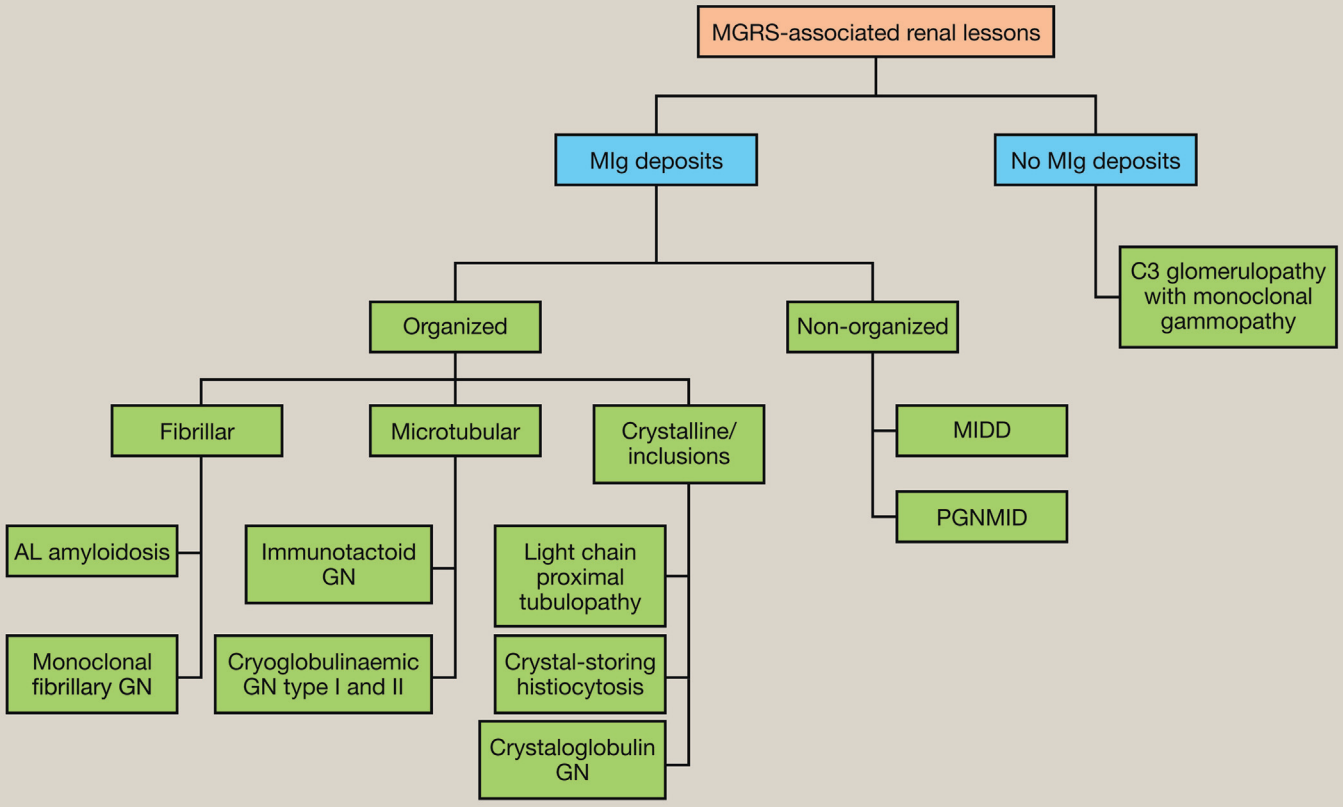
The range of haematological conditions that can produce a nephrotoxic MIg and result in MGRS includes smouldering MM, smouldering Waldenström macroglobulinaemia (WM), monoclonal B cell lymphocytosis, low-grade chronic lymphocytic lymphoma and other low-grade lymphomas. Once the haematological condition progresses to requiring treatment in its own right, i.e. to overt MM, WM, advanced chronic lymphocytic lymphoma or malignant lymphoma, it is no longer considered an MGRS and is instead managed according to disease-specific protocols.[1]

Varied histological diagnoses can be defined as MGRS-associated kidney diseases, and the histological findings are categorized according to the ultrastructural characteristics of the kidney deposits (Figure 1). The innate structural and physiochemical properties of the individual light or heavy chain in combination with the renal environment determine the type of renal lesion. In most cases of immunoglobulin light chain (AL) amyloidosis λ light chains are found, whereas monoclonal κ light chains are found in three-quarters of light chain deposition disease (LCDD). The MIg can cause renal injury by intratubular cast formation as in cast nephropathy, direct tubular toxicity, or deposition in various compartments as in amyloid.

## Diagnosis

Individuals with unexplained urinary abnormalities (proteinuria and/or haematuria) or renal impairment should have a full clonal screen. This includes serum protein electrophoresis with

**Classification of MGRS-associated renal lesions based on the ultrastructural appearance of deposits**




AL, immunoglobulin light chain amyloidosis; GN, glomerulonephritis; MGRS, monoclonal gammopathy of renal significance; MIg, monoclonal immunoglobulin; MIDD, monoclonal immunoglobulin deposition disease; PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits.
Source: Adapted from Leung et al. (2019).[1]

**Figure 1**

immunofixation, urine protein electrophoresis with immunofixation and serum free light chain (sFLC) analysis.

A renal biopsy is integral to diagnosing the underlying renal lesion, which can help to guide treatment and is prognostically important. Processing of the kidney biopsy should include immunofluorescence and electron microscopy to establish monoclonality and characterize the immunoglobulin deposit ultrastructurally (Figure 2).

A detailed haematological work-up (bone marrow aspirate and biopsy, flow cytometry, immunohistochemistry, fluorescence *in situ* hybridization, possibly lymph node biopsy) is required to correlate the specific immunoglobulin found on renal biopsy with that found on haematological work-up, to establish a link between the paraprotein and the kidney disease.

## Myeloma

MM is a cancer of plasma cells and accounts for almost 10% of all haematological malignancies. The worldwide incidence varies from 4 to 50 cases per million population per year. In the UK, 5500 new cases of MM are diagnosed each year. The median age at onset is 70 years, and the condition is more common in men and African American individuals.

Renal impairment is a common complication of MM: up to 50% of patients present with some degree of dysfunction, which is often reversible with hydration. Approximately 20% of patients have severe renal disease, classifying the disease as a myeloma-defining event, and up to 5% have severe acute kidney injury (AKI) requiring dialysis[2]; 90% of severe AKI in myeloma is the result of myeloma cast nephropathy. Despite this, the overall renal prognosis at 12 months is good, with 60% of individuals reported to have no change in renal function, 22% having improved renal function and only 16% experiencing a significant decline.[3]

The revised International Myeloma Working Group diagnostic criteria for MM comprise the presence of clonal plasma cells and a myeloma-defining event of one or more of the classic 'CRAB' features — hyperCalcaemia, Renal failure, Anaemia and/or destructive Bone lesions — or evidence of a heavy tumour burden; the latter is defined by one or more of >60% plasma cells on bone marrow biopsy, an sFLC ratio >100, or >1 focal bone lesion on magnetic resonance imaging. Patients can present with systemic clinical features such as weight loss, anaemia, recurrent infections, hypercalcaemia and bone pain. Some individuals present with AKI, low-grade proteinuria and a bland urinary sediment.

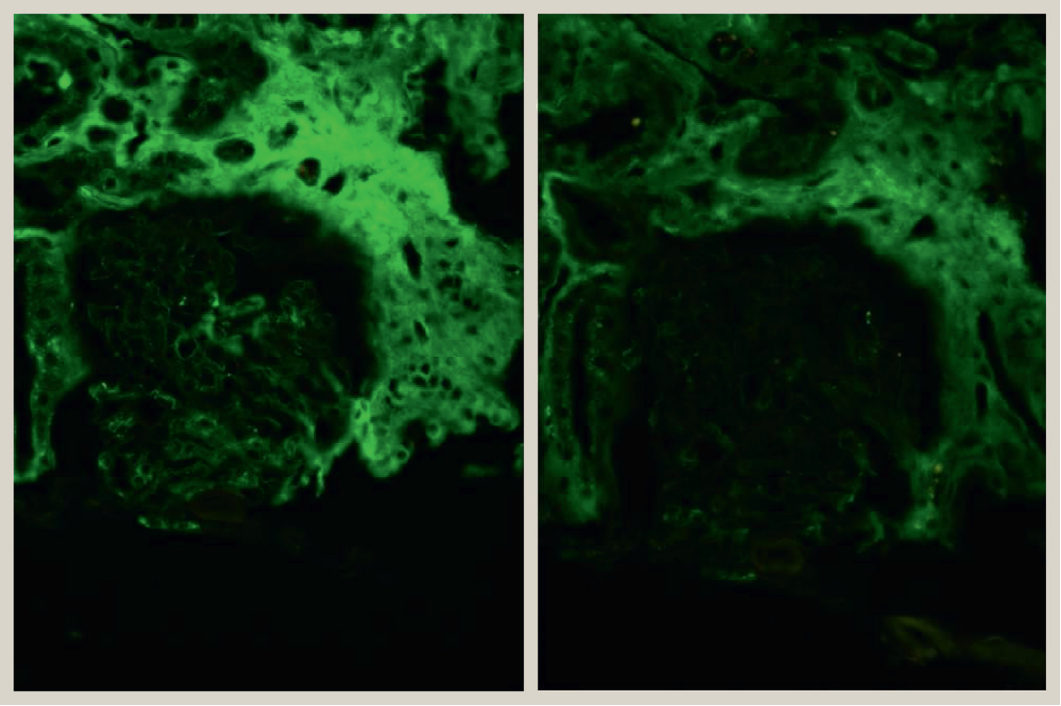


**Figure 2** Direct immunofluorescence staining for κ (left) and λ (right) light chains. The images show positive κ staining in the renal interstitium.

The current overall survival from first diagnosis is 4 years, and disease-free survival (from first remission to relapse) is around 18 months. With the introduction of new therapies, there has been an improvement in the past decade in overall survival for patients with MM.

## Myeloma cast nephropathy

Monoclonal FLCs aggregate with Tamm–Horsfall protein to produce casts. Histologically, they are often seen as large, fractured or laminated casts within the distal tubule or collecting ducts. They are often surrounded by multinucleated giant cells, and there is evidence of chronic interstitial damage. Myeloma casts cause tubular obstruction that in turn leads to AKI.

Certain situations, such as dehydration, hypercalcaemia, sepsis or insults from radiological contrast media or non-steroidal anti-inflammatory drugs, give FLCs a higher propensity to precipitate as casts and can worsen the renal insult.

Cast nephropathy is more common when the sFLC concentration is >500 mg/litre. In patients presenting with severe AKI and evidence of a high concentration of light chains, the haematological work-up should take priority to enable treatment to begin quickly; a renal biopsy is not usually indicated as it will not alter management.

Severe renal impairment is an adverse determinant of outcome, and survival improves if there is early recovery of kidney function. Since the introduction of bortezomib-based chemotherapy and better supportive care, around 50% of patients with MM who require dialysis at presentation recover independent kidney function.

Studies have shown no benefit of plasma exchange in myeloma cast nephropathy. Treatment with chemotherapy has been shown to provide more renal protection than using high cut-off membranes to remove light chains. The MYRE and EuLITE trials reported no difference in renal recovery at 3 months in patients treated with dialysis using high cut-off membranes compared with standard high-flux haemodialysis. There was an increase in overall renal recovery in the MYRE study, but not in EuLITE, where an increased mortality was reported at 2 years in patients who were in the high cut-off membrane arm of the study because of excess infection.

## Waldenström macroglobulinaemia

WM is caused by a clonal proliferation of lymphoplasmacytic cells. Renal complications are less common than in patients with MM. The renal lesion is typically caused by intracapillary thrombi, secondary to immunoglobulin M deposition, and can be associated with cryoglobulinaemia. WM can also cause light chain cast nephropathy, nephrotic syndrome (caused by amyloid deposition) and non-amyloid nephrotic syndrome (with a minimal change-like picture). Treatment is generally rituximab-based chemotherapy.

## AL amyloidosis

Amyloidosis is a disorder of protein misfolding and refers to the extracellular deposition of low-molecular-weight proteins as fibrils. AL amyloidosis results from the deposition of light chains, which undergo a conformational change and are deposited in the extracellular space as amyloid fibrils. Accumulation of these fibrils causes a progressive disruption of organ structure and function.

An estimated 500–600 people are diagnosed with AL amyloidosis every year in the UK. The median age at diagnosis is 64 years, and it is more common in men. The clinical presentation in AL amyloidosis depends on the number and nature of the organs affected (Table 1). Many individuals present with non-

specific symptoms such as malaise and weight loss leading to delayed diagnosis.

The diagnosis of AL amyloidosis requires evidence of a monoclonal plasma cell disorder and direct demonstration of amyloid fibrils on biopsy. The presence of amyloid fibrils can be confirmed by their characteristic appearance on electron microscopy and by their ability to bind Congo red with green birefringence under polarized light. The type of protein within the amyloid fibrils can be determined by immunohistochemical staining, immunofluorescence or laser microdissection with mass spectrometry. Whole-body $^{123}$I-labelled serum amyloid P scintigraphy can identify amyloid in solid organs and can be used in serial follow-up assessments to track the total body amyloid load (Figure 3).

Median survival in untreated patients is only 12–15 months depending on the organs involved, cardiac involvement conferring a worse outcome. Poor prognostic factors in patients with renal amyloid include high N-terminal (NT)-pro B-type natriuretic peptide, older age, higher total sFLC concentration, lower serum albumin, hypotension and hyperbilirubinaemia.

The degree of renal impairment, serum albumin concentration and amount of proteinuria are all associated with progression to dialysis. The outcome on dialysis is only slightly better than in patients with myeloma but is improving with time, and individuals with isolated renal involvement can do well. Renal transplantation in selected patients with sustained clonal remissions can achieve an excellent outcome, and recurrence in the graft is not commonly found.[4]

## Monoclonal immunoglobulin deposition disease (MIDD)

MIDD is characterized by deposition of MIg or its components in various organs; the kidney is most commonly affected. The diagnosis differs from amyloidosis as here the light (or heavy) chain fragments do not form fibrils and deposits are Congo red negative. Three subtypes are LCDD, heavy chain deposition disease, and light and heavy chain deposition disease. Of these, LCDD is the most common, accounting for 80% of cases.

LCDD is characterized by the deposition of non-organized granular deposits composed of MIg light chains along the glomerular and tubular basement membranes. The diagnosis is usually made by electron microscopy. The kidney is the principal target organ as light chains are filtered by the glomeruli, reabsorbed in the proximal tubules and degraded in the tubular cells by lysosomal enzymes.

LCDD usually presents in the sixth decade and is more common in men. Presentation is typically with hypertension and microscopic haematuria, and 50% of cases have associated nephrotic syndrome. Most individuals have advanced chronic kidney disease, and ESRF occurs in up to 30%. LCDD is associated with κ light chains in 80% of patients, and >60% have underlying myeloma. Extra-renal manifestations of LCDD are seen in approximately 30% of patients, with cardiac infiltration occurring in 20% and clinically overt liver involvement in 10–20%. There have also been reports of LCDD in gastrointestinal tract, lung and skin biopsies, but this is extremely rare.

LCDD has a better outcome than other paraprotein-related renal diseases, with a median survival of 7 years. LCDD should be aggressively treated with chemotherapy, as achieving a deep clonal response prolongs renal survival and prevents graft failure from recurrent LCDD in those given renal transplants.[5] Extra-renal involvement and lack of a clonal response to chemotherapy are both associated with a poor prognosis.

## Other paraprotein-related renal diseases

**Fibrillary glomerulonephritis** is a glomerular disease characterized by Congo-red-negative fibrils that are randomly arranged and larger than amyloid fibrils. The heat shock protein DNAJB9 is a major component of the fibrils, and immunohistochemical

### Clinical manifestations of AL amyloidosis

**Visible tissue infiltration (10% of cases)**
Easy bruising (often periorbital)
Macroglossia with altered taste and dry mouth
Thyroid and salivary gland enlargement
Muscle and joint pseudohypertrophy

**Renal (70% of cases)**
Progressive chronic kidney disease
Proteinuria

**Cardiac (60% of cases)**
Restrictive cardiomyopathy with congestive cardiac failure
Low limb voltages and pseudo-infarct pattern on ECG

**Hepatic**
Hepatomegaly
Increased ALP and GGT
Hepatic failure (rare)

**Pulmonary**
Recurrent pleural effusions
Interstitial lung involvement — usually asymptomatic

**Autonomic neuropathy (15% of cases)**
Orthostatic hypotension
Cardiac arrhythmias
Diarrhoea
Erectile dysfunction and impaired bladder emptying

**Peripheral neuropathy (20% of cases)**
Carpal tunnel syndrome
Symmetrical distal axonal sensorimotor neuropathy

**Gastrointestinal**
Weight loss, anorexia, bloating
Blood loss
Constipation

**Adrenal axis**
Biochemical hypoadrenalism (rare)

**Lymphoreticular system**
Splenomegaly, features of hyposplenism
Lymphadenopathy

ALP, alkaline phosphatase; GGT, γ-glutamyl transferase.

**Table 1**

**Figure 3** Anterior whole-body scintigraphic image after injection of $^{123}$I-human serum amyloid P in a patient with AL amyloidosis. Uptake is seen in the bones, liver and spleen.

staining or mass spectroscopy for DNAJB9 is now used as the gold standard for diagnosis.

The presentation is similar to LCDD, with 50% of patients presenting with nephrotic-range proteinuria. Haematuria and hypertension are also common features. There are associations with hepatitis C, B and HIV, diabetes mellitus and autoimmune conditions, as well as the potential for a paraprotein-associated renal lesion. Renal prognosis is poor, with ESRF estimated in 50% of patients at 2 years. Treatment of an underlying clone has been shown to improve renal function, whereas immunosuppression has had limited success.

**Immunotactoid glomerulonephritis** is rare; fibrils are larger, usually >30 nm in diameter and arranged in parallel microtubules. There can be an underlying lymphoplasmacytic disorder.

**Proliferative glomerulonephritis with monoclonal immunoglobulin deposits** mimics an immune complex glomerulonephritis. The most common pattern is a membranoproliferative glomerulonephritis (MPGN). Immunofluorescence reveals monotypic deposits, and 20% of individuals have a detectable paraprotein. Patients with MPGN on light microscopy should be evaluated for an underlying clone. Immunoglobulin deposits may not stain on frozen tissue and patients can be misdiagnosed as having C3 glomerulopathy. When an MGRS is suspected, special techniques are required to enable antigen–antibody binding and subsequent positive immunofluorescence staining. Samples should be sent to specialized laboratories for processing.

**C3 glomerulopathy with monoclonal gammopathy** is characterized by a lack of renal MIg deposits, although 60–80% of patients aged >50 years have a clone at the time of diagnosis. Here the MIg activates complement through the alternative pathway, resulting in deposition of C3; this results in glomerular inflammation and endocapillary proliferation. Observational studies support targeted chemotherapy if a clone is detected, or based upon the isotype of the circulating monoclonal protein detected in the serum or urine.

**Light chain proximal tubulopathy** is caused by the formation of localized crystals or inclusions of light chains within the proximal tubules. Patients present with Fanconi syndrome (e.g. aminoaciduria, normoglycaemic glycosuria, hypophosphataemia, hypouricamia, subnephrotic-range proteinuria). In those who have significant renal impairment and/or proteinuria, treatment with clone-directed chemotherapy seems a reasonable approach.

**Crystalglobulin-induced nephropathy** is the result of the MIg precipitating as crystals in small arterioles, capillaries and in some cases glomeruli.

## General treatment principles

Treatment of paraprotein-related kidney disease is indicated to preserve or restore kidney function and prevent recurrence after kidney transplantation. The choice of chemotherapy regimen depends on the nature of the underlying clone, i.e. whether it is lymphocytic or plasmacytic in origin. The renal response correlates strongly with the nature of the haematological response, and rapid suppression of MIg secretion with chemotherapy is required to improve outcomes. Effective treatment involves disease-specific management and supportive care.

## Chemotherapy

The aim of treatment is to rapidly suppress paraprotein production, producing a deep and sustained clonal response while minimizing treatment-related mortality and morbidity. The response to treatment is assessed by measuring the change in the sFLC and paraprotein concentrations.

The choice of chemotherapy depends on the underlying haematological diagnosis, the degree of renal failure and/or other organ involvement and the local availability of therapeutic agents. Treatment options for MM have advanced over the last decade. Current first-line treatment is usually with a combination of novel therapies (proteasome inhibitors such as bortezomib, immunomodulatory (IMid) drugs such as lenalidomide, and biologics such as daratumumab) in combination with chemotherapy such as

cyclophosphamide and corticosteroids. Once remission has been achieved individuals with MM who are not eligible for a haematological transplant continue with maintenance therapy until there is evidence of disease progression; the treatment is then changed to a different combination of drugs.

### General management

The most common cause of death is sepsis, so individuals on chemotherapy require prophylaxis to reduce the risk of bacterial and viral infections. Prompt treatment of suspected infection is vital. In patients with proteinuria, scrupulous attention must be paid to salt and water balance, and maintenance of circulating volume. Hypercalcaemia is a common cause of renal impairment in patients with MM and should be treated promptly with hydration and bisphosphonates. Elective surgery and general anaesthesia are best avoided, and care must be taken to avoid exposure to potentially nephrotoxic drugs, particularly analgesics, contrast media and antimicrobials.

The response to vaccination may be impaired because of the disease and chemotherapy treatment. Full vaccination is still recommended to prevent viral infections such as coronavirus disease (COVID-19), seasonal influenza and *Haemophilus influenzae* type B.

### Preservation and replacement of organ function

The requirement for dialysis has a major impact on both survival and quality of life, but patient outcomes are improving. The responses to chemotherapy in individuals undergoing dialysis are equivalent to those in dialysis-independent individuals, but chemotherapy can be difficult in ESRF, with a higher incidence of adverse effects, even with novel agents.

MGRS can recur frequently and sometimes rapidly after kidney transplantation, so it is recommended that complete haematological remission is achieved before transplantation. All these haematological conditions are likely to eventually recur so, unlike in solid tumours, there is little rationale for requiring evidence of several years of complete response before listing individuals for transplant. Instead there should be an agreed viable plan for further chemotherapy should it be required after renal transplantation. ◆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## TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

### Question 1

A 79-year-old woman presented feeling generally unwell. Her blood results revealed that she had acute kidney injury (AKI) stage 3.

**Investigations**

- Haemoglobin 71 g/litre (130–180)
- Mean corpuscular volume 84 fl (80–96)
- Serum corrected calcium 2.28 mmol/litre (2.20–2.60)
- Creatinine 361 micromol/litre (60–110)
- Estimated glomerular filtration rate 11 ml/minute/1.73 $m^2$ (70–140)
- Albumin:creatinine ratio 11.3 mg/mmol (<2.5)
- Immunofixation showed only an immunoglobulin (Ig) band on electrophoresis
- Serum free light chains:
  - κ light chain 15.0 mg/litre (3.3–19.4)
  - λ light chain 15,310 mg/litre (5.7–26.3)
  - κ:λ ratio 0.003 (0.26–1.65)
- Ultrasonography of the kidneys was normal

**What is the next step in managing this patient acutely?**

A. Start the patient on dialysis
B. Perform a kidney biopsy to understand the cause of the AKI
C. Start dexamethasone and arrange an urgent bone marrow biopsy
D. Refer the patient to an urgent outpatient haematology clinic for review
E. Transfuse the patient

### Question 2

A 62-year-old man presented with generalized swelling and was found to have renal impairment and heavy proteinuria.

**Investigation**

- Renal biopsy showed fibrillary glomerulonephritis

**Which group of tests are required in the initial assessment of fibrillary glomerulonephritis?**

A. Protein electrophoresis, serum free light chains, hepatitis C serology, DNA JB9 serum level
B. Hepatitis C serology, protein electrophoresis, serum free light chains, $HbA_{1c}$
C. Serum free light chains, serum amyloid A protein, DNA JB9 serum level, $HbA_{1c}$
D. Serum amyloid A protein, hepatitis C serology, $HbA_{1c}$
E. Immunoglobulins, hepatitis C serology, serum amyloid A protein, DNA JB9 serum level

## Question 3

A 78-year-old man presented for review. While under follow-up for monoclonal gammopathy of undetermined significance he had been found to have increasing proteinuria and ankle swelling.

On clinical examination, the oedema was confirmed. His blood pressure was 127/82 mmHg.

**Investigations**

- Haemoglobin 143 g/litre (130–180)
- Serum corrected calcium 2.60 mmol/litre (2.20–2.60)
- Creatinine 103 micromol/litre (60–110)
- Estimated glomerular filtration rate 60 ml/minute/1.73 $m^2$ (70–140)
- Serum albumin 31 g/litre (35–50)
- Albumin:creatinine ratio 248 mg/mmol (<2.5) (118.1 mg/mmol 6 months previously, 138 mg/mmol 3 months previously)
- Immunofixation showed IgG paraprotein 20.1 g/litre
- Serum free light chains:
  - κ light chain 21.5 mg/litre (3.3–19.4)
  - λ light chain 64.67 mg/litre (5.7–26.3)
  - κ:λ ratio 0.33 (0.26–1.65)
- Ultrasonography of the kidneys showed echo-bright kidneys: right 10.4 cm, left 12.6 cm

**What is the next most appropriate step in this patient's management?**

A. Perform a bone marrow trephine
B. Increase the dose of the angiotensin-converting enzyme inhibitor
C. Screen the patient for diabetes mellitus
D. Add a sodium-glucose co-transporter-2 inhibitor
E. Arrange a renal biopsy