Moving Points in Nephrology

Light Chains, Casts, Sheets and Fibrils: Monoclonal Immunoglobulin Diseases and Immunotactoid/Fibrillary Glomerulopathy

Laura M. Dember

Renal Section, Department of Medicine, Boston University School of Medicine

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Immunoglobulin (Ig)-mediated kidney disorders can be divided into those that result from deposition into the kidney of intact Ig molecules and those caused by components of Ig molecules—usually light chains or light chain fragments, and, less frequently, heavy chains or heavy chain fragments. In the intact Ig disorders, such as IgA nephropathy, membranous nephropathy, lupus nephritis, and anti–glomerular basement membrane disease, the Ig molecules are typically polyclonal and deposit either as pre-formed immune complexes or interact directly with kidney antigens. In contrast, in the disorders caused by Ig components, the pathogenic protein is usually produced by a clonal population of plasma cells or B lymphocytes and thus is monoclonal. Monoclonal light chains can impair kidney function in a variety of ways: (*1*) by depositing into the glomerular basement membrane and/or tubular basement membranes as in light-chain deposition disease, (*2*) by forming casts within tubular lumens as in myeloma cast nephropathy, (*3*) by directly injuring proximal tubule epithelial cells as in Fanconi syndrome, and (*4*) by forming fibrils high in β-pleated sheet content that deposit in the basement membranes, mesangium, interstitium and vessels, as in light-chain (AL) amyloidosis.

The subject of this Moving Points in Nephrology series is disorders associated with monoclonal Ig-mediated kidney disease and immunotactoid/fibrillary glomerulopathy. One might wonder why immunotactoid/fibrillary glomerulopathy is included in the series when, in this entity (or group of entities), the Ig component of the fibrils often appears not to be monoclonal and, in many cases, the fibrils contain intact Ig molecules rather than simply light chains or heavy chains. However, the fibril-forming capacity of the pathogenic protein(s) makes the disorder similar in an important respect to AL amyloidosis, and the morphologic uniformity of the fibrils within individual patients, as well as the presence of a lymphoproliferative disorder in some patients, raises the question of whether a monoclonal component is a critical factor in the formation of the fibrils. Although clearly not established, it is plausible that the apparent polyclonality of immunotactoid/fibrillary glomerulopathy results from incorporation of Ig molecules into a fibril that has a monoclonal "core."

Dr. Laura Dember is an Associate Professor of Medicine and a member of the Renal Section and the Amyloid Treatment and Research Program at the Boston University School of Medicine.

Treatments for multiple myeloma and AL amyloidosis have progressed remarkably rapidly during the past decade, making these diseases particularly well-suited for a series entitled "Moving Points." In the article on multiple myeloma, Seema Singhal and Jayesh Mehta point out that the recent identification of three new therapeutic agents for this disease (thalidomide, lenalidomide, and bortezomib) has been associated with a substantial increase in median survival and has provided treatment options for the high proportion of patients who have disease relapse after an initial response to high-dose melphalan-based chemotherapy. AL amyloidosis, previously a nearly uniformly fatal disease, is now curable in a sizable proportion of patients with the use of myeloablative chemotherapy and autologous hematopoietic stem cell transplantation. Applying this treatment approach to AL amyloidosis may seem like an obvious extension of the experience using aggressive anti-plasma cell chemotherapy for multiple myeloma, a much more common disease. However, as described in the article by Vaishali Sanchorawala, the use of high-dose chemotherapy in systemic AL amyloidosis has unique challenges imparted by the substantial organ dysfunction present in individuals with this disease. Indeed, it is the treatment for those patients too ill to undergo high-dose chemotherapy with stem cell transplantation that is one of the current "moving

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Address correspondence to: Dr. Laura Dember, Renal Section, Department of Medicine, Boston University School of Medicine, EBRC 504, 650 Albany Street, Boston, MA 02118. Phone: 617-638-7331; Fax: 617-859-4579; E-mail: ldember@bu.edu

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points" in AL amyloidosis. Undoubtedly, lessons learned from the AL amyloidosis experience will be important as myeloablative chemotherapy with stem cell transplantation begins to be used for autoimmune diseases such as systemic lupus erythematosis and systemic sclerosis, both of which are characterized by multi-organ dysfunction. The articles on AL amyloidosis and multiple myeloma are both written by hematologist/oncologists and thus provide perspectives that are not widely available in the nephrology literature. The focus of both of these articles is on diagnostic and treatment advances rather than on kidney-oriented issues, as review articles addressing the latter have been published recently (1) or are currently in press (2).

Light chain (or heavy chain) deposition disease can be associated with full-blown multiple myeloma but often occurs in the absence of a plasmacytosis or other evidence of a plasma cell dyscrasia. It has been appreciated only relatively recently that the progressive nature of the associated kidney disease and the frequent presence of extra-renal disease justify the use of aggressive and potentially toxic treatment for this disorder even in the absence of an overt hematologic malignancy. Pierre Ronco and colleagues describe progress in understanding the pathophysiology of light and heavy chain deposition disease and suggest that identification of the molecular events triggered by these monoclonal Ig proteins may help elucidate general mechanisms of kidney fibrosis.

The final article, written by Stephen Korbet and colleagues, addresses immunotactoid/fibrillary glomerulopathy. This disease is probably the least common and the least well understood of those included in this Moving Points series. Given our relatively limited knowledge of its pathogenesis, it is not surprising that controversy remains about whether to classify this morphologically heterogeneous entity as "one disease or two" and that effective treatment for the disease(s) has not been identified. Hopefully, the future will bring more "moving points" to immunotactoid/fibrillary glomerulopathy.

References

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