

Henry Ford Health

## Henry Ford Health Scholarly Commons

---

Nephrology Articles

Nephrology

---

9-1-2012

### Monoclonal Gammopathies: Disambiguation

Jerry Yee

*Henry Ford Health, JYEE1@hfhs.org*

Follow this and additional works at: [https://scholarlycommons.henryford.com/nephrology\\_articles](https://scholarlycommons.henryford.com/nephrology_articles)

---

#### Recommended Citation

Yee J. Monoclonal Gammopathies: Disambiguation. *Advances in Chronic Kidney Disease* 2012; 19(5):277-278.

This Article is brought to you for free and open access by the Nephrology at Henry Ford Health Scholarly Commons. It has been accepted for inclusion in Nephrology Articles by an authorized administrator of Henry Ford Health Scholarly Commons.

## Monoclonal Gammopathies: Disambiguation

Nearly two years ago, at one of Detroit's Intra-City Kidney Grand Rounds, two prominent nephrologists somewhat feverishly debated the basics concerning the management of a case of acute kidney injury in a patient with multiple myeloma who required hemodialysis. Hypercalcemia was not present and had been ruled out of the usual differential diagnostic possibilities. Intravenous radiocontrast had not imperiled the renal organs, and antibiotic-associated nephrotoxicity was also absent. Any question of the adequacy of the effective circulatory volume had been dispensed with and there was no outpouring of urate and/or phosphate from cells as a consequence of chemotherapy. Were Bence Jones proteins, which appear in nearly two-thirds of cases of multiple myeloma, the causative agent?<sup>1</sup> They were, and the fractured casts of myeloma kidney (cast nephropathy) on kidney biopsy resolved the riddle.

What's next for the patient? On one hand, a therapeutic "go all out" approach was proffered by the protagonist, and this would include light chain plasmapheresis and potentially other therapies. The antagonist purveyed the opinion of therapeutic nihilism, to a degree, because of the extent of renal impairment that the patient had incurred. Plasmapheresis therapy should be eschewed. This opinion was the product of many years of clinical experience and an approach that had been substantiated nearly four decades earlier: patients with myeloma and acute kidney disease do not fare well, particularly when hemodialysis is required.<sup>2</sup> However, with the passage of time, despite advances in the treatment of light-chainopathies and myeloma, diagnostic and therapeutic ambiguity for this group of disorders remains, as underscored our debaters.

The genesis of the topic for this multinational issue of *Advances in Chronic Kidney Disease*, with Guest Editors Colin Hutchinson and Paul Sanders, began that evening. These individuals, as representatives of the International Kidney and Monoclonal Gammopathy Research Group, have undertaken several tasks: (1) acknowledging the importance of preclinical work that has facilitated a modern

approach to diagnosis and therapy, (2) emphasizing the importance of establishing monoclonal gammopathy early on because paraprotein toxicity is cumulative, (3) describing state-of-the-art treatments, and (4) accentuating the importance of multidisciplinary collaboration in the clinical management of a given patient, wherein hematologist and nephrologist are synchronously engaged.

Paraproteins are generally categorized as 3 types: light chains, heavy chains, and intact or whole immunoglobulins. The prefix "para" has produced more confusion among medical students, residents, and faculty than intended but was intentional. Coined "paraprotein" before the advent of amino acid determination, knowledge that the 22-kDa, 214-amino acid Bence Jones paraprotein was a protein required the vision, innovation, and indefatigable effort of Frank Putnam, PhD.<sup>3</sup> His extended body of work elucidated the constant and variable regions of kappa light chains and their disulfide bridges. Therefore, we must be specific when discussing paraproteins, since we now know what they are. "Para" means beside, and the term paraprotein must be cast aside in deference to specificity.

Now we have more powerful techniques and serum free light chain analysis is one of them. This highly sensitive test, performed by calculation of the serum kappa-to-lambda free light chain ratio, may signal the onset of amyloid light chain amyloidosis or multiple myeloma, even the smoldering or nonsecretory types. An earlier identification of a rogue  $\kappa$  or  $\lambda$  light chain is far superior to its later detection in urine, where it will be heralded by its coprecipitation—particularly in a high chloride concentration milieu—with Tamm-Horsfall mucoproteinaceous polymers, having now escaped its usual fate of proximal tubular reabsorption, attributable to the

*The author has nothing to disclose.*

© 2012 by the National Kidney Foundation, Inc. All rights reserved.

1548-5595/\$36.00

<http://dx.doi.org/10.1053/j.ackd.2012.07.007>

impairment rendered by constant engorgement of the selfsame light chain, ie, overflow proteinuria. Simply, light chains poison the kidney by virtue of their entry into the urine from the plasma. Therefore, one should look there first. Combined with serum protein electrophoresis and reflex serum immunoelectrophoresis, the specificity of free light chain analysis becomes substantially greater. The free light chain evaluation also bears prognostic significance in monoclonal gammopathy of undetermined significance, multiple myeloma, and chronic lymphocytic leukemia.<sup>4-6</sup> Finally, the reference range for serum free light chain immunoassays should be adjusted for patients with estimated glomerular filtration rates  $<60$  mL/min/1.73 m<sup>2</sup> to reduce the false-positive rate of this test.<sup>7</sup>

With regard to diagnosis in patients with monoclonal gammopathy, percutaneous kidney biopsy is safe and necessary.<sup>8</sup> Although it is an issue that many would avoid, Fish and colleagues amply demonstrated with real-time ultrasound imaging that the frequency of major renal hemorrhage in their 148-patient study (4.1%) was equivalent to that of a control population (3.9%) who had undergone native biopsies. It is best to heed this group's cautious advice: "The conclusion that the presence of a paraprotein in the context of renal injury equates to a causal association cannot be drawn because of the high frequency of incidental paraproteins in this setting. For this reason, assessment of renal pathology is essential. In addition to confirming the underlying disorder and therefore, allowing the initiation of disease-specific treatment, pathologic features are also prognostic of clinical outcomes." I agree. So, "just do it," because acute kidney injury of unknown cause in two nonobstructed, normal size kidneys remains a clear-cut motive for histologic examination.

If myeloma is present along with kidney dysfunction, the prognosis is poorer, as alluded to previously; however, if light chain levels are reduced, the possibility of the kidney recovering is likely improved. Independence from kidney replacement therapy for those who require it may even occur. Reduction in the light chain burden can be achieved by combinations of high-dose pulse dexamethasone and newer agents, particularly the first-in-class, boronic acid-containing, proteasomal inhibitor bortezomib. This agent may offer the most rapid responses to therapy and does not require kidney dose adjustment. It is important to note that in monoclonal gammopathy, patients with acute kidney injury who require dialytic therapy, the speed of reduction of the light chain burden corresponds with the rate of kidney recov-

ery. The rate of removal of light chains can now be hastened by using specialized high cutoff membranes that permit enhanced flux of light chains from the extracorporeal circuit.<sup>9</sup> The introduction of these membranes represents a substantial advancement over plasmapheresis, which has not been a consistently effective therapeutic modality.

It has been 165 years since the English physician Henry Bence Jones discovered his eponymous paraprotein.<sup>10</sup> Anomalous at first because of its unusual characteristics, the light chains that constituted it were subsequently dissected by Putnam and now can be characterized and treated. The situation of acute kidney injury in the presence of a monoclonal gammopathy continues to loom large, but there is now more hope than ever, attributable to the advances described in this epistolary by Hutchinson and Sanders, who have expertly disambiguated the monoclonal gammopathies.

Jerry Yee, MD  
Editor-in-Chief

## References

- Hoffbrand V, Moss P, Pettit J. *Essential Haematology*. 5th ed. Malden, MA: Blackwell Publishing, 2006:218.
- Defronzo RA, Humphrey RL, Wright JR, Cooke CR. Acute renal failure in multiple myeloma. *Medicine*. 1975;54:209-223.
- Kresge N, Simoni RD, Hill RL. The structure of Bence-Jones Proteins: the work of Frank W. Putnam. *J Biol Chem*. 282:e32. Available at: [http://www.meddybemplake.com/html/frank\\_putnam\\_sr\\_.html](http://www.meddybemplake.com/html/frank_putnam_sr_.html). Accessed July 23, 2012.
- Dispenzieri A, Kyle R, Merlini G, et al. International Myeloma Working Group guidelines for serum-free light-chain analysis in multiple myeloma and related disorders. *Leukemia*. 2009;23:215-224.
- Kyrtsonis MC, Vassilakopoulos TP, Kafasi N, et al. Prognostic value of serum free light chain ratio at diagnosis in multiple myeloma. *Brit J Haematol*. 2007;137:240-243.
- Pratt G, Harding S, Holder R, et al. Abnormal serum free light chain ratios are associated with poor survival and may reflect biological subgroups in patients with chronic lymphocytic leukaemia. *Br J Haematol*. 2009;144:217-222.
- Hutchison CA, Plant T, Drayson M, et al. Serum free light chain measurement aids the diagnosis of myeloma in patients with severe renal failure. *BMC Nephrol*. 2008;9:11.
- Fish R, Pinney J, Jain P, et al. The incidence of major hemorrhagic complications after renal biopsies in patients with monoclonal gammopathies. *Clin J Am Soc Nephrol*. 2010;5:1977-1980.
- Hutchison CA, Heyne N, Airia P, et al. Immunoglobulin free light chain levels and recovery from myeloma kidney on treatment with chemotherapy and high cut-off haemodialysis. *Nephrol Dial Transplant*. 2012 Jan 23. [Epub ahead of print].
- Rosenfeld L. Henry Bence Jones (1813-1873): The best "chemical doctor" in London. *Clin Chem*. 1987;33:1687-1692.