

Bence Jones proteinuria and myeloma kidney

D. Chauveau and G. Choukroun

Department of Nephrology, Hôpital Necker, Paris, France

Key words: Bence-Jones proteinuria; myeloma kidney; Tamm-Horsfall protein; Bence-Jones proteinuria and myeloma kidney; treatment

Bence-Jones proteinuria refers to urinary excretion of monoclonal light chains. It results from exclusive production of one light chain, or the unbalanced synthesis of heavy and light chains, with the latter being in excess. Free κ - or λ -light chains are therefore excreted alone or in addition to complete immunoglobulin molecules carrying the same light chain type. Free light chains are low molecular weight proteins that diffuse to the whole extracellular compartment. Within the kidney they are filtered through the glomeruli, reabsorbed in the proximal tubule by receptor-mediated endocytosis and degraded in the tubular cells by lysosomal enzymes. Light chains appear in the urine when the metabolizing capacity of the nephron is exceeded. They are not detected by dipstick analysis, but the conventional sulphosalicylic acid test is generally reliable for screening. Free light chains usually migrate with α -2 mobility on electrophoretic techniques. Identification of the isotype (κ or λ) requires immunoelectrophoresis or immunofixation of the urine.

Associated conditions

With only rare exceptions, Bence-Jones proteinuria reflects a malignant condition. Multiple myeloma is the leading disorder, with 20% of patients excreting Bence-Jones proteinuria at presentation, and 60–80% during the course of the disease. Of note, multiple myeloma may exhibit the usual aggressive form, or follow a more smouldering course. AL amyloidosis, Waldenström's macroglobulinaemia, chronic lymphocytic leukaemia, and papular mucinosis are additional B-cell related disorders to be considered. In addition, long term follow-up of patients with 'idiopathic' Bence-Jones proteinuria indicates that most patients ultimately develop a malignant process, after an interval of as long as 20 years.

Although daily excretion of Bence-Jones protein varies widely, trends shown by monthly serial determinations furnish a useful index of progression of the underlying disease; an increment usually reflects a more aggressive form or relapse, while reduction implies responsiveness to chemotherapy. Gross variations have

less significance in patients with severe renal impairment. Once Bence-Jones proteinuria is identified, the variations are best determined by chemical quantification of proteinuria rather than repeated electrophoresis. On follow-up the latter is useful in large modifications suggestive of superimposed glomerular symptoms related to AL amyloidosis or monoclonal immunoglobulin deposition disease (Randall type).

What are the nephrotoxic consequences of Bence-Jones proteins?

The diversity of the pathologic features arising from monoclonal light chain is remarkable. Deposits in the kidney consist of fibrils in light chain (AL) amyloidosis, precipitates in light-chain deposition disease, crystals in the rare acquired Fanconi's syndrome or casts within the tubule in myeloma or cast nephropathy. Detection of monoclonal light chain in the urine is a prerequisite for myeloma kidney. However, the structural features that distinguish pathogenic from nonpathogenic light chains remain unknown. In this regard each light chain has its own intrinsic toxicity. Hence many patients excreting large amounts do not exhibit renal involvement. Isoelectric point (pI) and light chain isotype have been ruled out as risk factors for casts deposits. In contrast, physicochemical characteristics of the variable domain (V_L) light chain are likely to play a major role in the nephritogenic potential, as suggested by: (i) its recurrence in the renal graft, already documented 15 years ago and (ii) the emergence of animal models mimicking the various patterns of human renal lesions after injection of Bence-Jones proteins [1]. In these models, the experimental disease induced by nephritogenic monoclonal light chains is strikingly concordant with human lesions. Of note, nonnephritogenic Bence-Jones proteins in humans only rarely promote experimental disease.

The characteristic lesion of myeloma nephropathy consists of intratubular protein casts located in the distal nephron and collecting tubules which are surrounded by macrophagic reaction. Tubular atrophy, interstitial fibrosis and interstitial calcifications are often present. On rare occasions typical features of light chain deposition disease or crystalline deposits within proximal tubule cells may be associated. Casts essentially consist of Bence-Jones proteins that coagulate with Tamm-Horsfall protein (THP) [2]. The latter is a glycoprotein synthesized only in cells of the thick ascending limb of the loop of Henlé. It is released from the lipid bilayer of the apical membrane into the lumen of the distal nephron. The binding site for

Correspondence and offprint requests to: Dr D. Chauveau, Département de Néphrologie, Hôpital Necker, 161 rue de Sèvres, 75743 Paris Cedex 15, France.

Bence-Jones protein lies on the peptide portion. The precise role of the carbohydrate moiety of the molecule which expresses eight glycosylation sites is not yet known. Experimental models have shed light on environmental factors enhancing cast formation in the distal nephron. A high concentration of sodium chloride or calcium, extracellular fluid volume depletion, and direct perfusion of nephron with furosemide all enhance coaggregation. Colchicine prevents cast formation by decreasing THP release and altering the carbohydrate superstructure [3]. In addition, a propensity for both homotypic aggregation of THP and self association of nephrotoxic Bence-Jones protein forming polymeric aggregates has been shown *in vitro* under conditions comparable to those found in the kidney. Some of these aspects are in keeping with the clinical experience in humans: for instance, reduced GFR resulting from dehydration or use of nonsteroidal anti-inflammatory drugs (NSAIDs) promotes nephron obstruction by myeloma casts. Also, hypercalcemia *per se* or by initiating dehydration favors acute renal failure. Whether furosemide aggravates renal dysfunction in myeloma nephropathy has not been clearly determined in humans.

The pathogenic link between casts and tubulointerstitial damage is not clear. Resistance of myeloma casts to urinary proteases has been postulated. What then causes accumulation of multinucleated giant cells surrounding the casts? Disruption of the tubular basement membrane by casts may possibly allow THP to gain access to interstitial tissue. Recently it was demonstrated that THP is able to activate mononuclear cells and neutrophils *in vitro* [4].

Prevention and therapy of myeloma kidney

Specific aims of treatment in this disorder are to avoid the intratubular precipitation of light chains (symptomatic treatment) and to decrease their production (specific treatment). Symptomatic management is always indicated in patients with Bence-Jones proteinuria. Potentially nephrotoxic drugs including aminoglycosides and nonsteroidal anti-inflammatory drugs should be avoided. Radiocontrast media are also contraindicated, whatever their osmolality. Hypercalcaemia and possibly hyperuricaemia facilitate the coprecipitation of light chains with THP, and require specific therapy. Lessons from animal models suggest that alkalization of the urine and low concentration of sodium chloride in the distal nephron are useful to prevent cast formation. Although the corresponding data in patients are missing, we strongly support moderate salt intake, water intake in order to induce a 2–3 l of alkaline (pH \geq 7) diuresis per day and avoidance of loop diuretics.

Two additional therapeutic approaches have been proposed. First, the daily use of colchicine or a reducing agent capable of preventing binding between light chains and THP. The beneficial effects are not yet proven. Possibly specific inhibitors of the bond could

be designed in the near future. Second, in order to decrease more rapidly the circulating monoclonal protein while awaiting the effect of chemotherapy, some authors have used plasma exchange in the acute phase of renal failure. The results of the few studies available are controversial. Nevertheless, in a short randomized study of myeloma patients, improvement in renal function and survival was better when plasmapheresis was used [5].

In patients with myeloma kidney and acute renal failure a significant decrease of serum creatinine may be observed in the first month of treatment, most probably resulting from symptomatic treatment rather than chemotherapy. In those with end-stage renal failure (ESRF), regular dialysis is indicated as long as required to assess responsiveness to chemotherapy. Late regression of severe renal failure is rare but may occur up to 12 months and supports this approach. When ESRF is irreversible, dialysis should be pursued as long as extrarenal symptoms related to multiple myeloma are not too disabling.

The general approach to specific treatment of multiple myeloma applies to patients with cast nephropathy, except for dose and duration of chemotherapy. In addition, we specifically consider that any nephrotoxic Bence-Jones protein requires treatment whatever the stage of multiple myeloma. Despite the development of many drug combinations the classical melphalan-prednisone treatment (MP) introduced by Alexanian 25 years ago is still indicated for newly diagnosed symptomatic patients. MP induces remission in 50% of myeloma patients, is associated with a mean remission duration of 24 months and increases the median survival. In patients with glomerular filtration below 25 ml/min, the dose of melphalan should be reduced by approximately 50%. Multi-drug regimens, including VBMCP or VMCP/VBAP, produce better objective responses but median survival similar to MP [6]. The marginal benefit of these complex regimens and the poor haematologic tolerance in uremic patients contribute to retaining MP as first line treatment in this setting. In those who relapse during or soon after stopping first line therapy, the VAD association (vincristine, adriamycin, dexamethasone or methylprednisolone) leads to a 75% response rate. In newly diagnosed patients, the response rate is approximately 55%, with a more rapid onset of remission. This regimen can be applied without dosage adjustment in patients with renal failure. We currently use it as first line therapy especially in hypercalcaemic patients and those with acute renal failure. Interferon α (IFN α) has shown a modest activity as single agent for the treatment of myeloma, inducing responses in approximately 15% of previously untreated patients and in 10% of those with refractory myeloma. Its use has been advocated in the maintenance phase of the treatment. However, at the present time, there is no proof that IFN α can improve the survival rate in multiple myeloma.

The duration of chemotherapy in uraemic patients is still controversial. In responder patients without renal failure, the treatment is usually prolonged 6–12

months after obtaining a steady-state because pursuing chemotherapy does not improve overall survival. In patients with myeloma kidney, no definite information is available. In myeloma patients with stable chronic renal failure, we occasionally observed an accelerated course toward ESRF simultaneous with disruption of antineoplastic drugs. Therefore we recommend long-term maintenance of well tolerated chemotherapy in all patients exhibiting nephrotoxic light chains.

Due to poor prognosis of the disease, several groups have developed an aggressive therapeutic approach combining high-dose radiochemotherapy followed by allogenic or autologous bone marrow transplantation (BMT). This is currently applied in patients less than 55–60 years of age and having a severe form of multiple myeloma. Serum creatinine below 300 $\mu\text{mol/l}$ has been regarded as an exclusion criteria. Compared with autologous BMT, allogenic transplantation results in better efficiency with complete remission in 40% of the patients and a survival rate of 40% at 5 years but only applies to the rare patients who have an HLA-matched sibling. Because of its wide availability, the shorter period of cytopenia and the lesser risk of reinjecting tumoral cells, autologous peripheral blood-stem cells may be used after high dose chemotherapy (either cyclophosphamide and/or melphalan) with or without total body irradiation. Current results are encouraging with a median survival of 60 months and an event-free survival time of 45 months after transplantation [7]. Using the same procedure Pruna *al.* (unpublished observations) have treated 10 patients (median age

51 years) with myeloma renal failure ($\text{Ccr} \leq 60 \text{ ml/min}$, including two with $\text{Ccr} < 20 \text{ ml/min}$). Duration of aplasia was 15 days. No death was observed during the acute phase of the treatment but three patients required temporary haemodialysis. Four patients remain in complete remission at three years. Long-term tolerance of kidney irradiation in this setting is not yet known.

References

1. Solomon A, Weiss DT, Kattine AA. Nephrotoxic potential of Bence-Jones protein. *N Engl J Med* 1991; 324: 1845–1851
2. Huang ZQ, Kirk K, Connelly KG, Sanders PW. Bence-Jones proteins bind to a common peptide binding segment of Tamm-Horsfall glycoprotein to promote heterotypic aggregation. *J Clin Invest* 1993; 92: 2975–2983
3. Sanders PW, Booker BB. Pathobiology of cast nephropathy from human Bence Jones proteins. *J Clin Invest* 1992; 89: 630–639
4. Thomas DBL, Davies M, Williams JD. Release of gelatinase and superoxide from human mononuclear phagocytes in response to particulate Tamm-Horsfall protein. *Am J Pathol* 1993; 142: 249–260
5. Jonson WJ, Kyle RA, Pineda AA, O'Brien PC, Holley KE. Treatment of renal failure associated with multiple myeloma. Plasmapheresis, hemodialysis and chemotherapy. *Arch Intern Med* 1990; 150: 863–869
6. Alexanian R, Dimopoulos MA. Management of multiple myeloma. *Sem Hematology* 1995; 32: 20–30
7. Femand JP, Chevret S, Ravaud P, Divine M, Leblond V, Dreyfus F, Mariette X, Brouet JC. High-dose chemoradiotherapy and autologous blood-stem cell transplantation in multiple myeloma: Results of a phase II trial involving 63 patients. *Blood* 1993; 82: 2005–2009

Non-invasive circulating indicators of bone metabolism in uraemic patients: can they replace bone biopsy?

H. Schmidt-Gayk¹, T. Drüeke² and E. Ritz³

¹Endocrine Laboratory, Laboratory Group, Heidelberg, Germany; ²INSERM Unit 90, Nephrology Department, Necker Hospital, Paris, France; ³Department of Internal Medicine, University of Heidelberg, Germany

Key words: bone biopsy; PTH; aluminium; adynamic bone disease; bone-specific alkaline phosphatase; osteocalcin; procollagen type I C-terminal; propeptide; tartaric-resistant acid phosphatase; type I collagen cross-linked telopeptide; pyridinolines (cross-links, XL); pyridinolines (PYD, free and total); deoxypyridinoline; pyridinium cross-links

Introduction

Bone biopsy was indispensable in the early years of dialysis treatment, but in the following decades it was

felt by most workers that the diagnosis of hyperparathyroid bone disease could be established with sufficient reliability by a combination of X-rays of the hands, the skull and the long bones, serum alkaline phosphatase (AP), and plasma parathyroid hormone (PTH). The interest in bone biopsy was revived by the aluminium tragedy, as the extent of aluminium deposition and toxicity in bone cannot be deduced simply from plasma aluminium levels. With improved dialysis water treatment and the substitution of aluminium by calcium-containing phosphate binders it appeared that bone biopsies are unnecessary in most patients with chronic renal failure (CRF) if adequate treatment is provided and the serum chemistry (calcium, phosphate, creatinine, AP, 25-hydroxyvitamin D, and PTH levels) is adequately monitored. The introduction of plasma

Correspondence and offprint requests to: H. Schmidt-Gayk, MD, Endocrine Laboratory, Laboratory Group, Im Breitspiel 15, D-69126 Heidelberg, Germany