Light Chain–Only Immunotactoid Glomerulopathy: A Case Report

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The monotypic variant of immunotactoid glomerulopathy (ITG), strongly associated with low-grade lymphoproliferative disorders, is characterized histologically by glomerulonephritis and microtubular deposits of monoclonal immunoglobulin G (IgG). We report a patient with high-risk κ light chain multiple myeloma who presented with acute kidney injury, hematuria, proteinuria, and hypocomplementemia. Kidney biopsy revealed immunotactoid glomerulopathy concomitant with κ light chain myeloma cast nephropathy. The glomerular microtubular deposits stained for κ light chain and C3 only. Proteomic analysis of glomeruli and atypical casts detected κ light chain constant domain and a single VL variability subgroup (IGKV3) in both glomeruli and casts (without γ, α, or μ heavy chain or λ light chain). C3, C5, C6, C7, and C9 were detected in glomeruli. No autoantibodies against alternative pathway of complement proteins were detected. Despite clone-directed chemotherapy, the patient remained on dialysis treatment. For this light chain–only variant of immunotactoid glomerulopathy, pathogenesis potentially involves activation of the alternative pathway of complement by a nephrotoxic κ light chain.

Introduction

Immunotactoid glomerulopathy (ITG) is a rare glomerular disease characterized by glomerular immunoglobulin deposits of microtubules, with a distinct hollow center, that are arranged at least focally in parallel arrays, in the absence of a clinicopathologic diagnosis of cryoglobulinemic glomerulonephritis or lupus nephritis. Two-thirds of ITG cases are characterized by monoclonal immunoglobulin deposits on immunofluorescence and are strongly associated with hematologic disease, usually low-grade lymphoma or monoclonal gammopathy of renal significance (MGRS), whereas an association with symptomatic multiple myeloma (MM) is very rare. The remaining cases show polyclonal immunoglobulin deposits and are less commonly associated with hematologic conditions.

Here we describe a unique case of ITG composed exclusively of immunoglobulin light chain deposits. Proteomic, immunofluorescence, and complement system studies suggest activation of the alternative pathway of complement (APC) by a nephrotoxic κ light chain.

Case Report

A 76-year-old woman with no notable medical history presented with generalized malaise, weakness, and epistaxis. She was found to have a systolic blood pressure in the range of 220–230 mm Hg, acute kidney injury with serum creatinine of 7.7 mg/dL (it had been within the reference range 2 months prior), potassium of 6.3 mmol/L, and hemoglobin of 7.7 g/dL, without edema, skin rash, and peripheral lymphadenopathy. Urinalysis showed protein (3+), blood (3+), trace leukocytes, bacteria (4+), 123 white blood cells per high-power field, >182 red blood cells per high-power field, and a urinary protein-creatinine ratio of 1.024 mg/g. Other laboratory results included serum albumin of 3.1 g/dL, calcium of 8.6 mg/dL, normal liver function tests, and negative results upon testing for antibodies to myeloperoxidase, proteinase 3, glomerular basement membrane, phospholipase A2 receptor, hepatitis C virus, hepatitis B virus surface antigen, and antinuclear antibody. C3 level was 76 mg/dL (reference range: 80-165 mg/dL) and C4 level was 35.9 mg/dL (reference range: 14-44 mg/dL). Serum cryoglobulin was not tested. Prednisone was initiated. Urine protein electrophoresis with immunofixation (IFE) revealed 525 mg/dL protein (27% albumin) with an M spike of 239.3 mg/dL (45% free κ light chain on IFE). Serum protein electrophoresis with IFE showed 2 M spikes at the beta-gamma region of 0.2 g/dL and 0.1 g/dL (both free κ light chain). Serum κ and λ free light chains were 30,045 mg/L (reference range: 3.3-19.4 mg/L) and 12.7 mg/L (reference range: 5.7-26.3 mg/L) respectively, with the κ:λ free light chain ratio at 2,365.8 (reference range: 0.26-1.65).

Kidney biopsy (Fig 1) revealed endocapillary proliferative and exudative glomerulonephritis. The tubulointerstitial exhibited acute cast nephropathy, acute tubular injury, mild interstitial inflammation, and moderate tubular atrophy and interstitial fibrosis. By immunofluorescence, there was diffuse global granular mesangial and glomerular basement membrane staining for C3 (3+) and κ light chain (2+) in a similar distribution, and the casts stained positive for κ light chain with negative staining for λ light chain in the glomeruli and tubular casts. Glomeruli were negative for γ, α, or μ heavy chains; γ heavy chain subclasses 1-4; C1q; and C4d. Immunofluorescence on
paraffin tissue sections after pronase digestion confirmed negative staining for γ heavy chain and λ light chain, and positive staining for κ light chain in the glomeruli and the casts. Next, we used heavy chain/light chain immunofluorescence (HLC-IF), which probes junctions of the heavy chain and light chain constant regions to detect intact heavy chain–light chain pairs. This revealed weak (1+) glomerular and tubular cast staining for the γ heavy chain–κ light chain junction with negative staining for γ heavy chain–λ light chain junction. Ultrastructurally, there were massive mesangial, segmental subepithelial, and subendothelial deposits composed entirely of straight, large microtubules with the mean external diameter of 53 nm (range: 30–87 nm) with focal parallel alignment. The pathologic diagnosis was light chain–only ITG concomitant with myeloma cast nephropathy (MCN).
Additional Investigations

To characterize the proteomic content, we performed laser microdissections of the glomeruli and atypical casts, followed by liquid chromatography–tandem mass spectrometry (Fig 2, Item S1, and Fig S1). A κ light chain constant region and a variable region derived from a single V_L variability subgroup (IGKV3) were detected in both glomeruli and casts, without γ, α, or μ heavy chains or λ light chain. Additionally, C3 and complement terminal complex proteins (C5, C6, C7, and C9) were detected in glomeruli (but not in tubular casts), without proteins of the classical complement pathway (C1, C2, and C4). As expected, uromodulin was detected only in the casts.

In addition, patient serum sample was screened for autoantibodies of γ heavy chain or κ or λ light chain specificity targeting 6 proteins of APC (factor H, factor I, complement receptor 1, C3b, factor B, and properdin) by ELISA (Item S1) and no autoantibodies were identified.

Bone marrow biopsy with flow cytometry immunophenotyping showed a large κ light chain–restricted plasma cell population involving 90% of total marrow cellularity. The neoplastic cells stained negative for γ heavy chain and λ light chain and positive for κ light chain (Fig S2). Cytogenetics were normal but fluorescence in situ hybridization analysis was consistent with high-risk MM (MAFB/IGH fusion, 17p−, 1q−, trisomy(3,7,11), t(14;20)). Positron emission tomography scan revealed diffuse marrow stimulation. The patient was diagnosed with high-risk κ light chain MM. Hemodialysis was initiated and she was treated with daratumumab, cyclophosphamide, bortezomib, and dexamethasone (CyBoRd DARA). Five months post-biopsy (3 months after initiation of chemotherapy), she had a serum M-spike of 0.2 g/dL and κ:λ free light chain ratio to 532. She remained on maintenance dialysis.

Discussion

Because of their low molecular weight, immunoglobulin light chains are filtered through the glomerulus and may produce tubular injury (eg, MCN, light chain proximal tubulopathy). Deposition of monoclonal nephrotoxic light chains often involves all renal compartments, including glomeruli, vessels, and tubules (eg, AL amyloidosis, light chain deposition disease). In these light chain nephropathies, glomerular inflammation is generally absent or mild, and C3 deposition is rare. In contrast, entire monoclonal immunoglobulin molecules are less likely to filter through the glomerulus and therefore can deposit in glomeruli, leading to complement activation, leukocyte infiltration, and glomerular cell proliferation, culminating in glomerulonephritis (eg, proliferative glomerulonephritis with monoclonal immunoglobulin deposits [PGNMID], cryoglobulinemic glomerulonephritis type I and II, and monotypic variant of ITG). However, intriguingly, a light chain–only variant of PGNMID, a proliferative glomerulonephritis associated with κ light chain fibrils, a case of light chain–only ITG, and a case of light chain–only immunotactoid gastropathy have recently been described.6–9

Here we describe a unique case of ITG composed of light chain only. The patient presented with acute kidney injury, hematuria, proteinuria, and hypocomplementemia and was diagnosed with light chain MM, an uncommon variant of MM (15%-20%) characterized by only light chain in the serum or urine (without heavy chain) and associated with a higher incidence of kidney failure.10 Kidney biopsy revealed κ light chain ITG concurrent with MCN. Our case is different from classic ITG in 3 aspects: (1) the glomerular deposits are composed of light chain only; (2) it is associated with high-tumor-burden MM (contrary to classic ITG, which is generally associated with low-grade lymphoma and/or MGRS); and (3) it is likely...
mediated by APC activation, similar to light chain PGNMID. In contrast, the immunofluorescence and proteomic findings in classic ITG favor activation of the classical pathway of complement by IgG.

Findings that favor APC activation by nephrotoxic κ light chain in our patient include the glomerular co-deposition of C3 (without C1q or C4d), the detection of C3 and C5-C9 (but not C1, C2, and C4) by proteomic analysis of glomeruli, and the low serum C3 (but not C4). APC activation (initiated in the fluid phase or locally on the glomerular surface) likely initiates downstream inflammatory mediators, leading to proliferative glomerulonephritis. About half of patients with C3 glomerulopathy associated with a monoclonal gammopathy have anti-complement autoantibodies (particularly anti-CR1 and anti-FH). Direct activation of APC by monoclonal immunoglobulin has been confirmed in 2 patients with monoclonal immunoglobulin C3 glomerulopathy. In both patients, the monoclonal immunoglobulin (λ in 1 and IgGk in 1) inhibited FH. We did not detect autoantibodies of γ heavy chain or κ or λ light chain specificity against 5 proteins of the APC (FH, factor I, complement receptor 1, factor B, or properdin) in our patient. Interestingly, it was recently shown that in patients with monoclonal immunoglobulin C3 glomerulopathy, the monoclonal immunoglobulin could directly activate APC by serving as a complement-activating surface. The mechanisms by which κ light chain activated APC in our patient are unknown. The nephrotoxic κ light chain in our patient is derived from the IGKV3 variability subgroup, which has also been reported in light chain PGNMID, another light chain glomerulopathy associated with APC activation, but is infrequent in renal AL amyloidosis (most commonly IGKV6), light chain deposition disease (most commonly IGKV4), and light chain proximal tubulopathy (most commonly IGKV1).

The weak glomerular staining for the γ heavy chain–κ light chain junction by HLC-IF likely represents cross-reactivity of the antibody detecting this junction with free κ light chain deposits for multiple reasons: (1) the neoplastic plasma cells were negative for γ heavy chain, and no monoclonal γ heavy chain was detected in the serum or urine; (2) the weak glomerular staining was accompanied by similar staining of atypical casts; (3) the glomeruli and casts were negative for γ heavy chain by pronase immunofluorescence, which, contrary to HLC-IF, has an antigen retrieval step; (4) no γ heavy chain was detected in glomeruli or casts by mass spectrometry; and (5) we have observed cross-reactivity of antibodies probing γ or μ heavy chain–κ light chain junction with κ light chain deposits in few cases of other light chain nephropathies, including AL-κ amyloidosis (eg, case 23 in the validation study) and a recent case of light chain PGNMID (S.H.N., unpublished observation).

### Supplementary Material

**Supplementary File (PDF)**

**Figure S1:** Examples of microdissected glomeruli and atypical tubular casts for proteomic analysis.

**Figure S2:** Immunohistochemical stains of γ heavy chain and κ and λ light chain on bone marrow biopsy of κ light chain MM.

**Item S1:** Supplementary methods.


