Paraprotein-related renal disease and amyloid

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Abstract

Paraproteins are produced by a wide spectrum of haematological conditions, most commonly by plasma cell dyscrasias. Paraprotein production is frequently incidental in patients with renal disease but can directly cause renal impairment through a variety of underlying pathological processes. Diagnosis is usually through the detection of a monoclonal protein, either in the serum or urine. Monoclonal free light chain assays are more sensitive than electrophoresis or immunofixation and are useful in monitoring clonal response to treatment. Renal biopsy is necessary to establish a definitive diagnosis. The general supportive management of all paraprotein-related renal lesions is meticulous fluid balance, early treatment of infections and avoidance of nephrotoxic insults. 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 and thus progressive renal damage. Early diagnosis and use of the newer rapidly effective chemotherapy agents has improved patient and renal outcomes.

Keywords amyloid; cast; chemotherapy; myeloma; paraprotein; plasma cell; proteinuria; serum free light chains

What's new?

- Highly effective chemotherapy regimens with new agents, such as the proteozome inhibitor, bortezomib, may improve the chance of renal recovery
- Removal of free light chains by extended dialysis using high-flux dialysers
- Renal transplantation in patients with a good haematological response is now a potential option

Introduction

A paraprotein is a monoclonal immunoglobulin or light chain present in the blood or urine. It is produced by a clonal population of mature B cells, most commonly plasma cells. In the elderly it is a relatively common finding and the reported incidence in people over 50 years old is 3.2%. In a minority of patients the paraprotein can be pathogenic, causing 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).[1] The pathological effects of deposited paraproteins are due to a combination of specific properties of the monoclonal immunoglobulin, their concentration and the local microenvironment.[2] It is well recognized that two or more paraprotein-related renal lesions can co-exist.

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General treatment principles

At present, the treatment of all paraprotein-related diseases involves reducing the supply of the paraprotein and supporting or replacing compromised organ function.

Chemotherapy

A variety of regimens are available, from low-dose oral regimens to high-dose melphalan with autologous stem cell rescue. The choice of chemotherapy depends on the underlying haematological diagnosis and the degree of renal failure and/or other organ involvement. The aim of treatment is rapidly to suppress paraprotein production, producing a sustained clonal response while minimizing treatment-related mortality and morbidity.

General management

The most common cause of death is sepsis. Prompt treatment of infection is vital. Scrupulous attention must be paid to salt and water balance, and maintenance of circulating volume. In patients with myeloma, hypercalcaemia is a common cause of renal impairment; it should be treated promptly with hydration, and bisphosphonates if required. 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.

Preservation and replacement of organ function

Although proteinuria and, to a lesser extent, impaired renal function can improve, renal replacement therapy is often necessary. The outcome on long-term dialysis is relatively poor; compared with other disease groups, 2-year survival is about 30% less. Mortality is usually due to sepsis. The response to chemotherapy in patients on dialysis is the same as in those not on dialysis but chemotherapy can be difficult to administer in patients on dialysis, who have a higher incidence of adverse effects, even with novel agents. The outcome of renal transplantation in carefully selected patients who have achieved a complete haematological remission has proved surprisingly favourable, despite early post-transplant mortality due to sepsis.

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

Diseases resulting in paraprotein production

Paraproteins (whole immunoglobulins and/or excess free immunoglobulin light chains (FLC)) are produced in a wide variety of haematological conditions covering a spectrum from low-grade to florid malignancy (Table 2).[3] Monoclonal proteins can be detected by serum or urine electrophoresis and immunofixation. FLCs are filtered freely 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 ~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 FLC can be used both diagnostically and to monitor treatment responses.[4] A renal biopsy is the key to diagnosing the underlying renal lesion, 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.[5]

Simplified classification of paraprotein-producing conditions

Plasma cell disorders

Monoclonal gammopathy of undetermined significance (MGUS) – premalignant plasma cell clone

Myeloma–malignant plasma cell

Solitary plasmacytoma–localized collection of malignant plasma cells

Lymphoproliferative disorders –malignant B cell clones

Lymphoplasmacytoid lymphoma (includes Waldenström's macroglobulinaemia) – IgM-producing malignant B cell clone

Non-Hodgkin's lymphoma

Chronic lymphocytic leukaemia (CLL)

Other

Viral related

- Hepatitis C related (usually cryoglobulinaemia)
- HIV related

Autoimmune

- Sjögrens syndrome
- Cryoglobulinaemia

Table 2

Myeloma

Multiple myeloma accounts for almost 10% of all haematological malignancies with an annual incidence of 4.3 per 100,000 population.[6] More than 50% of patients with myeloma will have some degree of renal impairment, which usually occurs early in the course of the disease. In the majority of cases, renal dysfunction is mild to moderate, due to a combination of volume depletion, hypercalcaemia and sepsis, compounded in many cases by nephrotoxic drugs, and will reverse with simple measures. 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: myeloma cast nephropathy tends to be asymptomatic and is often diagnosed at a late stage. Patients present with advanced myeloma and fatigue, infections or bone pain. Histologically, cast nephropathy is characterized by large, often fractured or laminated casts within the distal tubules and collecting ducts (Figure 1). Monoclonal FLCs aggregate with Tamm–Horsfall protein to produce casts, often surrounded by multinucleated giant cells and chronic interstitial damage. Myeloma casts are more likely to precipitate, causing tubular obstruction and acute renal failure in the presence of dehydration, hypercalcaemia, sepsis, or insults from contrast or non-steroidal anti-inflammatory drugs.[7] Although myeloma and its