

Plasma cell dyscrasia - The nephrology perspective

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Abstract

Plasma cell dyscrasias are known to cause various manifestations in the kidney. The International Myeloma Working Group has proposed updated criteria for diagnosis of multiple myeloma in 2014, which has included free light chain assay in the diagnosis. Due to the short half-life of FLCs, the assay can be useful potentially for earlier monitoring of the efficacy of a given therapeutic program but their role in prognosticating myeloma is a matter of debate. When FLC production is increased, FLCs can be isolated from urine but they can also remain in distal tubular structures, forming crystalline aggregates with the Tamm-Horsfall glycoprotein or uromodulin, appearing as eosinophilic casts under light microscopy examination; the so called myeloma cast nephropathy. Our experience with regards to the clinicopathological profile, use of free light chain assay and stem cells at Amrita Institute of Medical Sciences, which is a tertiary care hospital at Kochi - is a compilation of three studies conducted at the Department of Nephrology, AIMS. The study population was 162. Renal failure was detected in 53% of study population. Renal biopsy was performed in 42 patients. The renal manifestations of multiple myeloma were amyloidosis 15%, cast nephropathy 41%, MIDD 12% and others 4.7%. Renal failure was noted in 100% of MIDD, 94% cast nephropathy and 39% amyloidosis patients. Kappa FLC was much more prevalent than lambda chains in renal failure and non-renal failure groups. Lambda FLC - higher risk for renal failure. Delta FLC - better prognostic marker for renal failure. Kappa FLC involvement has better renal prognosis. LCDD -better renal prognosis at 12 months following treatment. Out of the study population, 35 patients underwent autologous stem cell transplantation. Mortality rate was 3%. Two patients developed worsening AKI following stem cell transplant. Dialysis dependency is more common with cast nephropathy. Lambda FLC is associated with renal failure. Autologous stem cell transplant is a viable treatment option for myeloma patients. Efficacy on FLC reduction by High cut off -HD filters has been demonstrated, but its impact on renal clinical outcomes remains unclear. It seems that some factors could influence the outcomes of these therapies. Certainly, the information provided by the kidney biopsy is relevant for guiding treatment in cases with severe renal involvement. More efforts are needed to improve kidney outcomes in patients with MM and renal injury.

Introduction:

The term 'plasma cell dyscrasia' may be interpreted broadly as any type of anatomical, developmental, or functional alteration in the B cell or humoral system. Specifically, the diseases or syndromes associated with plasma cell dyscrasias result from under or over proliferation of the most differentiated cellular elements of this system, plasma cells and their immediate B lymphocyte precursors, or from immunoglobulin molecules which are produced by these cells and function as antibody. The plasma cell dyscrasias include a spectrum of diseases. They may be inherited or acquired, reactive or neoplastic, but all are characterized by some type of Ig alteration. In addition, these diseases may be intrinsic to B cells only or may involve other types of cells or factors that control B cell growth and maturation. Quantitative and qualitative alterations in Ig synthesis are hallmarks or 'biomarkers' of the plasma cell dyscrasias. These changes, which are characterized by the under or over production of Ig, can involve any of the protein components that constitute the humoral immune system. Proliferative disorders that involve a particular B cell clone are typically manifested by the particular Ig product of that clone. These homogeneous Ig products are called monoclonal Igs or M-proteins. Monoclonal Igs occur as 'complete' Ig molecules, or as 'incomplete' components that are

subunits, fragments, or atypical forms of the native protein. The most common example of an Ig subunit is Bence Jones protein, which represents monoclonal light chains. Alternatively, proliferative multiclonal B cell disorders are characterized by multiple Ig products. The term polyclonal Ig refers to the heterogeneous Ig products of this type of alteration. The fact that Igs serve as indicators of plasma cell and other B cell related dyscrasias has considerable diagnostic import. The widespread use of electrophoretic and other types of serological analyses provides a ready means to detect and identify Ig abnormalities in serum and urine specimens. Plasma cell dyscrasias represent a group of diseases characterized by the clonal expansion of abnormal plasma cells. The result of this clonal expansion is the overproduction of a monoclonal protein which could be either the whole immunoglobulin or a fragment. Thus, these disorders are also collectively referred to as monoclonal gammopathies.

The most common monoclonal plasma cell disorders are monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, multiple myeloma, light-chain amyloidosis, and Waldenström macroglobulinemia. MGUS and SMM are asymptomatic disorders that by definition lack end-organ damage. On the other hand, multiple myeloma is characterized by the presence of end-organ damage, most commonly anemia, hypercalcemia, renal failure, and osteolytic

bone lesions. AL amyloidosis is a less common disorder that can affect any organ, the most common being heart, kidney-nephrotic syndrome or renal failure, liver, gastrointestinal tract, and peripheral nerves. Waldenström macroglobulinemia is associated with an immunoglobulin M monoclonal protein, and can cause hyperviscosity syndrome, anemia, lymphadenopathy, and hepatosplenomegaly. Monoclonal plasma cell disorders are common with monoclonal gammopathy of undetermined significance (MGUS) affecting up to 3.2% of all patients over the age of 50 and with multiple myeloma (MM) accounting for 10% of all hematologic malignancies.^{1,2} Renal insufficiency, defined by abnormal creatinine clearance, is present in up to half of myeloma patients at presentation, contributes to excessive early mortality, and diminishes eligibility and clinical outcomes after both systemic therapy and high-dose stem cell transplantation, as well as novel treatments. Indeed, reversibility of myeloma-associated renal impairment is a critically important prognostic factor and even supercedes response to systemic therapy as a predictor of improved survival.⁵ This review will discuss the mechanisms of kidney injury in monoclonal plasma cell disorders, while highlighting recent advances in the detection of monoclonal immunoglobulin, the availability of new renoprotective chemotherapeutic approaches, and the ongoing research into the roles of plasmapheresis and kidney transplantation in these diseases.

Conclusion:

A number of significant challenges remain in the diagnosis of these conditions, some of which will be discussed in this article. Dealing with these challenges will require additional translational efforts and close cooperation between basic researchers, clinicians, and pathologists in order to improve the diagnostic tools available to renal pathologists and to acquire a more complete understanding of clinical and pathologic manifestations associated with these conditions. Plasma cell malignancies are commonly associated with kidney injury, often as a result of nephrotoxic monoclonal Ig. Traditional electrophoretic techniques remain the gold standard for identifying monoclonal Ig, whereas the serum FLC assay provides an additional tool for identifying and monitoring monoclonal Ig levels, particularly FLCs. Bortezomib, lenalidomide, and other agents appear to be more effective and selective for plasma cells and their microenvironment, with clear superiority now evident over traditional chemotherapy, and bortezomib appears to have a particular role in patients with myeloma-associated kidney injury. Autologous SCT remains a critical part of myeloma management but its use is limited in patients with kidney disease and its overall role will continue to evolve as systemic therapy improves. The value of plasma exchange for myeloma-associated kidney injury is an area of active research. Kidney transplantation is an option only in well-selected patients who have enjoyed prolonged remission and have low monoclonal Ig levels. Wider use of kidney biopsy to identify monoclonal protein deposition in patients with mild degrees of kidney dysfunction may be indicated as therapeutic options improve.