Dysproteinemia and the Kidney: Core Curriculum 2019

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Dysproteinemic kidney diseases occur when B- or plasma cell clones produce pathogenic monoclonal immunoglobulins or light chains that cause kidney damage. The clinical presentation of these disorders ranges from sub–nephrotic-range proteinuria or microscopic hematuria with preserved kidney function to severe nephrotic syndrome to severe acute kidney injury or rapidly progressive glomerulonephritis. These monoclonal immunoglobulins can cause a variety of histologic patterns of injury, including cast nephropathy, glomerular and tubular deposition diseases, amyloidosis, and inflammatory glomerulonephritis. The underlying clonal disorder may meet criteria for overt multiple myeloma or systemic lymphoma. In recent years, there has been increased recognition and study of dysproteinemic kidney diseases that occur in the setting of smaller clonal plasma and B-cell populations, which are classified as monoclonal gammopathies of renal significance. Regardless of clonal cell burden, the goal of treatment is to achieve a hematologic response (ie, improvement or resolution of the monoclonal protein) by eradicating the underlying clone. Organ-specific responses are dependent on achieving hematologic response. Without appropriate treatment, many of these disorders are associated with high rates of progressive kidney disease and end-stage kidney disease. In this installment of *AJKD*'s Core Curriculum in Nephrology, we review the pathogenesis, diagnosis, and treatment of dysproteinemic kidney diseases.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Monoclonal gammopathy signifies the presence of a monoclonal immunoglobulin or its component. This is produced by a B-cell or plasma cell clone. When there is no end-organ damage, the condition is referred to as monoclonal gammopathy of undetermined significance (MGUS). MGUS is a premalignant condition that precedes all cases of multiple myeloma and immunoglobulin light chain (AL) amyloidosis. The rate of transformation averages 1% per year. Factors such as the size of the monoclonal protein, type of immunoglobulin, degree of changes in serum free light chain (FLC) assay, and chromosome abnormalities detected using fluorescence in situ hybridization can affect the rate of transformation.

MGUS is rare at age younger than 30 years but starts to increase after age 50 years. For people in their 50s, the prevalence is 2% in men and 1.4% in women; this increases to 8.3% in men and 6% in women for those in their 80s. Despite this, screening for monoclonal gammopathies is currently not recommended in asymptomatic individuals. When screening is indicated, serum protein electrophoresis (SPEP), which is inexpensive and widely available, is the most common test performed. The sensitivity of SPEP is 88% for detecting a monoclonal gammopathy in patients with multiple myeloma and 66% in patients with AL amyloidosis (Table 1). Protein electrophoresis (PEP) can also be performed on a 24-hour urine collection, which can increase the detection rate when added to SPEP but by itself has low sensitivity. The sensitivity of SPEP in detecting monoclonal gammopathy can be increased with serum immunofixation (IFE) to 94% in patients with multiple myeloma and 74% in patients with AL amyloidosis. The detection rate is further increased by the addition of the serum FLC assay. When combined with serum IFE, nearly 100% of monoclonal gammopathy is detectable in patients with multiple myeloma and 96% of patients with AL amyloidosis. A urinary FLC test is available, but individual variability makes the results difficult to interpret and so it is not currently recommended.

It is important to recognize that PEP is quantitative but not capable of fully characterizing the type of monoclonal immunoglobulin, whereas IFE identifies the monoclonal immunoglobulin but is not quantitative. In addition, clonality in the serum FLC assay is inferred by the ratio of κ to λ light chains; an elevated ratio suggests a κ light chain–producing clone and a depressed ratio advocates a λ light chain–producing clone. Furthermore, the kidney is responsible for a significant portion of FLC elimination from the body. Therefore, when kidney function is substantially decreased, FLC results are altered. Since κ FLC is affected more than λ FLC, normal values of the

Table 1. Sensitivity of Serum Paraprotein Testing for Multiple Myeloma, Smoldering Myeloma, and AL Amyloidosis

	Multiple Myeloma	Smoldering Multiple Myeloma	AL Amyloidosis
SPEP	87.6%	94.2%	65.9%
Serum IFE	94.4%	98.4%	73.8%
Serum FLC assay	96.8%	81.2%	88.3%
SPEP and serum FLC	100%	99.5%	94.2%
SPEP, serum IFE, and serum FLC assay	100%	100%	97.1%

Note: Based on information in Katzmann et al (Screening panels for detection of monoclonal gammopathies. *Clin Chem.* 2009;55(8):1517-1522).
Abbreviations: FLC, free light chain; IFE, immunofixation; SPEP, serum protein electrophoresis.

κ:λ ratio shift from 0.26-1.65 to 0.37-3.1. The most exciting novel test is the use of mass spectrometry for the detection of monoclonal protein. This test developed at the Mayo Clinic can determine the type of monoclonal protein and is quantitative. Although sensitivity appears to be superior to serum FLC, more data are required for a complete comparison.

Monoclonal protein testing should be separated into screening, confirmation, and assessment of disease response. Screening tests should be performed if a monoclonal gammopathy is suspected but not yet confirmed by kidney biopsy or fat aspirate for amyloid. The least expensive tests would be as SPEP and serum FLC assay; however, serum IFE combined with a serum FLC assay would increase sensitivity from 94.3% to 97.4%. When a monoclonal immunoglobulin–related kidney lesion is found on kidney biopsy, the circulating monoclonal immunoglobulin needs to be identified. Testing could begin with SPEP, IFE, and serum FLC assay. This is because the PEP is needed to quantify the monoclonal protein while the IFE is required for classification of immunoglobulin, particularly if the paraprotein is present at low concentrations. If these tests are negative, urine PEP (UPEP) and IFE should be used to maximize the sensitivity to detect the monoclonal protein. For response assessment, SPEP and sometimes UPEP and serum FLC assay are used if a monoclonal (M) spike is measurable. For complete response assessment, based on experience with multiple myeloma and AL amyloidosis, serum IFE and serum FLC assay are also required.

In addition to the malignant transformation of premalignant plasma and B cells into overt myeloma or lymphoma, it is now recognized that some monoclonal proteins are toxic even at low serum concentrations and thus can cause organ damage independent of the underlying clonal cell burden. A monoclonal protein may be toxic due to its ability to bind other proteins, misfold, or deposit in tissues. These properties are determined by the physiochemical properties of the protein, which is influenced by its amino acid sequence. When monoclonal gammopathy–related kidney damage occurs in the absence of overt malignancy, the hematologic disorder is categorized as monoclonal gammopathy of renal significance (MGRS). MGRS is an even newer concept to denote hematologic conditions distinct from MGUS, which by definition does not have evidence of end-organ damage. Table 2 lists types of kidney biopsy diagnoses for patients with paraprotein-mediated kidney disease. The kidney lesions of MGRS can be categorized by the presence or absence of monoclonal immunoglobulin deposits and ultrastructural characteristics of the deposits. Although they all share some characteristics, each entity has its own unique features and prognosis that are discussed further later.

The treatment of dysproteinemic kidney diseases is directed at the underlying clonal proliferative disorder, with the goal of achieving a hematologic response; that is, improvement or normalization of paraprotein levels in blood and urine. For nephrologists, understanding the concept and definitions of hematologic response are imperative in the management of patients with dysproteinemia-associated kidney disease because achieving hematologic response has been associated with overall survival and organ-specific response in patients with multiple myeloma (Box 1) and AL amyloidosis (Box 2), as well as renal response in some of the MGRS disorders. In addition, each kidney disease may require individual attention. For example, patients with immunoglobulin-related amyloidosis usually have nephrotic syndrome, which requires diuretic management, while diuretic is not necessary and is potentially contraindicated in light chain cast nephropathy.

Additional Readings

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Table 2. Dysproteinemia-Associated Kidney Diseases

Kidney Biopsy Diagnosis	Clinical Presentation	Hypothesized Mechanism of Injury	Clone Detection Rate	Paraprotein Detection Rate
Light chain cast nephropathy	AKI, decreased kidney function, nonalbumin proteinuria	Light chain binds to uromodulin and precipitates in distal tubules, resulting in obstruction and interstitial nephritis	~100%	~100%
Monoclonal immunoglobulin amyloidosis • Light chain (AL) amyloidosis • Heavy chain (AH) amyloidosis • Light and heavy chain (AHL) amyloidosis	Proteinuria, NS, decreased kidney function	Monoclonal immunoglobulin forms amyloid fibrils in extracellular tissue	~100%	~100%
Monoclonal immunoglobulin deposition disease (MIDD) • Light chain deposition disease (LCDD) • Heavy chain deposition disease (HCDD) • Light and heavy chain deposition disease (LHCDD)	Decreased kidney function long term, proteinuria	Deposition of pathogenic light chain; in HCDD, almost all patients have C_H1 deletion leading to production of truncated HC	LCDD: 90%-100% HCDD: 100% LHCDD: 90%-100%	LCDD: 90%-100% HCDD: 80%-100% LHCDD: 100%
Type I (monoclonal) cryoglobulinemic GN	Nephritic syndrome, rapidly progressive GN, decreased kidney function	Deposition of monoclonal immunoglobulin	90%-100%	90%-100%
Type II (mixed monoclonal and polyclonal) cryoglobulinemic GN	Nephritic syndrome, rapidly progressive GN, chronically decreased kidney, NS	Deposition of monoclonal immunoglobulin	NA	NA
Immunotactoid glomerulopathy	Proteinuria, decreased kidney function	Deposition of monoclonal immunoglobulin, glomerular inflammation	67%	63%
Proliferative GN with monoclonal immunoglobulin deposits (PGNMID)	Proteinuria, decreased kidney function	Deposition of monoclonal immunoglobulin, glomerular inflammation	30%-40%	30%-40%
Monoclonal gammopathy-associated C3 glomerulopathy	Proteinuria, decreased kidney function	Activation of alternative complement pathway by monoclonal immunoglobulin	Unknown	100%[a]
Light chain proximal tubulopathy	Proximal tubular dysfunction/Fanconi syndrome	VκI light chains are resistant to proteolysis and interfere with proximal tubular absorption	90%-100%	90%-100%
Monoclonal IgM-mediated kidney disease	Proteinuria, decreased kidney function	Deposition of monoclonal immunoglobulin, glomerular inflammation	~100%	~100%
Monotypic fibrillary GN	Proteinuria, decreased kidney function	Deposition of monoclonal immunoglobulin, glomerular inflammation	NA[b]	NA[b]

Abbreviations: AKI, acute kidney injury; GN, glomerulonephritis; HC, heavy chain; IgM, immunoglobulin M; NA, data not available; NS, nephrotic syndrome.
[a]By definition, monoclonal gammopathy–associated C3 glomerulopathy requires detection of a monoclonal gammopathy.
[b]Case reports only.

Box 1. Hematologic Response Criteria for Multiple Myeloma

Stringent complete response
- Complete response (see below) plus normal sFLC ratio and absence of clonal plasma cells on bone marrow biopsy

Complete response
- Negative sIFE and uIFE, disappearance of plasmacytomas, <5% plasma cells on bone marrow biopsy

Very good partial response
- SPEP and UPEP negative but monoclonal protein detectable by sIFE or uIFE or >90% reduction in serum monoclonal paraprotein with urine monoclonal protein < 100 mg/24 h

Partial response
- >50% reduction in serum monoclonal protein, >90% reduction in 24-h urine monoclonal protein (or to <200 mg/24 h), >50% reduction in baseline plasmacytoma size (if present)
- If monoclonal protein is unmeasurable, >50% reduction in difference between involved and uninvolved FLC levels
- If FLC not measurable, >50% reduction in plasma cells in bone marrow from baseline (requires >30% plasma cells at baseline)

Minimal response
- 25%-49% reduction in serum monoclonal protein, 50%-89% reduction in 24-h monoclonal protein in urine
- 25%-49% reduction in size of plasmacytomas (if present)

Stable disease
- Does not meet criteria for any of response pattern above or for progressive disease

Progressive disease
- 25% increase from lowest response value in serum monoclonal protein (increase > 0.5 g/dL) and/or urine monoclonal protein (increase > 200 mg/24 h)

Note: Based on information in Kumar et al (International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol.* 2016;17:e328-e346).

Abbreviations: sFLC, serum free light chain; sIFE, serum immunofixation; SPEP, serum protein electrophoresis; uIFE, urine immunofixation; UPEP, urine protein electrophoresis.

Light Chain Cast Nephropathy

Case 1: *A 63-year-old man with a history of hypertension was admitted to the hospital with generalized fatigue, weakness, abdominal pain, and acute kidney injury (AKI). He was in his usual state of health until 6 weeks before presentation, when he developed acute low-back pain after performing manual labor. He began using ibuprofen and hydrocodone for pain. Two weeks before presentation, he developed generalized weakness, fatigue, poor appetite, and right-sided abdominal pain. He was evaluated by his primary care physician and initial laboratory tests revealed a serum creatinine (Scr) level of 13.5 mg/dL (from 0.6 mg/dL 2 months earlier), hypercalcemia (calcium, 13.2 mg/dL), and normal complete blood cell count (hemoglobin, 14.1 g/dL). SPEP and serum IFE revealed an immunoglobulin G (IgG)κ M spike of 3.6 g/dL. Serum FLC assay showed κ FLC of 1,050 mg/dL (reference range, 3.3-19.4 mg/L), λ FLC of 1.0 mg/dL (reference range, 5.7-26.3 mg/L), and serum FLC ratio of 1,050 (reference range, 0.26-1.65). A 24-hour urine collection found 402 mg of total protein. UPEP found M spikes of 49 mg/d and 154 mg/d, and urine IFE identified these as monoclonal κ light chains. He was treated with intravenous normal saline solution, which resulted in normalization of serum calcium level, but Scr level remained elevated at 9.5 mg/dL. A skeletal survey was negative for lytic lesions. Percutaneous kidney biopsy was performed, which showed intraluminal fractured casts in the distal tubules that were periodic acid–Schiff (PAS) negative and silver negative (Fig 1). There was significant tubular injury exhibited by luminal ectasia, epithelial simplification, and coarse cytoplasmic vacuolization. Immunofluorescence microscopy showed that tubular casts stained 3+ for κ light chain and negative for λ light chain. Bone marrow biopsy revealed 40% κ-restricted plasma cells. The kidney biopsy diagnosis was acute myeloma cast nephropathy with acute tubular injury. He was treated with 4 sessions of plasma exchange therapy and started on weekly anti–plasma cell therapy with cyclophosphamide-bortezomib-dexamethasone (CyBorD). With this treatment, after 3 weeks, serum light chains were improving (κ FLC, 116 mg/dL) and had evidence of renal recovery (Scr, 3.2 mg/dL). He did not require hemodialysis.*

Box 2. Hematologic Response Criteria for AL Amyloidosis

Complete response
- Negative SPEP, sIFE, UPEP, uIFE, and normal sFLC ratio

Very good partial response
- dFLC < 40 mg/L

Partial response
- Decrease in dFLC by >50% (in patients with baseline dFLC > 50 mg/L)

No response
- Improvement in paraprotein levels but less than partial response

Progression
- From complete response: any detectable monoclonal protein or abnormal sFLC ratio (involved light chain must be at least double the normal range)
- From partial response: 50% increase in serum monoclonal protein to >5 g/dL or 5% increase in urine monoclonal protein to >200 mg/d
- At any time: sFLC increase of 50% to >100 mg/L

Note: Based on information in Palladini et al (New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. *J Clin Oncol.* 2012;30(36):4541-4549).

Abbreviations: dFLC, difference in free light chains (involved minus uninvolved light chain in serum); sFLC, serum free light chain; sIFE, serum immunofixation; SPEP, serum protein electrophoresis; uIFE, urine immunofixation; UPEP, urine protein electrophoresis.

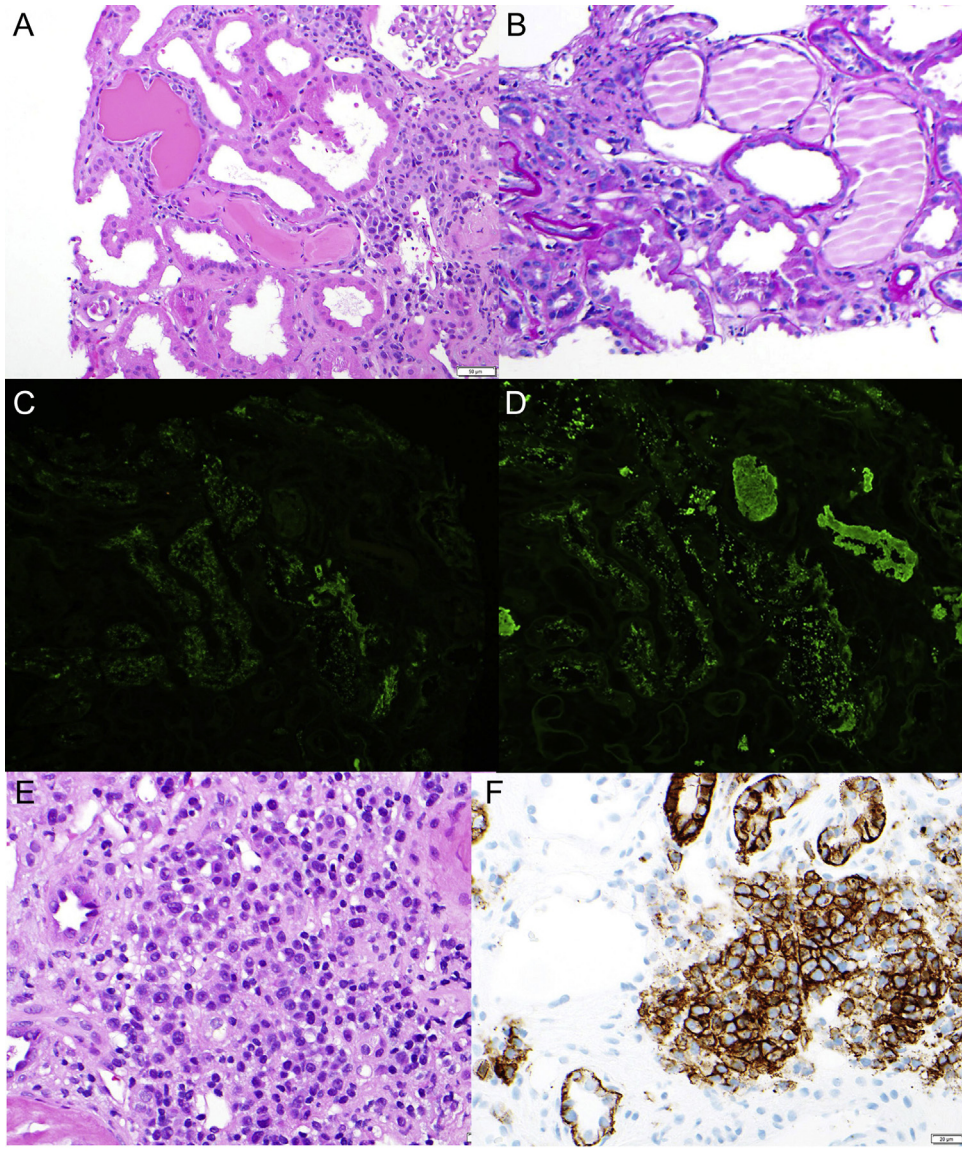

Figure 1. Kidney biopsy specimen from a patient with light chain cast nephropathy. (A) Hypereosinophilic fractured casts are seen within tubules (hematoxylin stain; original magnification, ×400), (B) which are periodic acid–Schiff (PAS) negative (PAS stain; original magnification, ×400). On immunofluorescence (IF) microcopy, (C) casts do not stain with κ light chain (κ stain on IF; original magnification, ×400), (D) but demonstrate λ light chain–restricted staining (λ stain on IF; original magnification, ×400). (E) Plasma cell infiltrate is noted within the interstitium of the renal parenchyma (hematoxylin stain; original magnification, ×400), (F) with immunohistochemical staining that is positive for CD138 (original magnification, ×400).

Multiple myeloma is one of the most common hematologic malignancies, with an annual incidence of about 11 per 100,000 patients. In patients with multiple myeloma newly diagnosed, 20% to 30% will present with estimated glomerular filtration rates (GFRs) < 30 mL/min/1.73 m^2 at the time of diagnosis. Dialysis is required in up to 5% of patients. Patients may also develop decreased GFRs later in the disease course, usually during relapse. The most common cause of decreased GFR in patients with multiple myeloma is light chain cast nephropathy. In an autopsy series, more than two-thirds of patients with myeloma with renal involvement had cast nephropathy. Cast nephropathy occurs when monoclonal FLCs bind and precipitate with Tamm-Horsfall protein in the distal nephron. The formation of the casts causes tubular obstruction (typically distal) that elicits an intense immune response, resulting in a giant cell reaction around the casts and interstitial inflammation. This is mediated by hydrogen peroxide produced by the FLC that induces ASK1 (apoptosis signal-regulating kinase 1) and NFκB (nuclear factor-κB) through an Src kinase pathway. ASK1 and NFκB promote the inflammatory reaction.

The tubular obstruction causes a kidney injury that is usually rapid, often occurring within days to weeks. Some of these patients may be taking nonsteroidal anti-inflammatory drugs as a result of compression fractures that may aggravate or even precipitate the kidney injury. Other medications that may be associated with light chain cast nephropathy include angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Intravenous contrast has also been implicated as an associated risk for cast nephropathy, although a recent study found the association to be less significant.

Cast nephropathy is now recognized by the International Myeloma Working Group as one of the myeloma-defining events that makes up the CRAB criteria (hypercalcemia, renal impairment, anemia, and bone lesions). This occurred because cast nephropathy characteristically occurs with high plasma cell and serum FLC burdens. Patients with cast nephropathy usually have other CRAB features of multiple myeloma, but it is important to note that cast nephropathy does not occur exclusively in patients with multiple myeloma. Cast nephropathy has also been described in patients with Waldenström macroglobulinemia and chronic lymphocytic leukemia, which reflects the pathogenicity of light chains in these patients to form casts. Therefore, a full evaluation is required to diagnose the hematologic condition after a diagnosis of cast nephropathy has been made.

The gold standard for diagnosing cast nephropathy is kidney biopsy. Eosinophilic casts, often fractured, are seen in the distal tubules with giant cells around the casts. Casts will stain for a single light chain on immunofluorescence microscopy and may have crystalline features on electron microscopy. Intense interstitial infiltrates are common. Glomeruli are spared in pure cast nephropathy, but other lesions have been found to coexist in individual cases, such as AL amyloidosis, monoclonal immunoglobulin deposition disease (MIDD; discussed later), light chain proximal tubulopathy (LCPT), and crystal storing histiocytosis. The serum FLC assay is the most sensitive in cast nephropathy and has abnormal results in 100% of patients. Serum FLC level is almost always >50 mg/dL and is often >150 mg/dL. SPEP and IFE are ~85% and 95% sensitive, respectively. This is because some patients produce only a monoclonal FLC, rather than a heavy chain or intact immunoglobulin. Proteinuria is also present in all patients. However, the proteinuria in patients with cast nephropathy is mainly composed of FLC (Bence Jones protein) and albuminuria has albumin excretion < 10%. In 1 study, urinary FLC to creatinine ratio correlated with the percentage of patients with decreased kidney function. Although high serum FLC and low albumin proteinuria values are characteristic of cast nephropathy, up to 40% of patients may have a secondary kidney lesion even when both features are present.

When diagnosed, anti–plasma cell treatment should be initiated as soon as possible because persistently decreased kidney function is associated with poor overall survival and early mortality in patients with multiple myeloma. Recovery of kidney function requires a minimum reduction in serum FLC level by 60% within 2 to 3 weeks of presentation. This is most successfully accomplished with a 3-drug regimen, of which one should be bortezomib. Bortezomib has been shown to inhibit NFκB production, which may have added benefit beyond its effects on plasma cells. Cyclophosphamide, thalidomide, and doxorubicin are effective as second-line drugs. The third drug is high-dose steroids, which may also have extra benefit as an anti-inflammatory agent.

Adjunctive efforts to increase the removal of FLCs with extracorporeal devices has been tried. A small randomized trial of plasmapheresis and hemodialysis versus peritoneal dialysis found superior kidney and patient outcomes in the hemodialysis and plasmapheresis group. However, a larger trial comparing hemodialysis versus hemodialysis plus plasmapheresis failed to show significant benefits. Two recent trials (MYRE and EuLITE) that used high cutoff dialyzers with pore size of 50 kDa also showed conflicting results. A significant difference in renal recovery was found with use of a high cutoff dialyzer in MYRE at 6 (but not 3) months, whereas no improvement was noted in EuLITE. Therefore, the role of extracorporeal removal of FLCs remains undetermined.

Additional Readings

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Immunoglobulin-Related Amyloidosis

Case 2: *A 54-year-old woman with a medical history of well-controlled hyperlipidemia was referred for evaluation of leg swelling and proteinuria. At the time of initial evaluation, blood pressure was 98/66 mm Hg, and the rest of her examination was notable only for bilateral lower-extremity edema (2+). Laboratory measurements included Scr level of 0.7 mg/dL and serum albumin level of 2.7 (reference range, 3.5-5.5) g/dL, and urinalysis showed protein (3+), negative blood, and no cells on urine microscopy. SPEP revealed a M spike measuring 0.1 g/dL that was identified as immunoglobulin A (IgA) λ light chain. Serum FLC assay showed κ FLC of 8.4 mg/dL (reference range, 3.3-19.4 mg/L), serum λ FLC of 42.4 mg/dL (reference range, 5.7-26.3 mg/L), and κ:λ FLC ratio of 0.19 (reference range, 0.26-1.65). A 24-hour urine collection showed 5.6 g of protein and urine IFE showed λ light chains. Complete blood cell count, serum calcium level, and skeletal survey results were all normal. Bone marrow biopsy revealed 5% plasma cells that were λ light chain restricted on immunohistochemical staining.*

The patient underwent kidney biopsy, which showed glomerular and vascular deposition of amorphous material that stained positive for Congo red, with apple-green birefringence under polarized light. Immunofluorescence microscopy showed mesangial glomerular capillary wall and vessel wall staining (3+) for λ light chain, with negative staining for κ light chain, the immunoglobulin heavy chains (IgG, IgM, and IgA), C3, and C1Q. Electron microscopy showed widespread glomerular deposition of randomly oriented fibrils with an average diameter of 10 nm and extensive podocyte foot-process effacement. She did not have evidence of other organ involvement by amyloidosis.

Question 1: After discussion with the patient's hematologist/oncologist, which of the following is the next appropriate next step in management?

a) Start a bortezomib-based regimen
b) Obtain laser capture dissection and mass spectrometry on the kidney biopsy specimen
c) Start high-dose melphalan (HDM) treatment followed by autologous stem cell transplantation (ASCT)
d) A or C
e) Start lisinopril treatment and monitor given bone marrow findings

For the answer to the question, see the following text.

Amyloidosis is the result of protein misfolding that produces a precursor that is capable of self-aggregation. The self-aggregation produces proto-fibrils that twist to form a fibril. Characteristically, these fibrils stain with Congo red, producing an apple-green birefringence under a polarized light. Currently, more than 30 different types of amyloid have been described. Only immunoglobulin-related amyloidosis is the result of a clonal proliferative disorder. This is most commonly a plasma cell dyscrasia, but B-cell lymphoproliferative disorders, especially Waldenström macroglobulinemia and chronic lymphocytic leukemia, have also resulted in immunoglobulin-related amyloidosis. The incidence is approximately 8 per million per year. Three subtypes of immunoglobulin-related amyloid exist based on the composition of the amyloidogenic protein. AL amyloidosis is the most common subtype, making up nearly 95% of cases, with monoclonal λ light chain being the most common immunoglobulin related. Heavy and light chain (AHL) amyloidosis is the next most common, which is composed of the entire immunoglobulin, while the rarest is immunoglobulin heavy chain (AH), which makes up 1.5% of cases. Some subtle differences exist, but all 3 types of immunoglobulin-related amyloidosis have similar clinical presentations. Approximately 75% of patients present with proteinuria, half of whom have nephrotic syndrome. Elevated Scr levels can also be found in half the patients on presentation, but only 20% have an Scr level > 2.0 mg/dL. It is important to recognize that cardiac involvement is as common as kidney, and the extent of cardiac involvement determines survival, whereas the extent of kidney involvement determines renal survival.

On kidney biopsy, amyloidosis appears as eosinophilic deposits that stain poorly with PAS and silver stain. They characteristically stain for Congo red, which appears apple-green when viewed under a polarized light source. Light chain restriction by immunohistochemistry or immunofluorescence microscopy is present in AL and AHL amyloidosis, while heavy chain restriction is seen in AHL and AH. On electron microscopy, amyloid fibrils are solid and randomly arranged, with a diameter between 7 and 12 nm. Deposits are commonly found in the mesangium, interstitium, and vessel walls. Spikes can sometime be seen along glomerular basement membranes on light and electron microscopy. About 5% of patients have predominately vascular deposits in the kidney and may present with little or no proteinuria.

Immunoglobulin-related amyloidosis is a low tumor burden disease. Approximately 40% of patients will have >10% plasma cells in bone marrow, but <10% of patients meet criteria for multiple myeloma. Therefore, immunoglobulin-related amyloidosis is most commonly an MGRS. A monoclonal protein can be detected using SPEP in 65% of cases. This increases to 75% with serum IFE and the addition of urine IFE can increase sensitivity to ~95%. However, the most sensitive test is serum FLC assay, which has abnormal results in >98% of patients and is used to inform diagnosis, prognosis, and treatment response.

The treatment of immunoglobulin-related amyloidosis has advanced significantly over the past decades. Initial treatment with melphalan and prednisone or high-dose dexamethasone had produced limited survival benefit because complete hematologic response was rarely achieved. The introduction of HDM followed by ASCT increased the complete hematologic response rate to ~40%, which translated to better survival. Median

survival with ASCT is nearly 8 years. Despite its advantages, the most significant drawback of ASCT is the high rate of treatment-related mortality. Identification of risk factors (cardiac troponin T, N-terminal pro–brain natriuretic peptide, serum albumin, and estimated GFR values) has significantly reduced the treatment-related mortality in AL amyloidosis to 1% to 2% by identifying and excluding patients who are at highest risk for severe peri-ASCT complications. However, other therapies have also improved outcomes. These include melphalan-dexamethasone, CyBorD, bortezomib-melphalan-dexamethasone and, more recently, the anti-CD38 antibody daratumumab. Achieving a minimum of a hematologic very good partial response is associated with improved overall and renal survival. Kidney transplantation has been found to be an acceptable option in patients who achieve a good hematologic response.

For the patient in case 2, her diagnosis is AL (λ light chain) amyloidosis with kidney involvement. As is usually the case, mass spectrometry was not necessary because immunofluorescence microscopy on kidney biopsy tissue identified a monotypic light chain. Anti–plasma cell therapy with bortezomib-based regimens or HDM followed by ASCT are first-line therapies for patients with AL amyloidosis. Although bortezomib-based therapies lead to similar outcomes as HDM/ASCT, this patient was deemed to be a good candidate for HDM/ASCT due to the lack of severe extrarenal organ involvement and additional comorbid medical problems, as well as preserved kidney function. Thus, the correct answer is (d).

Case 2, cont: *The patient underwent HDM/ASCT, which was complicated by neutropenic sepsis and AKI, with Scr level increasing to 5.1 mg/dL. She did not require dialysis. Her neutropenia resolved and she was discharged. Six months after HDM/ASCT, serum FLCs were normal and serum and urine IFE tests were negative. Scr level was 2.1 mg/dL, serum albumin level was 2.6 g/dL, and 24-hour urine protein excretion was 4.5 g.*

Question 2: What would you recommend for this patient at this time with these results including this urine protein excretion?

a) Tacrolimus
b) Rituximab
c) Observation only
d) Cy/Bor/D

For the answer to the question, see the following text.

After achieving complete hematologic response, the renal response (proteinuria reduction) in AL amyloidosis can take months to years and may never resolve completely. There are no studies supporting the use of calcineurin inhibitors in AL amyloidosis. For this patient, treatment with further anti–plasma cell therapy with bortezomib-based therapies is not recommended because she has already achieved a complete hematologic response. Thus, the correct answer is (c), and the patient's laboratory measurements were monitored every 3 months. Serum FLC levels have remained normal and serum and urine IFE results have remained negative. Scr level and proteinuria continued to improve. At last follow-up 3.5 years after HDM/ASCT, Scr level was 1.4 g/dL, serum albumin level was 3.3 g/dL, and 24-hour urine protein excretion was 3.2 g.

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The MIDDs

Overview

The MIDDs comprise 3 histologically distinct disorders: light chain deposition disease (LCDD), heavy chain deposition disease (HCDD), and light and heavy chain deposition disease (LHCDD). The approach to managing the MIDDs is the same for all dysproteinemic kidney diseases, focusing on detection and treatment of the underlying clonal cell population. Important research on the MIDDs has both shed light on disease mechanisms and improved patient outcomes.

Light Chain Deposition Disease

LCDD is the most common subtype of MIDD. Early in the disease course, the kidney biopsy specimen may appear normal on light microscopy, whereas later stages of disease are characterized by nodular mesangial sclerosis and tubular basement membrane thickening (Fig 2). On immunofluorescence microscopy, there is linear staining for κ (80% of cases) or λ (20% of cases) light chain only in tubular basement membranes and glomeruli. Electron microscopy shows tubular and subendothelial deposits that are powdery or punctate in appearance. Characteristics of the light chain that lead to renal pathogenicity are not understood.

Patients with LCDD generally present with decreased kidney function and sub–nephrotic-range proteinuria. Patients with untreated LCDD or LCDD that does not respond to treatment typically progress to kidney failure. Cardiac involvement occurs in a minority of patients, but may be more common in patients with overt multiple

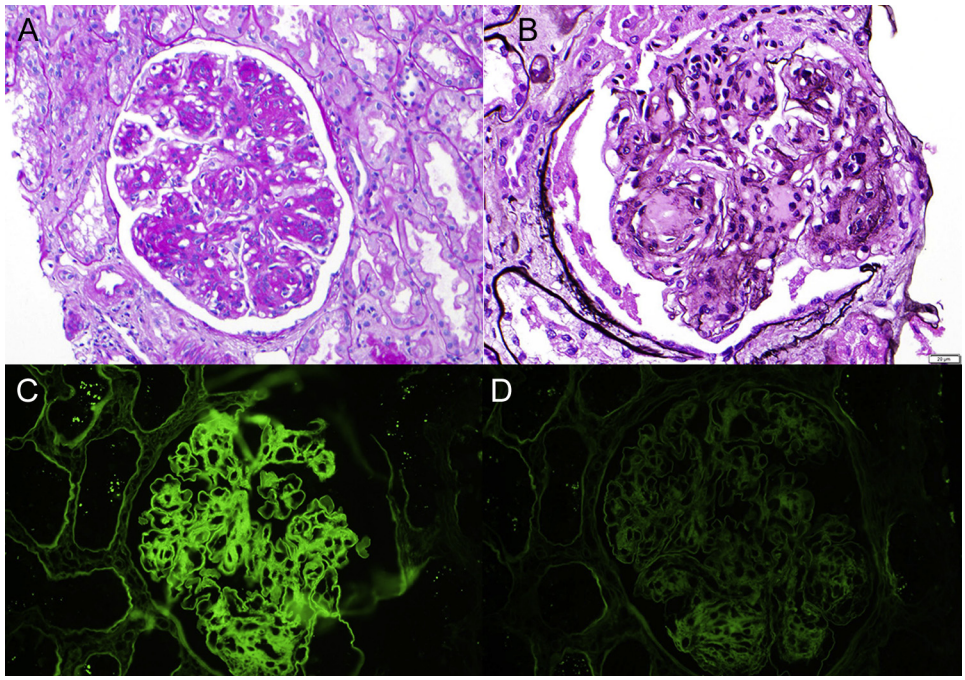

Figure 2. Kidney biopsy specimen from a patient with κ light chain monoclonal immunoglobulin deposition disease. Nodular glomerulosclerosis with (A) periodic acid–Schiff–positive but (B) silver-negative mesangial matrix expansion. (C) Glomeruli and tubular basement membranes stain brightly with κ light chain and (D) without staining for λ light chain.

myeloma. An underlying lymphoproliferative disorder is almost always found in patients with LCDD, with approximately 60% to 80% meeting criteria for MGRS. Overt multiple myeloma is present in ∼20% of patients with LCDD, and Waldenström's macroglobulinemia-associated LCDD has been rarely reported. The serum FLC assay result is abnormal in virtually all patients with LCDD, with a recent case series showing a diagnostic yield for serum and urine IFE of 64% and 68%, respectively.

Treatment of LCDD uses clone-directed therapy with the goal of achieving hematologic response. This therapy has most commonly included bortezomib-based regimens or ASCT. Patients who achieve complete or very good partial response have been shown to have better renal outcomes.

Heavy Chain Deposition Disease

HCDD is a rare disorder characterized by immunofluorescence microscopy staining for immunoglobulin heavy chain only, without an associated light chain. Light microscopy typically shows nodular glomerulosclerosis with Congo red–negative PAS-positive material, and tubular basement membrane thickening is common. Electron microscopy shows nonorganized electron-dense deposits. The most commonly involved heavy chain is IgG (γ), with even rarer cases showing IgA (α), IgM (μ), or IgD (δ). Extrarenal involvement of HCDD has been described. Of note, HCDD is distinct from heavy chain disease, a hematologic disorder characterized by production and secretion of a truncated heavy chain, but that does not result in organ deposition.

The pathogenic immunoglobulin in patients with HCDD is a truncated heavy chain that is not linked to a light chain. This truncated heavy chain is produced by a deletion in the heavy chain constant domain 1 (C_H1). The same C_H1 deletion is found in almost all patients with HCDD. Bonaud et al recapitulated HCDD in a transgenic mouse model expressing the C_H1 deletion heavy chain that fulfills the Koch postulates. The same group also found evidence suggesting that physiochemical properties of the heavy chain variable (V_H) region may be specifically responsible for deposition in the kidney.

A recent case series of 15 patients with HCDD described that the yield of paraprotein testing was 60% by SPEP, 80% by serum IFE, 47% by UPEP and 53% by urine IFE. Serum FLC ratio was abnormal in all tested patients with HCDD, reflecting that the underlying clone also makes a light chain that cannot bind with the truncated heavy chain. The truncated heavy chain in HCDD can also be detected using serum immunoblot and/or bone marrow heavy chain sequencing. As with all dysproteinemic disorders of the kidney, the treatment of HCDD is directed at the underlying clonal cell disorder. In the largest case series of HCDD, comprising 15 patients, 3 patients had overt myeloma, 1 patient had smoldering myeloma, and 1 patient had lymphoplasmacytic lymphoma. The rest of the patients had MGRS. Chemotherapy (including bortezomib-based therapy in 10 cases) resulted in hematologic

response in 11 patients, and renal response was predicated on having achieved hematologic response.

Light and Heavy Chain Deposition Disease

LHCDD is the rarest of the MIDDs and has similar light and electron microscopic features to HCDD. On immunofluorescence microscopy, there is staining for heavy chain and light chain (κ or λ) restriction, along with staining for C3. Unlike HCDD, the pathogenic features of the LHCDD paraprotein are not understood. The recent and largest description of LHCDD (n = 20) described that all patients have an abnormal serum κ:λ FLC ratio, but did not describe the yield of other paraprotein tests. Like the other MIDDs, treatment is directed at the underlying clone.

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Proliferative Glomerulonephritis With Monoclonal Immunoglobulin Deposits

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is characterized by a kidney biopsy specimen that exhibits mesangioproliferative, membranoproliferative, and/or endocapillary proliferative glomerulonephritis on light microscopy; monoclonal immunoglobulin deposition on immunofluorescence microscopy; and nonorganized electron-dense deposits on electron microscopy (Fig 3). PGNMID is distinguished from LCHDD by the presence of proliferative glomerulonephritis, rather than nodular glomerulosclerosis, on light microscopy and lack of tubular basement membrane staining. The most common monoclonal immunoglobulin found in PGNMID biopsies is IgG3κ (50%) followed by IgG3λ (15%). PGNMID is currently thought to be a kidney-limited disease because extrarenal

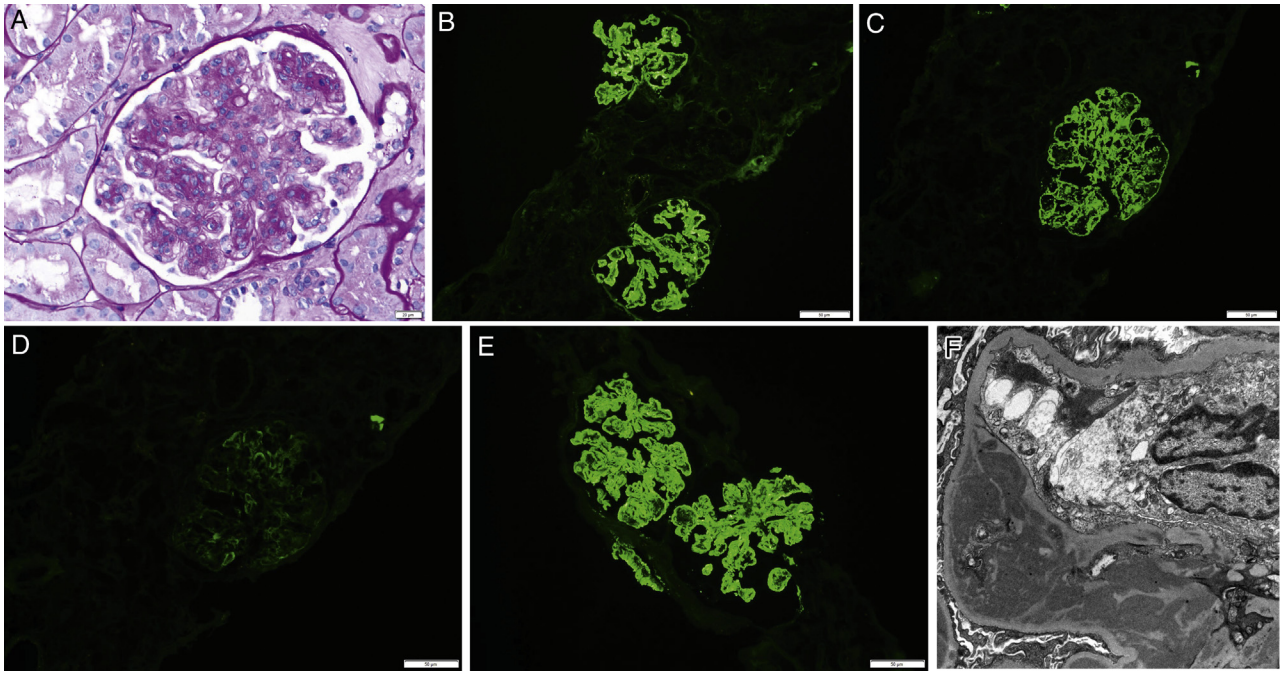

Figure 3. Kidney biopsy specimen from a patient with proliferative glomerulonephritis with monoclonal immunoglobulin G3 (IgG3) κ deposits. (A) Membranoproliferative pattern of glomerular injury is appreciated on periodic acid–Schiff–stained section. Granular mesangial and peripheral capillary wall deposits are noted that stain brightly with (B) immunoglobulin G (IgG) and (C) κ but (D) not λ. (E) Deposits show IgG3-restricted staining. (F) Ultrastructural studies show granular electron-dense deposits in the mesangium and peripheral capillary walls. The deposits do not have substructure.

organ involvement has yet to be described. The renal prognosis of patients with PGNMID after diagnosis was found to be poor during its initial description, with around half the patients reaching kidney failure within 2 to 5 years of diagnosis. Recurrence of disease in the allograft after kidney transplantation is well described.

In contrast to many of the other dysproteinemic kidney diseases, the majority of patients with PGNMID do not have detectable paraproteinemia or a detectable underlying B- or plasma cell clone. Recent retrospective case series describe monoclonal gammopathy detection rates of 30% to 37% and clone detection rates of 25% to 32%. The reason for these low detection rates is not understood. The presence of detectable monoclonal gammopathy may predict the presence of a detectable underlying clonal cell disorder, with a case series by Bhutani et al finding that all (n = 3) patients with positive serum IFE assays and abnormal κ:λ FLC ratios had a detectable clone on bone marrow biopsy, whereas all (n = 23) patients who had a negative serum IFE result and normal FLC ratio did not have a detectable clone.

Data for the treatment of PGNMID are limited. The first retrospective case series on PGNMID described a low clone detection rate and a wide variety of treatment strategies used. Extrapolating from the management of other paraprotein-mediated kidney diseases, it seems reasonable to advocate treating patients who have an underlying plasma or B-cell clone with clone-directed therapy. A special challenge exists for patients with PGNMID who do not have a detectable underlying clone, and the management of these patients remains controversial. In a recent case series of 19 patients with PGNMID, 13 of whom did not have a detectable underlying clone, empirical therapy directed at the hypothesized underlying clone led to a 90% renal response rate, with 30% of patients achieving a complete renal response (<500 mg/d or 500 mg/g of proteinuria). This approach often involved combination chemotherapeutic regimens; no patient who underwent treatment had reached kidney failure with a median follow-up of 2 years. While the patient outcomes of this series are encouraging compared with previous publications, they are hypothesis generating and require further validation in prospective studies with more uniform treatment approaches. PGNMID has a high rate of recurrence after kidney transplantation (∼90% at a median time of 6 months), making kidney transplantation difficult if the pathologic clone is not eliminated.

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Type I Cryoglobulinemic Glomerulonephritis

Type I cryoglobulinemia is diagnosed by the presence of monoclonal immunoglobulins in serum that also have features of cryoglobulins; that is, they precipitate at 2°C to −6°C. These are produced by B- or plasma cell clones, with the 2 largest recent case series (composed of 64 and 102 patients, respectively) identifying an underlying lymphoproliferative disorder in 90% to 100% of patients with type I cryoglobulinemia. Many of these patients will have MGUS, but overt or smoldering multiple myeloma is also commonly found, particularly in those whose cryoglobulins are of the IgG subtype. Multiple B-cell proliferative disorders have also been found, with lymphoplasmacytic lymphoma/Waldenström macroglobulinemia being common in patients with IgM cryoglobulins.

The skin and nervous system are the most common organ systems affected by cryoglobulins. Of patients with type I cryoglobulinemia, 20% to 30% will experience kidney involvement, which most often presents with proteinuria and decreased kidney function. Low serum complement component C4 levels are commonly detected. Nephrotic syndrome, microscopic hematuria, and hypertension are also common. On kidney biopsy, patients with type I cryoglobulin-associated glomerulonephritis exhibit a mesangio-, endocapillary, membranoproliferative, and/or extracapillary (crescentic) glomerulonephritis pattern of injury on light microscopy. They may also have intracapillary "cryoplugs" and leukocytoclastic vasculitis. Immunofluorescence microscopy reveals granular staining for the pathogenic monoclonal immunoglobulin in the capillary wall and/or mesangium. Electron microscopy shows mesangial, subendothelial, and/or subepithelial electron-dense deposits that have been described to exhibit various patterns of organized substructure (fibrillar, tactoids, and microtubular).

Treatment of type I cryoglobulinemic glomerulonephritis is focused on eradication of the underlying lymphoproliferative disorder. Although data for clone-directed treatment are limited, they suggest that this approach may lead to improvement or stabilization of disease in the majority of patients and that this may be predicated on improvement in serum cryoglobulin levels (ie, a hematologic response). Plasmapheresis has also been used in patients with cryoglobulinemia with severe end-organ damage, including rapidly progressive glomerulonephritis and hyperviscosity syndrome. However, because the literature is composed of case reports and case series, the

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Monoclonal Gammopathy–Associated C3 Glomerulopathy

C3 glomerulopathy (C3G) is a group of kidney diseases that feature predominant glomerular staining for complement component C3 on kidney biopsy in the absence of meaningful immunoglobulin staining. The 2 C3G histologic patterns of injury are C3 glomerulonephritis and dense deposit disease, which are distinguished on electron microscopy by the presence of glomerular electron-dense deposits in C3 glomerulonephritis and dense, osmophilic, intramembranous deposits in dense deposit disease. Overactivation of the alternative complement pathway is thought to be the common pathophysiologic abnormality accounting for all cases of C3G. The presence of a detectable monoclonal gammopathy in some patients with C3G has led to the hypothesis that the monoclonal gammopathy is causing activation of the alternative complement pathway. A recent case series of patients with C3G found a detectable monoclonal gammopathy in 36 of 95 (38%) patients using serum or urine IFE, and purified monoclonal λ light chains from 2 patients with hypocomplementemic membranoproliferative glomerulonephritis diagnosed have also been shown to activate the alternative complement pathway in vitro.

There is interest in using clone-directed therapy in patients with monoclonal gammopathy–associated C3G. The French Registry of C3G described the renal and hematologic characteristics and outcomes of 50 patients with monoclonal gammopathy–associated C3G. The majority of patients had MGRS; the rest had smoldering multiple myeloma (30%), symptomatic myeloma (4%), or chronic lymphocytic leukemia (6%). Patients treated with chemotherapy (n = 29, 22 of whom received bortezomib) experienced a higher rate of renal response versus those treated with conventional immunosuppressive (n = 8) or conservative therapy (n = 13), and having a hematologic response was associated with better renal outcomes. Although these data are limited, in the absence of specific tests to determine the pathogenicity of paraproteins in individual patients, these results suggest that it is reasonable to conduct a thorough hematologic workup and consider clone-directed therapy for patients with C3G and monoclonal gammopathy.

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Light Chain Proximal Tubulopathy

LCPT is a nonglomerular kidney disease associated with monoclonal gammopathy. LCPT is rare, accounting for just 5% of kidney biopsies in patients with monoclonal gammopathy in one series. The incidence could be higher because the diagnosis of LCPT can be made clinically without kidney biopsy if the characteristic electrolyte abnormalities associated with proximal tubular dysfunction (such as Fanconi syndrome) are present.

Patients with LCPT usually present with subacute decreases in kidney function and low-grade proteinuria. The decreased kidney function can be mild and slowly progressive over years, but kidney failure is also possible. Acquired Fanconi syndrome is common in patients with LCPT and manifests by hypokalemia, hypophosphatemia, hypouricemia, normoglycemic glycosuria, and aminoaciduria. As kidney function deteriorates, the electrolyte abnormalities may normalize, but aminoaciduria will remain. Also, some patients may not exhibit all the features, particularly glycosuria. These patients are considered to have a partial Fanconi syndrome. Patients with Fanconi syndrome can also present with osteomalacia and stress fractures due to phosphaturia and resultant hypophosphatemia.

The pathogenesis of LCPT has been studied with in vivo models, including a transgenic mouse model. Normally, immunoglobulin light chains are reclaimed by the proximal tubular cells after filtration. They enter the proximal tubular cell through the megalin/cubulin receptor by a clathrin-mediated endocytosis mechanism. After internalization, the light chains are shuttled to the lysosomes, where they are degraded. Pathologic light chains (usually VκI) associated with LCPT are resistant to the proteolysis. Evidence suggests that the pathologic monoclonal light chain may attenuate the acidification of the lysosomes, making degradation more difficult. These unhydrolyzed fragments often form rhomboidal, polygonal, rectangular, rod-shaped, or needle-like crystalline inclusions within the proximal tubular cells when examined using electron microscopy. Evidence also suggests that the pathologic light chains can interfere with the cell's normal reabsorptive function characteristics of Fanconi syndrome. A noncrystalline inclusion variant of LCPT also exists. The proximal tubules in these patients contain cytoplasmic droplets, granules, or

vacuoles. Abnormalities in lysosomes, phagosomes, and even mitochondria have also been noted. Interestingly, these patients commonly have a monoclonal λ light chain gammopathy.

A monoclonal gammopathy can be found in all patients with LCPT. Half the patients have an IgG monoclonal protein, whereas 30% have FLCs only. The light chain is κ in ~95% of patients. All patients have abnormalities in serum FLC assay results. MGRS is reported in 60% to 80% of patients, with multiple myeloma in up to 30% of patients. Patients with chronic lymphocytic leukemia and Waldenström macroglobulinemia can also present with LCPT.

In the past, due to its slow progression, conservative management with electrolyte replacement had been recommended due to concerns of excessive toxicity from alkylating chemotherapy. It was also noted that decreased kidney function rarely improved with therapy. However, this paradigm has changed with the advent of novel agents, particularly bortezomib. One series from the Mayo Clinic and France found that patients who achieved a hematologic very good partial response with bortezomib-based therapy also achieved improvement in kidney function.

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Immunotactoid Glomerulopathy

Immunotactoid glomerulopathy accounts for <1% of kidney biopsy results and is characterized by a kidney biopsy specimen showing Congo red–negative large microtubular

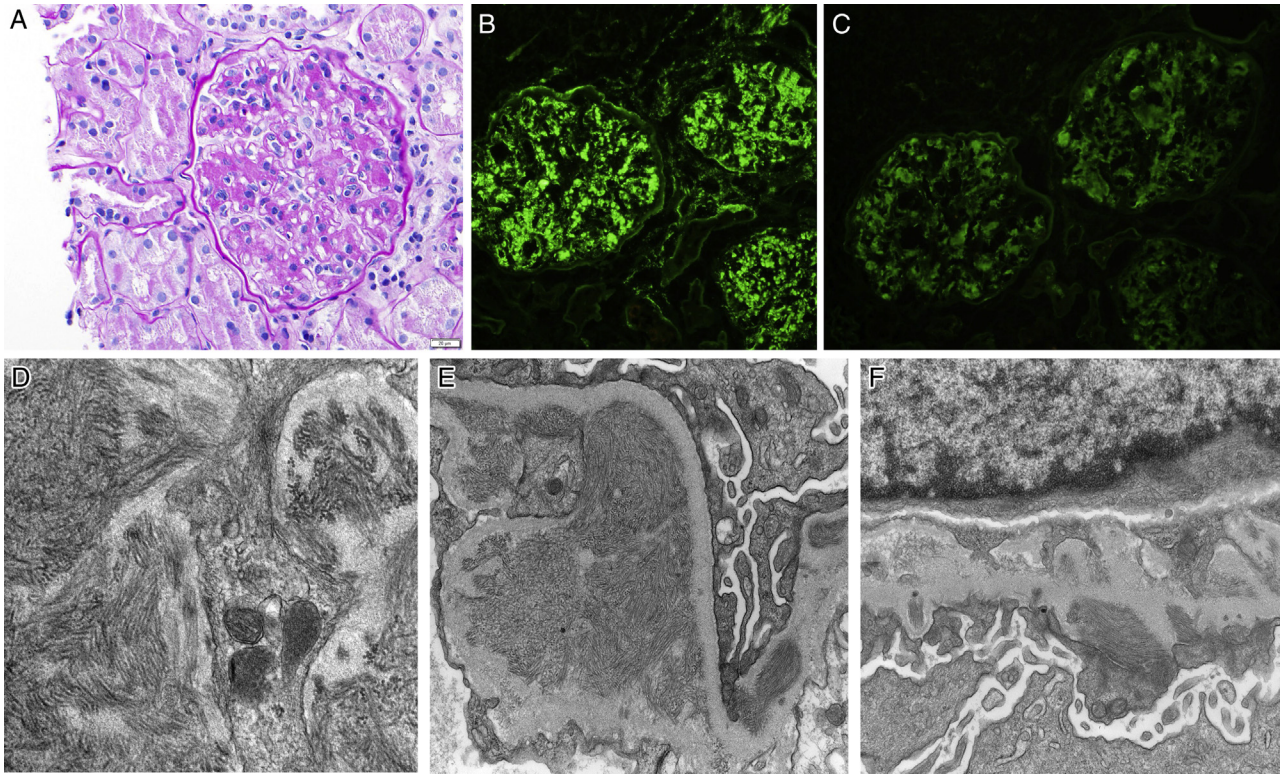

Figure 4. Kidney biopsy specimen from a patient with immunotactoid glomerulopathy. (A) Glomerulus shows mesangioproliferative pattern of injury with mildly thickened capillary walls (periodic acid–Schiff; original magnification, ×20). Glomeruli demonstrate coarse staining of mesangium and peripheral capillary walls with (B) immunoglobulin G (IgG; 3+) and (C) κ light chain (1+). There is no staining of glomeruli with λ light chain. Ultrastructural studies demonstrate organized microtubular deposits in (D) the mesangium and (E, F) subendothelial and subepithelial aspects.

structures (average, 30 nm) on electron microscopy (Fig 4). Proliferative glomerulonephritis is seen on light microscopy, with most cases showing a membranoproliferative pattern of injury. Although immunotactoid glomerulopathy had often been historically grouped with fibrillary glomerulonephritis based on the organized substructure of deposits noted on electron microscopy, the majority of these cases stain for monoclonal immunoglobulin on immunofluorescence microscopy and are associated with underlying clonal disorders, and the recent discovery of staining for the chaperone protein DNAJB9 (DnaJ homolog subfamily B member 9) staining as a sensitive and specific marker for the majority of cases of fibrillary glomerulonephritis, which provide strong evidence that these are distinct entities.

Patients with immunotactoid glomerulopathy present with decreased kidney function, microscopic hematuria, and proteinuria, with the majority of cases having full nephrotic syndrome. Hypocomplementemia is also common. Extrarenal involvement of paraprotein has been described, as have 2 cases of immunotactoid glomerulopathy in patients with the disorder of polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma proliferative disorder, and skin changes (POEMS syndrome).

The largest and best-characterized case series of immunotactoid glomerulopathy found that 11 of 16 patients had monoclonal staining on immunofluorescence microscopy (IgGκ, n = 6; IgGλ, n = 5). Paraproteinemia was detected in 63% of patients, and two-thirds (6/9) of patients who underwent bone marrow biopsy had a detectable underlying clone (n = 6 plasma cell, n = 2 plasma cell and lymphoma). Immunosuppressive treatment, which was not clone directed in the majority of cases, led to variable renal outcomes.

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Monoclonal IgM–Related Kidney Disease

Monoclonal IgM–related kidney disease is predominately seen in patients with Waldenström macroglobulinemia, which has an annual incidence of 5 per million. It is characteristically a lymphoplasmacytic lymphoma that secretes an IgM monoclonal protein. However, some definitions include nonlymphoplasmacytic lymphomas and non-IgM monoclonal gammopathies. All the definitions recognize that the need for treatment is based on progression of signs that include anemia, bulky adenopathy or organomegaly, hyperviscosity, severe neuropathy, amyloidosis, cryoglobulinemia, cold agglutinin disease, or evidence of disease transformation. More recently, mutational analysis of the MYD88 (myeloid differentiation primary response 88) gene found that leucine is substituted by proline at amino acid 265 (L265P) in >90% of patients with Waldenström macroglobulinemia. The MYD88 L265P mutation is not common in patients with IgM multiple myeloma or other low-grade lymphomas, suggesting that it could be a diagnostic marker of Waldenström macroglobulinemia.

One of the first descriptions of kidney lesion in patients with Waldenström macroglobulinemia was by Morel-Morager et al. This series of 16 patients found that in addition to 3 cases of immunoglobulin-derived amyloidosis, 6 patients with Waldenström macroglobulinemia had IgM thrombi plugging numerous capillary lumens. Unlike cryoglobulinemic glomerulonephritis, cellular proliferation was none or minimal in all cases. Three patients from the series had cryoglobulins identified: type I in 2 and type II in 1 patient. The term intracapillary monoclonal deposits disease was used to describe a similar lesion in a French series of 14 patients by Audard et al. The deposits are noncongophilic, polychromatophilic, and PAS positive and do not show organized structures on electron microscopy. Although intracapillary monoclonal deposits disease was the most common renal lesion in the Morel-Morager et al series, later studies have found it to be one of the less common lesions in patients with Waldenström macroglobulinemia. The reason for this difference is unclear. All patients with intracapillary monoclonal deposits disease should have a positive SPEP result and an IFE for a monoclonal IgM. Treatment and response data are not available for this lesion.

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Monotypic Fibrillary Glomerulonephritis

Fibrillary glomerulonephritis has traditionally been grouped with the dysproteinemic kidney diseases due to similarities in histologic features, in particular, the

presence of organized fibrillar deposits on electron microscopy. Light microscopy in fibrillary glomerulonephritis shows a mesangio-, endocapillary, and/or membranoproliferative glomerulonephritis, with granular staining for IgG heavy chain, C3, and both κ and λ light chains on immunofluorescence microscopy. The diagnosis historically required electron microscopy, which shows randomly oriented fibrillary deposits in glomeruli with an average diameter of 20 nm. Congo red staining is negative in fibrillary glomerulonephritis. Pathology laboratories have reported that fibrillary glomerulonephritis represents up to 1.0% of kidney biopsy diagnoses. Patients with fibrillary glomerulonephritis typically present with proteinuria and chronic kidney disease, and the renal prognosis is typically poor, with half the patients progressing to kidney failure within 2 years of diagnosis. There are no established treatments for fibrillary glomerulonephritis.

In 2018, two groups independently reported that DNAJB9 is present in virtually all cases of fibrillary glomerulonephritis, leading to the hypothesis that this is a common autoantigen in fibrillary glomerulonephritis. This finding, in addition to the lack of monotypic staining on kidney biopsy immunofluorescence microscopy, provides strong evidence that most cases of fibrillary glomerulonephritis should not be included as a dysproteinemic kidney disease. Rare cases of fibrillary glomerulonephritis with monotypic staining have been reported. A clone-directed approach to diagnosis and treatment should be used in cases of monotypic fibrillary glomerulonephritis that are negative for DNAJB9 staining.

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