Paraprotein-related renal disease and amyloid

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Abstract

Paraproteins are most commonly produced by plasma cell dyscrasias. A paraprotein is frequently an incidental finding in patients with renal disease but can cause renal dysfunction directly through a variety of underlying pathological processes. Diagnosis is usually through the detection of a monoclonal protein in combination with a renal biopsy. The general supportive management of all paraprotein-related renal lesions is meticulous fluid balance, early treatment of infections and avoidance of nephrotoxins. Patients with severe renal impairment may require renal replacement therapy and selected patients can benefit from renal transplantation. Treatment with chemotherapy can halt the production of the paraprotein, which in turn may benefit renal function. Early diagnosis and use of the newer rapidly effective chemotherapy agents has improved patient and renal outcomes.

Keywords amyloid; cast; glomerulonephritis; immunotactoid; myeloma; paraprotein; plasma cell; serum free light chain

What's new?

- High rates of renal recovery can be achieved when patients are treated early with highly effective chemotherapy, such as bortezomib-based regimens
- Free light chains can be removed effectively using high cut-off membranes, but whether this confers a benefit to renal recovery in randomized trials has yet to be established
- Renal transplantation is a potential option in highly selected patients with a good haematological response

Introduction

A paraprotein (M protein), is a monoclonal immunoglobulin or light chain detected in the blood or urine. Paraproteins are produced in a wide variety of haematological conditions covering a spectrum from low-grade to florid malignancy.[1] Paraproteins are however most commonly produced by monoclonal plasma cells. An incidental paraprotein is a relatively common finding in the elderly; the reported incidence in people over 50 years old is 3.2%. When a paraprotein is detected without evidence of end-organ damage, it is described as a monoclonal gammopathy of undetermined significance (MGUS). In a minority of patients the paraprotein is pathogenic, and can cause a variety of paraprotein-related renal diseases. These are rare causes of renal impairment and are the primary abnormality in less than 3% of native renal biopsies. Presentation is usually with proteinuric renal impairment with normal-sized kidneys, but histological appearances and propensities to extra-renal organ involvement differ (Table 1).[2] The pathological effects of deposited paraproteins are due to a combination of specific properties of the monoclonal immunoglobulin, their concentration and the local microenvironment. The general term for paraproteins that produce renal damage is now monoclonal gammopathy of renal significance (MGRS).

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Diseases resulting in paraprotein production

Monoclonal proteins can be detected by serum or urine electrophoresis and immunofixation. Free light chains (FLCs) are freely filtered by the glomerulus and actively reabsorbed by receptor-mediated endocytosis in the proximal convoluted tubules (PCT), where they are metabolized. The normal production of FLCs is about 500 mg/day. The PCT can handle only 10–30 g of protein per day and excess FLCs are detected in the urine as Bence Jones proteinuria. High-sensitivity assays for serum FLCs can be used both diagnostically and to monitor treatment responses.[3] A renal biopsy is integral to diagnosing the underlying renal lesion, which can help to guide treatment and is prognostically important. The incidence of bleeding complications in paraprotein-related renal diseases is no higher than in other renal diseases.

Myeloma

Multiple myeloma accounts for almost 10% of all haematological malignancies, with an annual incidence of 4.3 per 100,000 population. Renal impairment is common in patients with myeloma, but in the majority of cases renal dysfunction is mild to moderate and caused by a combination of volume depletion, hypercalcaemia and sepsis, compounded in many cases by nephrotoxic drugs. Approximately 10–15% of cases have more severe renal disease and in up to 70% of these this is due to myeloma-cast nephropathy.

Myeloma-cast nephropathy

Monoclonal FLCs aggregate with Tamm–Horsfall protein to produce casts (Figure 1). Histologically they can often be 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 acute kidney injury. Certain conditions, 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. Although myeloma and its renal complications can occur throughout adult life, most patients present in their seventh

Classification of the major paraprotein-related renal diseases

	Organization of deposited immunoglobulin	Frequency	Renal manifestations	Significant extra-renal involvement	Median survival (months)	ESRF (%)
Myeloma cast nephropathy	Crystalline	~1% of native renal biopsies	Renal failure >95% Proteinuria 80%	None	4–18	46
Fanconi's syndrome	Crystalline	Fewer than 50 reported cases	Renal tubular acidosis	Osteomalacia		
AL amyloidosis	Fibrillar	~1.5 % of native renal biopsies	Renal failure ~40% Proteinuria >70% Hypertension – unusual	Cardiac 30% Liver 30% Neuropathy 10%	15–48	40
GOMMID	Microtubular	Very rare	Renal failure >50% Proteinuria 100% Haematuria >75%	Very rare	>120	70
LCDD	Non-organized (granular)	~0.5% of native renal biopsies	Renal failure >95% Proteinuria >80% Haematuria ~60% Hypertension 60%	Cardiac ~20% Liver 10–20% Other organs less frequently	48	32

AL, amyloid light chain; ESRF, end-stage renal failure; GOMMID, glomerulonephritis with organized microtubular monoclonal deposits; LCDD, light chain deposition disease.

Table 1

decade. The condition is slightly commoner in men and usually presents with chronic kidney disease (CKD) stage 4 or 5, with low-grade proteinuria and a bland urinary sediment.

Renal dysfunction is associated with a significant increase in mortality. The degree of renal impairment and the amount of Bence Jones protein in the urine are both independent predictors of renal recovery.[4] Improvement in renal function is associated with better patient survival.[5] Salvaging renal function in cast nephropathy rests on reducing the amount of FLC in the serum. Newer chemotherapy agents, such as bortezomib, have been found to improve the rate of renal recovery and this may be due to their faster onset of action. Rates of renal recovery in advanced renal failure were previously very poor, with only 15% regaining renal function, but recovery rates are improving with early treatment and use of novel agents.[6]

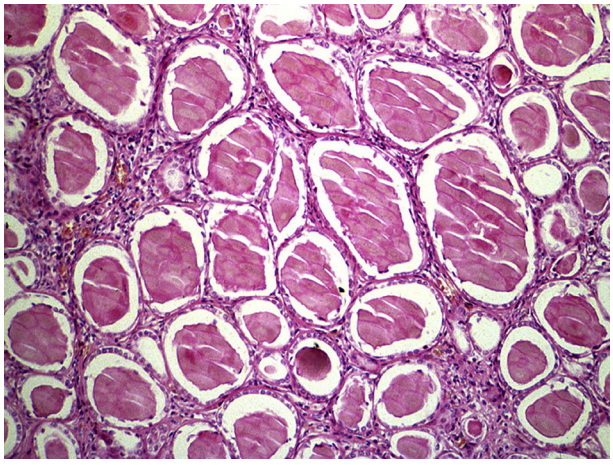

Figure 1 Myeloma kidney: multiple casts within distal tubules exhibiting fractured planes on H and E staining.

Plamapheresis to reduce the circulating paraprotein is controversial; the largest randomized controlled trial did not show a benefit.[7] Initial results from prolonged dialysis using high cut-off membranes (HCO-HD) have been encouraging. HCO-HD has been shown to achieve a sustained reduction in serum FLC concentration,[8] and a pilot study using this technique in combination with high-dose chemotherapy reported dialysis independence rates of over 70%.[9] The results of EULITE, a randomized controlled trial are currently awaited.

Waldenström's macroglobulinaemia

Waldenström's macroglobulinaemia is a lymphoid neoplasia. Renal complications are less common than in patients with multiple myeloma. Mild proteinuria and microscopic haematuria can occur. Typically, the renal lesion is due to intracapillary thrombi, secondary to immunoglobulin M (IgM) monoclonal deposition, and may be associated with cryoglobulinaemia. Treatment is of the underlying clonal abnormality, but plasma exchange may be beneficial.

Amyloid light chain (AL) amyloidosis

FLCs can undergo a conformational change and be deposited in the extracellular space as fibrils, known as amyloid.[10] Accumulation of these fibrils causes progressive disruption to organ structure and function. AL amyloidosis can complicate any clonal B cell dyscrasia and has an estimated incidence of 0.3/100,000 population, which peaks in those aged 60–79 years.[11] AL amyloidosis can affect any organ other than the brain, but the kidneys are affected in over 50% of cases (Table 2). Features such as macroglossia (Figure 2) and periorbital ecchymoses occur in about 10% of cases, many patients present with non-specific symptoms such as malaise and weight loss, and a