



Renal Involvement in Plasma Cell Dyscrasias

Sunil Prakash

Head of Nephrology Division, Department of Medicine, Central Hospital (N. Railways), New Delhi.

132

ABSTRACT

Multiple myeloma and amyloidosis are two main types of plasma cell dyscrasias. In multiple myeloma renal involvement is due to cast nephropathy and presentation is as ARF or as CKD.

In amyloidosis 75% patients have predominant glomerular deposition and present with heavy proteinuria and edema (nephrotic syndrome). In most patients only one type of renal disease is seen. Thus, patients with multiple myeloma (cast nephropathy) rarely develop the nephrotic syndrome due to amyloidosis and vice versa. Intratubular cast formation, direct tubular toxicity, high rate of light chain excretion, biochemical characteristics, concurrent volume depletion, hypercalcemia, hyperuricemia are main factors causing renal failure.

The clinical presentation of light and heavy chain diseases varies in part with the site of deposition. Patients with predominant glomerular deposition may present with nephrotic syndrome (similar to primary amyloidosis) while those with predominant tubular deposition may present with renal insufficiency and relatively mild proteinuria. The patients may also present with Fanconi's syndrome, osteomalacia etc. Proteinuric patients complaining of bone pains, who are anaemic, having neuropathies and unexplained cardiac failure must be evaluated by doing both electrophoresis and immunofixation studies (and not just one) of serum and urine.

Chemotherapy with avoidance of dehydration and hypercalcemia remains sheet anchor of therapy. NSAIDs and frusemide may worsen the nephropathy. There is also a general correlation between the presence and severity of renal disease and patient survival. Early dialytic support or plasmapheresis helps in quick recovery. Hemo or peritoneal dialysis may be required in patients who have reached end-stage renal disease. Autologous or allogenic hematopoietic cell transplantation improves survival by at least one year over and above other therapies.

Plasma cell disorders are monoclonal neoplasms with common B lymphocyte lineage. Multiple myeloma, primary amyloidosis, Waldenstrom's macroglobulinemia, light chain and heavy chain disease comprise this group.

MULTIPLE MYELOMA

It is also called myelomatosis, plasma cell myeloma, or Kahler's disease.

Definition

Multiple myeloma is malignant proliferation of plasma cells derived from a single clone. The tumor, its products (monoclonal immunoglobulins) and host response to it results in number of organ dysfunction and symptoms.

Clinical Features

- In 58% patients, bone pain, particularly in the back or chest, and less often in the extremities, was present at the time of diagnosis.¹

- Weakness and fatigue were common (32 percent).
- Weight loss was present in 24 percent, one-half of whom had a weight loss >9 kg.
- Pallor was the most frequent physical finding (in 80%).
- Palpable hepatomegaly, splenomegaly, and lymphadenopathy are rare (present in four, one, and one percent, respectively).
- Neurologic disease:
 - Radiculopathy usually in the thoracic or lumbosacral area is the most common neurologic complication of multiple myeloma.
 - Spinal cord compression from an extramedullary plasmacytoma occurs in 5 percent of patients.
- The incidence of infection is increased in multiple myeloma due to impairment in the antibody response, suppression of normal plasma cell function and during chemotherapy.
- Panhypogammaglobulinemia occurs in 10% of myeloma patients and 20 % patients of primary amyloidosis.

- Serum viscosity is increased in three-fourths of patients; signs and symptoms of hyperviscosity are seen in <10 %.
- Serum creatinine concentration is increased in almost one-half of patients at diagnosis.

Diagnosis of myeloma requires a bone marrow containing more than 10 percent plasma cells plus at least one of the following:

- A monoclonal protein (M-protein) in the serum (usually >3g/dl)
- M-protein in the urine
- Lytic bone lesions.

TYPES OF RENAL DISEASE

Four of the renal diseases in multiple myeloma, including the three of the most common (cast nephropathy, amyloidosis, and light chain deposition disease) are related to the overproduction of monoclonal immunoglobulin light chains.

The two major causes of renal insufficiency in patients with myeloma are cast nephropathy (also called myeloma kidney) and hypercalcemia.

Extent of problem: Serum creatinine concentration was increased in almost one-half of patients at diagnosis and was greater than 2 mg/dl (177µmol/l) in 19 percent. In many patients, renal failure is the presenting manifestation of multiple myeloma.

Renal involvement makes the prognosis grave.²

Myeloma Kidney

Myeloma kidney refers to acute or chronic renal failure that results from the filtration of toxic light chains which combine with Tamm-Horsfall mucoprotein (also called uromodulin), and this leads to both tubular injury and intratubular cast formation and obstruction. Large, waxy, laminated casts in the distal and collecting tubules are characteristic of cast nephropathy.^{3,4}

Amyloidosis

Primary (AL) or secondary (AA) amyloidosis can present with a variety of systemic symptoms or signs, including heavy proteinuria usually in the nephrotic range, edema, hepatosplenomegaly, otherwise unexplained congestive heart failure, and the carpal tunnel syndrome.

Primary (AL) amyloidosis: 20 percent of nephrotic patients over the age of 50 may have primary amyloidosis.

In contrast to myeloma kidney which comes as renal failure, these disorders typically produce nephrotic syndrome with a markedly positive dipstick for protein (albumin).

Here the amyloid fibrils are composed of fragments of monoclonal lambda light chains⁵ which are pathogenetically similar to light chain deposition disease except that the light chain deposits do not form fibrils and are mostly kappa light chains. The proportion of bone marrow plasma cells is usually below 20 percent, there are usually no lytic lesions, and the amount of Bence Jones proteinuria is generally modest. The diagnosis of primary amyloidosis is established by demonstrating amyloid on a biopsy of affected tissue, such as abdominal fat, bone marrow, rectum, or kidney. The amyloid fibrils have the ability to bind Congo red (leading to green birefringence under polarized light) and thioflavine-T (producing an intense yellow-green fluorescence)

- Different factors appear to predispose to the formation of amyloid deposits. Certain amino acids at specific sites on the light chain may facilitate protein unfolding and some light chains undergo self association thereby increasing the likelihood of forming tissue aggregates. In comparison, light chains from patients without renal disease generally do not form these aggregates.

Combination of Myeloma and Amyloidosis

In the great majority of patients, only one type of renal disease is seen. Thus, patients with multiple myeloma (cast nephropathy)⁶ rarely develop the nephrotic syndrome due to amyloidosis or light chain deposition disease, while patients with the latter disorders rarely develop acute renal failure from cast nephropathy.⁷ In a series of 1596 patients with primary amyloidosis seen at the Mayo Clinic between 1960 and 1994, only six (0.4 percent) showed delayed progression (at 10 to 81 months) to overt myeloma. This usually occurs in patients without cardiac or hepatic amyloid who live long enough to develop myeloma. It is important to distinguish this relatively strict separation of clinical disease from pathologic findings in which more than one type of disease is not so uncommon.

Renal tubular dysfunction

In some patients, the toxic effect of filtered light chains is limited to tubular dysfunction, with the glomerular filtration rate being relatively well maintained. The proximal tubules are most prominently affected, due to the reabsorption of filtered light chains and their subsequent accumulation in the proximal cells. The clinical manifestations of tubular dysfunction include-

Fanconi syndrome such as proximal renal tubular acidosis and phosphate wasting; the latter can lead to hypophosphatemia⁴ and osteomalacia. Proximal dysfunction can also exacerbate myeloma kidney by decreasing light chain reabsorption, thereby increasing light chain delivery to and promoting precipitation in the distal nephron.

Hypercalcemia

Hypercalcemia is a relatively common finding in multiple myeloma, with 15 percent of patients having a calcium concentration >11.0 mg/dl at the time of diagnosis. The rise in the plasma calcium concentration results from increased bone resorption, an effect that may be mediated in part by increased secretion of the bone resorbing cytokines lymphotoxin and interleukin-6. Hypercalcemia can contribute to the development of renal failure by causing renal vasoconstriction, by leading to intratubular calcium deposition, and perhaps by increasing the toxicity of filtered light chains. Patients with hypercalcemia and/or volume depletion of any cause are at risk of worsening renal function following the administration of a NSAID. As a result, NSAID therapy should be avoided if possible in patients with multiple myeloma.

Acute renal failure following radiocontrast agents

Acute renal failure is a potential, although infrequent (less than 1.5 %), complication of radiocontrast administration in patients with multiple myeloma. Prior volume depletion and urinary light chain excretion are present in almost all cases; the former may predispose to contrast nephropathy by enhancing light

chain precipitation within the tubules. Intratubular obstruction also may rarely develop via an interaction between the contrast agent and urinary light chains. Hydration prior to the study is likely to be protective if contrast must be given. It is not known if nonionic agents might be safer by minimizing any charge interaction between the contrast agent and the light chains.

Others

Type I cryoglobulinemia is a rare form of glomerular disease in patients with multiple myeloma.⁸ In this setting, the monoclonal immunoglobulin forms cryoprecipitates that can lead to a membranoproliferative pattern with intraluminal “thrombi” on renal biopsy.

Type II cryoglobulinemia is very rare (and probably unrelated) in myeloma.

Acute uric acid nephropathy is another potential problem, but sufficiently rapid tumor turnover is unusual, even after chemotherapy.

Plasma cell invasion of the kidney can occur in multiple myeloma, but it is rarely severe enough to impair renal function.

Renal involvement in Waldenström’s macroglobulinemia and heavy chain disease is uncommon.

Pathogenesis

Light chains have a molecular weight of approximately 22,000. They are freely filtered across the glomerulus and then largely reabsorbed by the proximal tubular cells. The normal rate of light chain excretion is less than 30 mg/day. In multiple myeloma, this reabsorptive capacity is exceeded due to overproduction of light chains resulting in their increased excretion that can range from 100 mg to more than 20 grams per day.

Light chains lead to renal failure by following mechanisms-

- Intratubular cast formation
- Direct tubular toxicity
- High rate of light chain excretion
- Biochemical characteristics (only some are nephrotoxic)
- Concurrent volume depletion (which may promote cast formation by slowing flow within the tubules).
- Hypercalcemia increases the nephrotoxicity of light chains, due to calcium in the tubular lumen promoting cast formation.
- Radiocontrast media. Although fluid restriction prior to the study is an important predisposing factor, an interaction between the dye and the light chains may promote intratubular obstruction.

Role of tubular injury

Cast formation is relatively minor in some patients in whom the degree of renal failure correlates best with tubular damage and atrophy. Tubular injury, at least in the proximal tubule, presumably results from the reabsorption of some of the filtered light chains into the tubular cell. Their accumulation within the cell may then interfere with lysosomal function and initiate giant cell reaction.⁹

Tubular injury can promote the development of renal failure, by decreasing further proximal light chain reabsorption, thereby

increasing delivery to the distal nephron where cast formation can occur. Light chains can also interfere with tubular function in the loop of Henle. The ensuing increase in tubular fluid sodium chloride concentration (since less is being reabsorbed) can also promote cast formation by increasing the aggregation of light chains with locally released Tamm-Horsfall mucoprotein. Frusemide can enhance cast formation by the same mechanism: an elevation in the luminal sodium chloride concentration. This may be important clinically, since loop diuretics are often given empirically (and perhaps deleteriously) to patients with myeloma kidney in an attempt to wash out obstructing casts.⁵

Recent understanding of cast nephropathy

- A specific binding site for immunoglobulin light chains has been identified on THMP; this site consists of a linear sequence of nine amino acids. Light chains with high affinity appear to be more likely to produce obstructing intratubular casts. Therefore different light chains have a variable nephrotoxic potential.
- Another contributing factor to THMP binding and the predisposition to cast nephropathy may be the isoelectric point (pI) of the light chain. Those Bence Jones proteins with a pI above 5.1 (that is, above the tubular fluid pH in the distal nephron) will have a net positive charge, a characteristic that may promote binding via charge interaction to anionic THMP (pI = 3.2). Urinary alkalinization might therefore be beneficial.¹⁰

Changing the charge on a single histidine residue in the binding site of Tamm-Horsfall mucoprotein appears to be largely responsible for the reduction in light chain binding with alkalinization. Raising the urinary pH will also cause the light chains to become less cationic or even anionic, another factor that could decrease the interaction with Tamm-Horsfall mucoprotein.

- **Interleukin-6** – Interleukin-6 (IL-6) is an important growth factor for plasma cells in multiple myeloma. This process may be enhanced in bone where myeloma cells may upregulate IL-6 production by osteoblasts and marrow stromal cells. IL-6 also may contribute to the development of hypercalcemia in multiple myeloma and other malignancies, in part by direct stimulation of osteoclast function.

Investigations

- The most important diagnostic finding in multiple myeloma is the demonstration of a monoclonal (M) protein in the serum and/or urine in 97 percent of patients.
- A normocytic, normochromic anemia (73 % at diagnosis and in 97 % at some time during the course of the disease)
- ESR >20 mm/h in 84 % and >100 mm in 33%
- Plasmacytosis in the peripheral smear was infrequent.
- **24-hour urine collection** – Patients with a serum M-protein concentration >1.5 g/dl or those with a diagnosis or clinical suspicion of a plasma cell dyscrasia should have electrophoresis and immunofixation on a 24-hour urine collection. This test is essential to detect the presence of potentially nephrotoxic concentrations of urinary light chains.
- If electrophoresis of the urine reveals a localized globulin band and immunofixation does not demonstrate a

monoclonal light chain, one should suspect the possibility of gamma heavy chain disease. Immunofixation should then be performed with antisera to IgG (gamma heavy chains).

- Light chains are usually not detected by the urinary dipstick, which primarily senses albumin. Thus, the urine in such a patient should be tested with sulfosalicylic acid (SSA) which detects all proteins. A markedly positive SSA test with a relatively negative dipstick is suggestive of the presence of non-albumin proteins, such as light chains. Their presence can be confirmed and quantitated in plasma and urine through the use of electrophoretic and immunofixation techniques.
- Immunofixation (IFE) is the diagnostic test as it is critical for the differentiation of a monoclonal from a polyclonal increase in immunoglobulins. Immunofixation will detect a serum M-protein at a concentration of at least 0.02 g/dl and a urine M-protein at a concentration of ≥ 0.004 g/dl.
- Bone disease - Conventional radiographs revealed an abnormality in approximately 80 percent of patients at the time of diagnosis. Focal lytic lesions were found in 57 percent and approximately 20 percent each had osteoporosis, pathologic fractures, or compression fractures of the spine. Osteosclerotic lesions are rare.
- Bone marrow containing more than 10 percent plasma cells (or presence of a plasmacytoma)
- Computed tomography or MRI may be helpful in patients who have bone pain but no abnormalities on the roentgenograms. MRI may also be of prognostic value in determining which patient with low cell mass myeloma is most likely to progress.

HOW TO SUSPECT AND DIAGNOSE?

- Heavy proteinuria in a patient over age 50, symptoms and signs of hypercalcemia, hypergammaglobulinemia, immunoglobulin deficiency, Bence Jones proteinuria, or recurrent infections.
- The combination of a 3+ or 4+ sulfosalicylic acid test (SSA test) and a negative or trace dipstick is usually indicative of a non-albumin protein in the urine. In the adult over age 50, this is most often a monoclonal light chain.
- IFE should always be performed in the presence of otherwise unexplained sensory motor peripheral neuropathy, nephrotic syndrome, refractory heart failure, orthostatic hypotension, carpal tunnel syndrome, malabsorption, or whenever the clinical situation strongly suggests the possibility of primary amyloidosis
- The findings of hypercalcemia, bone pain, or lytic bone lesions in a patient with a 3+ or 4+ urine dipstick for protein is suggestive of the combination of myeloma and amyloidosis.
- If the patient has nephrotic syndrome, the presence of a monoclonal light chain strongly suggests either primary amyloidosis (AL) or light chain deposition disease in almost all instances.

TREATMENT

1. Vigorous hydration and maintenance of a high urine output (>3 liters/24 hours)

2. Urinary alkalinization, raising the urinary pH>6.5
3. Administration of colchicine is another method to diminish intratubular cast formation. Colchicine⁵ may act by reducing the excretion of THMP and by modifying its ability to bind to light chains. The clinical applicability of these observations is at present uncertain.
4. Avoidance of loop diuretics unless the patient is hypercalcemic.
5. Bisphosphonates: There is increasing evidence that bisphosphonate therapy may prevent skeletal complications and improve survival in patients with multiple myeloma. Intravenous bisphosphonates have a beneficial impact on pain control and preventing impending fractures.¹¹
6. Chemotherapy e.g. VAD, melphalan + prednisolone etc. is not in the scope of this review.
7. Plasmapheresis: Rapidly lowers the circulating light chain load but does not prevent formation of new chains.¹²
8. Dialysis, as and when necessary. It is less effective than plasmapheresis in lowering light chain levels.¹³
9. Autologous or allogenic hematopoietic cell transplantation (HCT) may be of cord, peripheral blood or marrow stem cells.¹⁴ The absolute number of CD34+ cells/kg of recipient weight has proven to be the most reliable and practical method for determining the adequacy of a stem cell product.¹⁵ Interferon is required post-HCT.
10. End-stage renal disease- Patients can be treated with hemodialysis or peritoneal dialysis and survival is approximately 45 percent at one year, and 25 to 30 percent at two to three years.

Prevention

It remains the cornerstone of management of myeloma patients. Two modalities are indicated in almost all patients: 1) Chemotherapy or stem cell or bone marrow transplantation to decrease the filtered light chain load and 2) Prevention of volume depletion and maintenance of a high fluid intake to decrease the light chain concentration within the tubular lumen.

PROGNOSIS

- There is general correlation between the presence and severity of renal disease and patient survival. One year patient survival was 80 percent in those with a plasma creatinine concentration below 1.5 mg/dl (130 μ mol /L) versus 50 percent in those with a plasma creatinine concentration above 2.3 mg/dl (200 μ mol/L).
- The response of the renal disease to therapy also appears to have prognostic value. Renal functional recovery was seen in 26 percent of those with renal insufficiency at presentation. These patients had a median survival of 28 months compared to four months in those with irreversible renal failure.
- Patients who respond to chemotherapy with a reduction in light chain burden do much better, with a mean survival rate in one study being as high as 47 months versus only 17 months in non-responders.
- Serum concentrations of beta-2 microglobulin, C-reactive protein, and lactate dehydrogenase should be measured, since elevated values are associated with a worse prognosis.

- Plasma cell labeling index – The plasma cell DNA labeling index (PCLI) is helpful in differentiating MGUS *or* silent (SMM) from multiple myeloma. An elevated value is a powerful prognostic factor, strongly suggesting that the patient has, or will soon have, symptomatic disease. Such a finding is rare in patients with MGUS.
- Overexpression of cyclin D1 (bcl-1) was noted in 30 percent of patients with MM in one study, and, in a multivariate model, correlated significantly with reduced survival (relative risk 7.3, $p < 0.0007$).
- Autologous HCT adds at least a year to that achieved by chemotherapy.¹⁶

Mayo Clinic¹ suggests following adverse prognostic risk factors for survival: (Relative risks in brackets)

- Age \geq years (1.5)
- Performance status 3 or 4 (1.9)
- Serum albumin < 3 g/dL (1.7)
- Serum creatinine ≥ 2 mg/dL (1.5)
- Platelet count $< 150,000/\mu\text{L}$ (1.5)
- Beta-2-microglobulin > 4 mg/L (1.5)
- Plasma cell labeling index ≥ 1 percent (1.5)
- Serum calcium ≥ 11 mg/dL (1.3)
- Hemoglobin < 10 g/dL (1.3)
- Bone marrow plasma cell percentage ≥ 50 percent (1.2)

REFERENCES

1. Kyle, RA, Gertz, MA, Witzig, TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* 2003;78:21.
2. Lin J, Markowitz GS, Valeri AM, Kambham N, Sherman WH, Appel GB, D'Agati VD. Renal monoclonal immunoglobulin deposition disease: the disease spectrum. *J Am Soc Nephrol* 2001;12:1482-92.
3. Sanders PW. Pathogenesis and treatment of myeloma kidney. *J Lab Clin Med* 1994;124:484-8.
4. Winearls, CG. Acute myeloma kidney. Pathogenesis and treatment of myeloma kidney. *Kid Int* 1995;48:1347.
5. Solomon A, Frangione B, Franklin EC. Bence Jones proteins and light chains of immunoglobulins. Preferential association of the V lambda VI subgroup of human light chains with amyloidosis AL (lambda). *J Clin Invest* 1982;70:453-60.
6. Sanders PW, Booker BB. Pathobiology of cast nephropathy from human Bence Jones proteins. *J Clin Invest* 1992;89:630-9.

7. Hill GS, Morel-Maroger L, Mery JP, Brouet JC, Mignon F. Renal lesions in multiple myeloma: their relationship to associated protein abnormalities. *Am J Kidney Dis* 1983;2:423-38.
8. Moroni G, Banfi G, Maccario M, Mereghetti M, Ponticelli C. Extracapillary glomerulonephritis and renal amyloidosis. *Am J Kidney Dis* 1996;28:695-9.
9. Pirani CL, Silva F, D'Agati V, Chander P, Striker LM. Renal lesions in plasma cell dyscrasias: ultrastructural observations. *Am J Kidney Dis* 1987; 10:208-21.
10. Holland MD, Galla JH, Sanders PW, Luke RG. Effect of urinary pH and diatrizoate on Bence Jones protein nephrotoxicity in the rat. *Kidney Int* 1985;27:46-50.
11. Vinholes JJ, Purohit OP, Abbey ME, Eastell R, Coleman RE. Relationships between biochemical and symptomatic response in a double-blind randomised trial of pamidronate for metastatic bone disease. *Ann Oncol* 1997;8:1243-50.
12. Johnson 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;150:863-9.
13. Misiani R, Tiraboschi G, Mingardi G, Mecca G. Management of myeloma kidney: an anti-light-chain approach. *Am J Kidney Dis* 1987;10:28-33.
14. Hahn T, Wingard JR, Anderson KC, Bensinger WI, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of multiple myeloma: an evidence-based review. *Biol Blood Marrow Transplant* 2003;9:4-37.
15. Fruehauf S, Schmitt K, Veldwijk MR, et al. Peripheral blood progenitor cell (PBPC) counts during steady-state haemopoiesis enable the estimation of the yield of mobilized PBPC after granulocyte colony-stimulating factor supported cytotoxic chemotherapy: an update on 100 patients. *Br J Haematol* 1999;105:786-94.
16. Blade J, Vesole DH, Gertz Me. Controversy in hematology. Transplantation for multiple myeloma: who, when, how often? High-dose therapy in multiple myeloma. *Blood* 2003;102:3469-77.

FURTHER READING

- DeFronzo RA, Cooke CR, Wright JR, Humphrey RL. Renal function in patients with multiple myeloma. *Medicine (Baltimore)* 1978;57:151-66.
- Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol* 2003;121:749-757.
- Solomon A, Weiss DT, Kattine AA. Nephrotoxic potential of Bence Jones proteins. *N Engl J Med* 1991;324:1845-51.
- Jacobson JL, Hussein MA, Barlogie B, Durie BG, Crowley JJ. A new staging system for multiple myeloma patients based on the Southwest Oncology Group (SWOG) experience. *Br J Haematol* 2003;122:441-450.
- Following site gives updated articles on therapeutic aspects. http://www.cancercare.on.ca/access_PEBC.htm