Dysproteinemias and Glomerular Disease

By Paisit Paueksakon and Agnes B. Fogo

What is the current terminology for dysproteinemia-related kidney disease?

Dysproteinemias are characterized by abnormal Ig molecules or fragments and result from clonal proliferation of plasma cells or B lymphocytes. Thus, an alternative term for dysproteinemia is plasma cell dyscrasia (PCD). PCDs are classified clinically on the basis of several external parameters, including percentage of plasma cells in the bone marrow, the presence of a monoclonal (M) spike on serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP), osteolytic lesions on skeletal survey, and hypercalcemia. When the combination of findings meets precise criteria, patients may be classified as having multiple myeloma.

In 2012, the term monoclonal gammapathy of renal significance (MGRS) was introduced by the International Kidney Monoclonal Gammapathy Research Group. This approach distinguishes monoclonal gammapathy of undetermined significance, which has an isolated monoclonal spike on serum and/or urine electrophoresis without end organ damage, from MGRS, which is defined as kidney dysfunction due to monoclonal Ig (M Ig) deposition.

Where do monoclonal proteins deposit in the kidneys?

PCDs can cause disease in any compartment of the renal parenchyma, including glomeruli, tubules, interstitium, and blood vessels. These distribution patterns are mostly determined by the physicochemical properties of the pathogenic M Ig. Light chain nephropathy (LCN) is a purely tubulointerstitial pattern of renal injury due to the precipitation of light chain (LC) initially in the lumen of distal tubules, causing inflammatory reaction and injury. Approximately 90% of patients with LCCN have multiple myeloma, often with a high tumor burden. In contrast, LC proximal tubulopathy (LC Fanconi syndrome) is characterized by proximal tubular injury and intracellular crystalline deposits of monoclonal LC. Occasionally, LC proximal tubulopathy occurs in combination with LCCN.

The spectrum of renal diseases induced by M Ig also includes Ig-related amyloidosis (Alg): monoclonal Ig deposition disease (MIDD), which includes light chain deposition disease (LDD), light and heavy chain deposition disease, and heavy chain deposition disease; most patients with immunotactoid glomerulopathy; and proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID). Many cryoglobulins also have a monoclonal component. Most of these diseases have glomerular deposits, with varying deposits elsewhere. Amyloid deposits have randomly arranged fibrils, usually only light chain (AL) but rarely with heavy chain components or light and heavy chain components. These deposits are predominantly present in glomeruli and blood vessels and occasionally present in the interstitium. Nonorganized, punctate, powdery deposits are characteristic of MIDD; classically, they are along the inner aspect of glomerular basement membranes (Figure 1), causing nodular sclerosis, and they are also seen on the outer aspect of the tubular basement membrane. LCDD has been recognized to have limited proteinuria with dominant tubular deposits. Cryoglobulinemic GN often presents as mixed nephritic/nephrotic syndrome, often with systemic signs of vasculitis. In contrast, patients with LCCN present with less proteinuria and AKI, whereas those with LC proximal tubulopathy often show partial Fanconi syndrome. Of note, testing for monoclonal proteins in urine and serum (SPEP and/or UPEP) is a routine part of the prebiopsy evaluation of proteinuric adult middle-aged or older patients. However, in our practice, about 50% of patients undergoing renal biopsy with some evidence of a monoclonal protein had kidney disease unrelated to monoclonal protein.

What factors predict outcome?

To date, the clinical evaluation of free light chain (FLC) has been almost entirely on the basis of nephelometric immunosassays using sheep polyclonal antibodies against LC epitopes, which are exposed when the LCs are free but hidden when the LCs are bound. These assays, which have high sensitivity, suggest clonality by analyzing the concentration and ratio of k to γ in serum. The FLC assay significantly improves the detection of monoclonal proteins in AL amyloid nephropathy. Additionally, a decrease in FLC also correlates with renal survival in AL amyloid and MIDD, because it is likely the best indicator of response to treatment. However, patients with PGNMID often do not have detectable monoclonal protein in serum or urine. Thus, improved biomarkers are needed in MGRS.

What treatment approaches are used?

The goal of current treatment approaches for dysproteinemias associated with glomerular diseases is to eradicate the clonal plasma cells. High-dose intravenous melphalan followed by autologous stem cell transplantation to support bone marrow recovery has emerged as the most likely to remove the clonal plasma cells in Alg, although updated chemotherapy (or nontransplant) approaches may be at least as effective. In MIDD, a novel antitymema agent, bortezomib-based therapy, showed excellent hematologic and renal response rate, particularly when used early in the disease course. Rituximab therapy in addition to corticosteroids and antiangiogen blockade may improve the clinical course of patients with PGNMID or immunotactoid glomerulopathy. Combined therapy with corticosteroids, plasmapheresis, and rituximab is successful in MALT (macrophage-associated lymphoid tissue) lymphoma with cryoglobulinemic GN. Combined therapy with dexamethasone and bortezomib may show benefit in decreasing the serum titer of IgG anti-CFH (complement factor H) autoantibodies in patients with C3 GN and monoclonal gammapathy, although bortezomib may cause drug-induced acute interstitial nephritis.

What novel therapies are emerging?

In Alg, the effectiveness of cytotoxic chemotherapy to suppress the pathogenic clone is often limited by dysfunction of the amyloid-infiltrated organs. About 20% of patients with Alg die within 6 months after diagnosis, before the delayed benefits of chemotherapeutic drugs may be realized. Thus, new treatments attempt to improve organ function by eliminating systemic amyloid deposits at the time of diagnosis. A clinical trial was designed to engage potent normal pathogenic clearance mechanisms involving the use of a small molecule drug, (R)-1-[2-carboxy-methylpyridin-1-y]-6-oxo-hexanoyl]-pyrrolidine-2-carboxylic acid, to deplete circulating serum amyloid P component (SAP) followed by administration of a fully humanized monoclonal IgG1 anti-SAP antibody to activate macrophage destruction of the SAP-containing amyloid deposits in tissue. This novel therapy significantly decreased the amyloid load in the liver at 6 weeks. Reduction of amyloid load in the kidney and shrinkage of amyloid-laden lymph nodes were also shown. In the next clinical trial phase, patients with renal and cardiac amyloidosis will be studied. The patients will receive larger and if necessary, repeated doses of anti-SAP antibody, with the aim of achieving effective exposure in tissues that do not have highly permeable sinusoidal endothelium, like the liver and spleen.

Dysproteinemia causes a wide range of morphologic lesions in the kidney that can be diagnosed by renal biopsy. In addition to therapies aimed at eradicating the underlying plasma cell clone, disease-specific therapies are emerging (e.g., for AL amyloidosis).
Figure 1. Light chain deposition disease

Extensive powdery deposits along inner aspect of the glomerular basement membranes (transmission electron microscopy; original magnification, 5600).

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