Renal Manifestations of Common Variable Immunodeficiency

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ABSTRACT

Background: Common variable immunodeficiency (CVID) is one of the most common primary immunodeficiency syndromes, affecting 1/25,000-50,000. Renal insufficiency occurs in approximately 2 percent of CVID patients. To date, there are no case series of renal biopsies from CVID patients, making it difficult to determine whether individual cases of renal disease in CVID represent sporadic events or are related to the underlying pathophysiology. We performed a retrospective analysis of renal biopsies in our database from patients with a clinical history of CVID (n=22 patients, 27 biopsies).

Methods: Light, immunofluorescence, and electron microscopy were reviewed. IgG subclasses, PLA2R immunohistochemistry, and THSD7A, EXT1, and NELL1 immunofluorescence were performed on all membranous glomerulopathy cases.

Results: Acute kidney injury and proteinuria were the leading indications for renal biopsy in CVID patients. Immune complex glomerulopathy was present in 12 of 22 (54.5%) cases including 9 with membranous glomerulopathy, one case with a C3 glomerulopathy, and one case with membranoproliferative glomerulonephritis with IgG3 kappa deposits. All membranous glomerulopathy cases were PLA2R, THSD7A, EXT1, and NELL1 negative. The second most common renal biopsy diagnosis was chronic tubulointerstitial nephritis, affecting 33% cases. All tubulointerstitial nephritis cases showed tubulitis and a lymphocytic infiltrate with >90% CD3+ T cells. Other renal biopsy diagnoses within our cohort included acute tubular injury (n=1), AL amyloidosis (n=1), diabetic glomerulosclerosis (n=1), thin basement membranes (n=1), pauci-immune glomerulonephritis (n=1), and arterionephrosclerosis (n=1).

Conclusions: Membranous glomerulopathy and tubulointerstitial nephritis were the predominant pathologic findings in CVID patients. Membranous glomerulopathy cases in CVID patients were IgG1 subclass dominant and shown mesangial immune deposits. Four of the membranous glomerulopathy cases had associated proliferation, with mesangial and/or endocapillary hypercellularity, with or without crescent formation. CVID should be considered as a potential etiology when membranous glomerulopathy or chronic tubulointerstitial nephritis is seen in a young patient with a history of recurrent infections.
INTRODUCTION

Common variable immunodeficiency (CVID) is one of the most common primary immunodeficiencies, yet is overall rare affecting 1 in 25,000-50,000 Caucasians and 1 in 100,000 individuals worldwide and has near equivalent prevalence in males and females. CVID consists of a heterogeneous group of primary immunodeficiency disorders characterized by a marked reduction in antibody production (IgG, IgM, and IgA), poor humoral responses to protein or polysaccharide vaccines, and an exclusion of other causes of hypogammaglobulinemia. A genetic etiology for CVID can be identified in a minority of patients, with only 2-10% of patients showing monogenic forms. CVID is most often diagnosed between ages 20 and 40 years, usually with a long delay from onset of symptoms to clinical recognition (average 6 to 8 years), as the symptoms are not specific, and infections are common in children.

Patients with CVID have a variety of disease manifestations, including recurrent bacterial infections, autoimmunity, chronic lung disease, gastrointestinal disease, lymphoid hyperplasia, granulomatous disease, and an increased risk of malignancy. Treatment of CVID is aimed at life-long immunoglobulin replacement, which reduces risk of bacterial infections, but does not impact autoimmune and inflammatory manifestations of the disease.

Renal failure is a rare complication of CVID affecting approximately 2 percent of patients. In a cohort of 240 CVID patients, five were found to have chronic kidney disease. Immunoglobulin replacement therapy in hypertonic solutions has been shown to be nephrotoxic and can result in reversible acute tubular injury. The presence of proteinuria or an active urinary sediment is not typical for IVIG-induced renal injury, and is an indication for renal biopsy in CVID patients. To date, there are no case series of renal biopsies from CVID patients, making it difficult to determine whether individual case reports of renal disease in CVID represent sporadic events or are related to the underlying pathophysiology. Here, we present the first case series and review of the literature of the nephropathology in CVID patients.

MATERIALS AND METHODS

Case selection

Approval for this study was obtained by the Solutions Institutional Review Board, and the ethical principles highlighted by the Declaration of Helsinki were followed. A retrospective analysis of 10 years of renal biopsy specimens using our database from patients with a clinical history of CVID was performed (n=22 patients, comprising 27 renal biopsy specimens) from 01/01/2010 to 12/31/2019. During this time period, there were 27 renal biopsies from CVID patients of a total of 110,918 cases (0.02%). Patients with primary immunodeficiency of unknown etiology, as well as from patients with a clinical or family history with x-linked (Bruton’s) agammaglobulinemia, severe combined immunodeficiency, Wiskott-Aldrich syndrome, DiGeorge syndrome, IgA...
deficiency, chronic granulomatous disease, or hyper-IgE syndrome were also studied, but only a small overall number of patients available for analysis (n=18 cases in total).

Clinical notes at the time of biopsy and at follow-up were also reviewed. Data abstracted from the medical records included history of infections, co-morbid health conditions, medications (including IVIG therapy), serum creatinine and proteinuria. Patients without proteinuria on urinalysis did not have quantitative proteinuria or serum albumin values available. Follow-up serum creatinine and quantitative proteinuria values were also obtained. A history of infections, serum creatinine, and proteinuria values were available for the majority of patients. Serum creatinine values at the time of biopsy were available from 18 patients, 14 of which had follow-up creatinine values. Proteinuria data was available for 18 patients, 10 of which had quantitative proteinuria. Seven of the ten patients with quantitative proteinuria values had follow-up quantitative proteinuria data. Quantitative proteinuria included both spot urine protein-to-creatinine ratio values and 24 hour urine collections.

A literature review was performed of all reported cases of native renal biopsies in CVID patients that were indexed on Pubmed, Scopus, or Google Scholar (n=24 manuscripts and 2 conference abstracts).

Renal biopsy:

All cases were processed for light, immunofluorescence, and electron microscopy. Formalin-fixed tissue was prepared for light and electron microscopy. For light microscopy, biopsies were fixed in formalin, dehydrated using alcohols, and embedded in paraffin wax after microwave processing. Paraffin sections were cut at 3 µm thickness, and stained with hematoxylin and eosin (H & E), periodic acid-Schiff (PAS), Masson trichrome, Jones methenamine silver (JMS), and Congo Red. For preparation of electron microscopy, 1 mm cubes of formalin fixed tissue were removed, dehydrated with alcohols, and embedded in an epon/araldite resin. An ultramicrotome was used to cut 1 µm thick sections, stained with toluidine blue, and examined by light microscopy. Thin sections were examined by electron microscopy.

Samples for immunofluorescence microscopy were received in Michel’s transport medium, washed with Michel’s wash buffer, and frozen with OCT medium at -20°C. Sections were cut at 4 µm thickness, rinsed, and stained with fluorescein-tagged rabbit anti-human polyclonal antibodies. Evaluation for IgG, IgA, IgM, C3, C1q, fibrinogen, kappa, and lambda light chain were performed for all cases. Dako antibodies were added for 30 minutes, rinsed, and coverslipped in mounting medium. The staining intensity was semi-quantitative on a 0 to 3+ scale. For membranous glomerulopathy cases, if sufficient frozen tissue was available, sections were stained with mouse anti-human antibodies to IgG1, IgG2, IgG3, and IgG4.

Immunohistochemical and immunofluorescent staining:

For cases of membranous glomerulopathy (MG), immunohistochemistry for phospholipase A2 receptor (PLA2R, PLA2R rabbit polyclonal antibody, Sigma, cat #HPA012657), and
Immunofluorescence for thrombospondin type 1 containing 7A (THSD7A, THSD7A mouse monoclonal; antibody, Atlas antibodies, catalog # AMAB91234), exostosin-1 (EXT1, EXT1 rabbit polyclonal antibody, Invitrogen, catalog # PA5-60699), and neural epidermal growth factor-like 1 (NELL1, NELL1 rabbit polyclonal antibody, Invitrogen PA5-27958) were performed. PLA2R staining was performed on frozen tissue by immunohistochemistry. THSD7A, EXT1, and NELL1 staining was performed on formalin-fixed paraffin embedded (FFPE) tissue sections following pronase digestion. THSD7A antibodies were cross-linked with Alexa Fluor 488 goat anti-mouse IgG for detection by immunofluorescence. EXT1 or NELL1 antibodies were cross-linked with Rhodamine Red X Affinipure goat anti-rabbit IgG antibodies at 1:100 for 30 minutes (Jackson Immunoresearch, cat #111-295-144). Granular capillary loop staining was considered a positive result and negative if there was an absence of staining. IgG subclasses were performed on cases of membranous glomerulopathy. IgG antibodies were all goat polyclonal direct FITC conjugates (IgG1, Jackson Immunoresearch, catalog #115-095-205), IgG2, Jackson Immunoresearch, catalog #115-095-207, IgG3, Jackson Immunoresearch, catalog #F4641, and IgG4, Jackson Immunoresearch, catalog #F9889).

Immunophenotyping of interstitial lymphoid infiltrates in cases of tubulointerstitial nephritis (TIN) was done by CD3 (Cell Marque, catalog #103R-98), CD4 (Cell Marque, catalog #104R-18), CD8 (Cell Marque, catalog #108R-18), CD20 (Cell Marque, catalog #120M-88), and CD68 (Cell Marque, catalog #168M-98) immunohistochemistry on FFPE tissue for cases with TIN. The relative percentage of T cells (CD3+) to B cells (CD20+), and the CD4/CD8 ratio for T-cell rich infiltrates was assessed, as were estimates by evaluating multiple 400x microscopic fields.

Statistics: Student’s t-tests were used to evaluate differences between groups.

RESULTS

Clinical manifestations:

All 22 patients in our cohort had a clinical diagnosis of CVID. Two patients had a genetic diagnosis, with one patient having lipopolysaccharide responsive beige-like anchor (LRBA) gene deficiency and the other patient having an anomaly of chromosome pairs 3 and 18. In a majority of patients in our cohort, CVID was diagnosed by hypogammaglobulinemia for IgG, IgM, and IgA identified in a workup initiated due to recurrent or unusual infections. These included sinusitis, otitis media, pharyngitis, pneumonia, colitis (Clostridium difficile, CMV), and skin infections. Eighteen of twenty two patients received long-term IVIG therapy every 3 to 4 weeks. One patient underwent splenectomy, one rituximab therapy, and one was deceased at follow-up.

The mean age of CVID patients at the time of renal biopsy was 37.7 years (range = 2-69 years, standard deviation = ± 20.6 years). The mean serum creatinine was 1.97 ± 1.76 mg/dL, which was higher on average for patients with tubulointerstitial nephritis (mean = 2.75 mg/dL) than membranous glomerulopathy (mean = 1.62 mg/dL), although is not statistically significant (p=0.54, unpaired t-test). Mean proteinuria was 3.25 g ± 4.82 g/24 h.
The CVID patients presented with a variety of immunodeficiency-related manifestations and comorbid conditions, including developmental, hematologic, cardiovascular, pulmonary, gastrointestinal, endocrine, oncologic, and rheumatologic conditions (Supplemental Table 1). CVID patients with MG were more common to have IgE-mediated co-morbidities, including allergies, asthma, and eosinophilic esophagitis than patients with acute or chronic tubulointerstitial nephritis. As IgE is formed from cross-switching from IgG1 in germinal centers, there may be a link between IgG1-dominant membranous glomerulopathy and IgE-mediated disease manifestations.

Recurrent infections were frequent within the CVID patients, but there was no stratification between type of infection and renal manifestations. Patients with membranous glomerulopathy and CVID had a history of chronic otitis media, upper respiratory infections, including pharyngitis (in 2 patients) and sinusitis, lower respiratory infections (including pneumonia in 5 patients and bronchiectasis in 2 patients), colitis (CMV and *Clostridium difficile*), and skin infections (in 2 patients). CVID patients with tubulointerstitial nephritis similarly had a history of pharyngitis, pneumonia, and enteritis.

Acute kidney injury and proteinuria were the leading indications for renal biopsy in CVID. Proteinuria was present at the time of biopsy for 18 of 27 biopsies (67%). Acute kidney injury was present at the time of biopsy for 10 cases (36%), and two patients had anuria (9%). Four patients underwent repeat biopsy, and the findings within three cases were similar with only differences in activity and chronicity compared to the initial biopsy. In one case, a patient with a proliferative immune complex glomerulonephritis developed membranous glomerulopathy in addition to proliferative immune complex glomerulonephritis at follow-up.

**Immune complex glomerulonephritis in CVID patients:**

Thirteen of 22 (59%) patients had immune complex glomerulonephritis with capillary loop immune deposits. Nine patients had subepithelial deposits and met criteria for MG, one case had subendothelial deposits and was diagnosed as membranoproliferative glomerulonephritis with IgG3 kappa deposits (PGMID), one case had C3 glomerulopathy, and the remaining 2 cases showed a proliferative immune complex glomerulonephritis. In the patient with PGMID, serum immunofixation and free light chain assays were performed to exclude a paraprotein-related process, although presence of a clone below the limits of detection cannot be excluded. Immunofixation was negative for a paraprotein and a serum free light chain assay showed a normal kappa/lambda ratio. One of the biopsies containing a mesangioproliferative glomerulonephritis had co-existence of a severe thrombotic microangiopathy with impending cortical necrosis in addition to an immune complex glomerulonephritis. This biopsy had ischemic, hypoperfused glomeruli, severe tubular injury with focal acute tubular necrosis, and severe microangiopathic changes within glomeruli and vessels.

Of the MG cases, 8 of 13 contained mesangial deposits in addition to subepithelial and intramembranous deposits, while the remaining 5 had no mesangial or paramesangial deposits.
(Table 1). All cases were PLA2R, THSD7A, EXT1, and NELL1 negative (Supplemental Figure 1). IgG subclass staining shows strong IgG1 positivity along glomerular capillary loops in 4 of 4 tested cases. IgG2, IgG3, and IgG4 were negative (Figure 1). IgG deposits were present within all cases and there was variable expression of IgA (7 of 13, 54%), IgM (6 of 13, 46%), C3 (9 of 13, 69%), and C1q (4 of 13, 23%). Global glomerulosclerosis ranged from 1.5 to 36.7%. Interstitial fibrosis was mild in 11/13 patients, moderate in 1/13 patients, and severe in 1/13 patients. There was moderate arteriosclerosis in 3 of 13 cases (23%), with no cases showing severe vascular disease. Four cases showed an associated proliferative component, with mesangial hypercellularity, endocapillary hypercellularity, and/or fibrinoid necrosis or crescent formation (Figure 2).

Electron microscopy was evaluated from the CVID patients with MG to evaluate the stage of the electron dense deposits. All cases showed at least stage II electron dense deposits (range: stage II – IV), with reaction of the underlying glomerular basement membrane (Figure 2F).

At follow-up, CVID patients with MG had a mean serum creatinine of 1.06 ± 0.59 mg/dL. Proteinuria persisted in 6 patients. One patient died of complications of a concurrent acute thrombotic microangiopathy.

Tubulointerstitial nephritis in CVID patients:

The second most common diagnosis in our CVID cohort was acute or chronic tubulointerstitial nephritis, affecting 6 of 22 (27%) of CVID patients (Table 2). The lymphocytic infiltrates all contained >90% CD3+ T cells, and showed a normal CD4:CD8 ratio in 4 of 6 cases, whereas 2 cases had a reduced ratio (Figure 3). The normal ratio of CD4: CD8 T cells circulating within is approximately 1.5-2.5, and a ratio <1 is considered abnormal. Infiltrates within the interstitium should reflect that seen within the peripheral blood, however this could not be confirmed, as only one patient had peripheral blood flow cytometry performed (one of the CD8+ T cell dominant cases with a low CD4:CD8 ratio).

Mesangial immune complexes for IgG, kappa, and lambda were concurrently present in 3 of 6 CVID cases with tubulointerstitial nephritis (50%). Global glomerulosclerosis ranged from 0 to 87%. Interstitial fibrosis was moderate to severe in 3 of 6 cases (50%). In reported cases of tubulointerstitial nephritis due to CVID in the literature, all showed T-cell rich infiltrates, and 4 of 7 (57%) were CD8+ T cell dominant. There was mild arteriosclerosis in one case and there were no cases that showed moderate or severe vascular changes. At follow-up, 4 of 6 patients had persistent CKD stage 3 or above (83%). One patient who had a CD8+ T cell rich tubulointerstitial nephritis underwent bone marrow biopsy and was found to have a CD8+ NK-like T cell lymphoma. The other case of CD8+ T cell rich tubulointerstitial nephritis was favored to be a benign, reactive infiltrate.

Other renal biopsy findings in CVID patients:
Other renal biopsy diagnoses included acute tubular injury (n=1), AL amyloidosis (n=1), diabetic glomerulosclerosis (n=1), thin glomerular basement membranes (n=1), pauci-immune sclerosing glomerulonephritis (n=1), and arterionephrosclerosis (n=1). Three of these cases shown mesangial immune complexes of IgM and/or C3. Congo red staining was positive within the case of AL amyloidosis with apple green birefringence on polarization and was negative for all of the remaining cases. A summary of the clinical and histopathologic features of all CVID cases in our cohort is provided in supplemental table 2.

Renal biopsies of primary immunodeficiency, non-CVID patients:

To compare CVID renal biopsy findings to those of other primary immunodeficiencies, we performed a database search of cases of Bruton's agammaglobulinemia (n=2), Wiskott-Aldrich syndrome (n=1), severe combined immunodeficiency (n=2), DiGeorge syndrome (n=2), IgA deficiency (n=4), chronic granulomatous disease (n=1), hyper-IgE syndrome (n=1), and primary immunodeficiency not otherwise specified (n=5). The mean age of the patients was 29.7 years (range = <1 month to 86 years). Although a low number of overall cases (n=18), 9 patients with non-CVID primary immunodeficiency showed a proliferative glomerulonephritis (mesangial and/or endocapillary proliferative, with or without the presence of crescents) and two showed a membranous glomerulopathy. A single patient showed an acute tubulointerstitial nephritis. Therefore, similar renal biopsy manifestations may be seen in patients with other primary immunodeficiencies other than CVID. This data is provided in table 4.

DISCUSSION

The most common findings on renal biopsy in patients with CVID were membranous glomerulopathy and acute or chronic tubulointerstitial nephritis. MG in CVID patients often had mesangial immune deposits and were PLA2R, THSD7A, EXT1, and NELL1 negative with IgG1 restriction 7. Identification of MG in CVID patients is important as nephrotic range proteinuria results in increased renal losses of immunoglobulin, worsening their immunocompromised state and susceptibility to infections. In these patients, it is difficult to achieve IgG levels over 500 mg/dL despite high doses of IgG replacement 8. Persistently low immunoglobulin levels increases risk of recurrent infections and their complications. A total of 26 CVID biopsies were reported, including 24 manuscripts and 2 abstracts. Of these cases, 8 patients had an immune complex glomerulonephritis 9-16, including 6 patients with MG, and 2 with a membranoproliferative glomerulonephritis.

Eight patients had an acute interstitial nephritis 17-22, one of which was granulomatous, and one of which occurred concurrently with MG. Eight cases showed AA amyloidosis 23-30. Other reported cases include minimal change disease (n=1) 31, anti-GBM nephritis (n=1) 32, and acute tubular necrosis (n=1, see table 3). While our findings of an increased incidence of MG and acute interstitial nephritis parallel that in the literature, we did not have any cases in our series of AA amyloidosis. This may represent improved control of chronic infections in this patient cohort.
CVID patients with acute or chronic TIN had CD3⁺ T cell-predominant inflammatory infiltrates and increased tubulointerstitial fibrosis. Cases with chronic tubulointerstitial nephritis had a higher creatinine level and worsened kidney function than in patients with an immune complex glomerulonephritis. In a study of bone marrow biopsies from CVID patients, diffuse and nodular CD3⁺ T cell infiltrates are common within the marrow, which correlate with an increase in CD4, CD45RO, and soluble IL-2R expression on T cells. This correlates with increased memory T cells, as well as a block in B cell development from the pre-B-1 to the pre-B-II phase.

Autoimmunity is common in patients with CVID due to several possible mechanisms. There are B cell receptor editing defects, which lead to a loss of checkpoint control. These defects can lead to persistence of autoreactive B cell clones that escape apoptosis. In addition to B cell defects, there is defective T cell function, with impaired CD4⁺ T cell activation and a depletion of regulatory T cells. Chronic and recurrent infections could also induce autoimmune responses by bystander lymphocyte activation, superantigen activation, and via epitope spreading. As CVID is a heterogeneous disease from a loss of checkpoint inhibition, its histopathology mimics nephrotoxicities due to checkpoint inhibitors. Interestingly, in a 10 year single center case series of renal pathology due to checkpoint inhibitor therapies, the findings included acute tubulointerstitial nephritis, membranous glomerulopathy, C3 glomerulopathy, and AA amyloidosis, the same findings seen in CVID patients.

CONCLUSION

Common variable immunodeficiency is a primary immunodeficiency disorder characterized by hypogammaglobulinemia, recurrent infections, and systemic autoimmune/inflammatory manifestations. A majority of CVID patients do not display renal manifestations, but those who do show a disproportionate increase in MG and T-cell rich acute tubulointerstitial nephritis. These were the leading causes of nephropathology in CVID patients who underwent biopsy in our cohort and within the literature. CVID should be considered as a potential etiology of a PLA2R-, THSD7A-, EXT1-, and NELL1-negative MG or acute interstitial nephritis, especially when in a young patient without a known etiology who has a history of repeated infections.
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AUTHOR CONTRIBUTIONS

Tiffany Caza: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing - original draft; Writing - review and editing

Samar Hassen: Data curation; Investigation; Writing - review and editing

Christopher Larsen: Conceptualization; Formal analysis; Funding acquisition; Investigation; Project administration; Supervision; Validation; Visualization; Writing - review and editing

DISCLOSURES

The authors have nothing to disclose.
**TABLE AND FIGURE LEGENDS**

**Table 1.** Membranous glomerulopathy in CVID patients. Clinical and renal biopsy characteristics from 8 CVID patients with capillary loop immune deposits are shown. The frequency of immunofluorescence positivity is identified.

**Table 2.** Acute tubulointerstitial nephritis in CVID patients. Clinical and renal biopsy characteristics from 6 CVID patients with acute tubulointerstitial nephritis are shown. Immunohistochemical staining to characterize lymphoid infiltrates included CD3, CD20, CD4, and CD8, and all cases displayed T-cell dominance with >90% CD3+ T cells.

**Table 3.** Previously reported cases of CVID-associated kidney disease in the literature. Abbreviations: AIN - acute interstitial nephritis; FPE – foot process effacement; GIN – granulomatous interstitial nephritis; IVIG – intravenous immunoglobulins; MPGN – membranoproliferative glomerulonephritis; NRP – nephrotic range proteinuria.

**Table 4.** Histopathologic features of non-CVID primary immunodeficiencies. The diagnoses, as well as glomerular, tubulointerstitial, and vascular scarring as well as immunofluorescence staining are shown. Abbreviations: GGS – global glomerulosclerosis; IF/TA – interstitial fibrosis / tubular atrophy; AS – arteriosclerosis; AH – arteriolar hyalinosis; ATI – acute tubular injury; Pt – patient.

**Figure 1.** Membranous glomerulopathy in CVID patients is IgG1 subclass restricted. A PAS-stained section shows a glomerulus with mild mesangial expansion and prominent capillary loops (A). A JMS stain shows thickened glomerular capillary loops with formation of holes (B). IgG subclasses shows IgG1 granular capillary loop deposits (C), which were negative for IgG2 (D), IgG3 (E), and IgG4 (F) immune deposits.

**Figure 2.** Proliferative changes within glomeruli in CVID patients with MG. A) PAS stain showing a membranoproliferative pattern of glomerular injury; B) PAS stain showing mesangial and endocapillary hypercellularity, C) Cellular crescent formation on JMS stain, D) Focus of fibrinoid necrosis in a glomerulus with endocapillary hypercellularity, H & E stain, E) Segmental sclerosis, PAS stain, F) Subepithelial and mesangial electron dense deposits seen by electron microscopy.

**Figure 3.** CD8+ T cell rich tubulointerstitial nephritis in CVID. A PAS-stained section shows replacement of renal parenchyma with a diffuse lymphocytic infiltrate (A). Scattered CD68+ histiocytes are seen within the infiltrate (B). Immunohistochemistry shows that the infiltrate is comprised of predominantly CD3+ T cells (C) with rare CD20+ B cells (D). The infiltrate shows few CD4+ T cells (E) and is CD8+ T cell dominant (F), with a reduced CD4:CD8 ratio.
### Table 1. Immune complex glomerulonephritis in CVID patients

| Parameter                                      | Frequency of finding |
|-----------------------------------------------|----------------------|
| Male                                          | 6/13                 |
| Female                                        | 7/13                 |
| Proteinuria                                   | 13/13                |
| Capillary loop immune deposits                | 13/13                |
|     Subepithelial                              | 13/13                |
|     Subendothelial                             | 2/13                 |
| Membranous Glomerulopathy                     | 9/13                 |
|     With no mesangial deposits                 | 1/9                  |
|     With mesangial deposits                    | 8/9                  |
| Proliferative Glomerulonephritis with Monoclonal IgG3 kappa deposits | 1/13 |
| C3 Dominant Membranous-Like Glomerulopathy    | 1/13                 |
| IgG                                           | 12/13                |
| IgA                                           | 7/13                 |
| IgM                                           | 7/13                 |
| C3                                            | 12/13                |
| C1q                                           | 4/13                 |

### Table 2. Acute tubulointerstitial nephritis in CVID patients

| Parameter                                      | Frequency of finding |
|-----------------------------------------------|----------------------|
| Male                                          | 2/6                  |
| Female                                        | 4/6                  |
| Clinical presentation                         | 4/6                  |
|     AKI                                        | 2/6                  |
| Interstitial inflammatory infiltrates         | 1/6                  |
|     Patchy                                     | 5/6                  |
| CD3+ >> CD20+                                 | 6/6                  |
| CD4+ > CD8+                                   | 4/6                  |
| CD8+ > CD4+                                   | 2/6                  |
| Tubulitis                                     | 6/6                  |
| Interstitial fibrosis                         | 2/6                  |
|     Mild                                       | 4/6                  |
| Arteriolosclerosis                            | 3/6                  |
|     None /Mild                                 | 2/6                  |
|     Moderate/ Severe                           | 3/6                  |
|     Unable to assess                           | 1/6                  |
| Glomerular immune complexes                   | 3/6 have IgG, kappa, lambda in mesangium |
Table 3. Previously reported cases of CVID-associated kidney disease in the literature.

| No. | Age | Sex | Diagnosis            | Cr       | Prot. | Pathology                              | Treatment                        | Outcomes                          | Ref |
|-----|-----|-----|----------------------|----------|-------|----------------------------------------|----------------------------------|-----------------------------------|-----|
| 1   | 13  | M   | Membranous           | 0.39     | 7.7 g | IgG, IgM, C3, C4, C1q deposits         | Methylprednisolone, cyclosporine, IVIG | Reduced proteinuria               | 9   |
| 2   | 15  | M   | Membranous and AIN   | NA       | NA    | IgG capillary loop deposits            | Antimicrobial agents             | Died at age 15; pneumonia         | 10  |
| 3   | 17  | F   | MPGN                 | 1.1      | 3 g   | IgM, C3, C1q deposits                  | Methylprednisolone, IVIG, rituximab | No proteinuria at 4 months        | 11  |
| 4   | 33  | F   | Membranous           | 222 umol/L | 2.7 g | IgG, IgM, C3 deposits                  | Methylprednisolone               | Died at age 38; pneumonia         | 16  |
| 5   | 36  | F   | Membranous           | 0.6      | 8 g   | IgG, C3 deposits                       | Corticosteroids, rituximab       | Reduced proteinuria               | 12  |
| 6   | 55  | M   | Membranous           | 0.92     | 0.9   | IgG capillary loop deposits            | IVIG                             | Reduced proteinuria               | 13  |
| 7   | 59  | M   | Membranous           | NA       | 25 g  | IgG capillary loop deposits            | Methylprednisolone               | Died at age 61                    | 14  |
| 8   | 22  | M   | MPGN                 | NA       | 0.9 g | IgA, IgM, IgG, C3, C1q deposits        | Corticosteroids                  | Improved renal function           | 15  |
| 9   | 8   | F   | AIN                  | 10.1     | NA    | Mononuclear infiltrate, 50% IF         | Peritoneal dialysis              | Listed for renal transplantation | 17  |
| 10  | 21  | F   | AIN                  | 164 umol/L | NA    | CD8+ T cell infiltrate                 | IVIG                             | Stable renal function             | 18  |
| 11  | 24  | F   | AIN                  | NA       | NA    | CD8+ T cell infiltrate; severe IF      | Prednisone, MMF, cyclosporine    | Dialysis, listed for transplant   | 19  |
| 12  | 28  | F   | AIN                  | 2.7      | 0.4 g | CD3+ T cell infiltrate, CD4>8          | Corticosteroids                  | Recovery, then recurrence         | 20  |
| 13  | 31  | F   | AIN                  | NA       | NA    | CD8+ T cell infiltrate                 | Corticosteroids                  | Improved renal function           | 21  |
| 14  | 44  | M   | AIN                  | WNL      | NA    | CD8+ T cell infiltrate                 | Corticosteroids, azathioprine    | Improved renal function           | 22  |
| ID | Age | Sex | Diagnosis | Serum Cr | Proteinuria | Treatment | Outcome |
|----|-----|-----|-----------|---------|-------------|-----------|---------|
| 15 | 47  | M   | GIN       | 2.1     | NA          | Non-necrotizing granulomas | Corticosteroids | Improved renal function |
| 16 | 24  | F   | AA amyloid | 1.1     | 4.5         | AA amyloid deposition | IVIG | NA |
| 17 | 24  | F   | AA amyloid | NA      | NRP         | AA amyloid deposition (thyroid) | IVIG | NA |
| 18 | 28  | M   | AA amyloid | NA      | 9           | AA amyloid deposition | Ciprofloxacin, metronidazole | No improvement |
| 19 | 29  | F   | AA amyloid | NA      | 9           | AA amyloid deposition | Antibiotics, IVIG, Losartan, Cilazapril | Persistent NRP |
| 20 | 29  | M   | AA amyloid | 1.8     | 11.8        | AA amyloid deposition | Losartan, Ramipril, IVIG | Reduced proteinuria |
| 21 | 40  | M   | AA amyloid | NA      | 3.4         | AA amyloid deposition | Angiotensin receptor blocker | No |
| 22 | 48  | M   | AA amyloid | NA      | “massive”   | AA amyloid deposition | Antibiotics, IVIG | No infections in 2 years |
| 23 | 49  | F   | AA amyloid | 233 umol/L | 5.5       | AA amyloid deposition | IVIG | Stable renal function |
| 24 | 32  | M   | ATN (suspected) | 1.33   | NA          | Biopsy not performed | Cessation of IVIG | Improved renal function |
| 25 | 15  | F   | Anti-GBM nephritis | 486.2 umol/L | 29.4       | Necrotizing crescents, linear IgG staining | Corticosteroids, rituximab, cyclophosphamide | Died, age 15 CMV encephalomyelitis |
| 26 | 12  | M   | Minimal change | 0.5     | 8.2         | Mesangial hypercellularity, Diffuse FPE | Corticosteroids | No recurrence at 2 years |
Table 4. Histopathologic features of non-CVID primary immunodeficiencies.

| Pt | Immunodeficiency                          | Diagnosis                                      | %  | IF/TA  | AS     | AH     | Immunofluorescence                                                                 |
|----|------------------------------------------|-----------------------------------------------|----|--------|--------|--------|-----------------------------------------------------------------------------------|
| 1  | X-linked agammaglobulinemia              | Proliferative immune complex GN               | 36 | 20-30  | Mild   | None   | Trace IgA, 1+ IgG, 2+ C3, mesangial + capillary loop                              |
| 2  | X-linked agammaglobulinemia              | Proliferative immune complex GN               | 12 | None   | None   | None   | Trace IgA, 3+ IgG, trace C3, 1-2+ C1q, mesangial + capillary loop                |
| 3  | Wiskott-Aldrich                          | Proliferative GN + Membranous glomerulopathy  | 50 | 20-30  | None   | Mild   | 3+ IgA, 3+ IgG, trace IgM, 2-3+ C3, trace C1q, mesangial + capillary loop        |
| 4  | Severe combined immunodeficiency         | ATI                                           | 71 | >50    | None   | Moderate| None                                                                             |
| 5  | Severe combined immunodeficiency         | Congenital nephrotic syndrome, Finnish type   | 4  | 10-20  | None   | None   | None                                                                             |
| 6  | DiGeorge syndrome                        | Diffuse proliferative immune complex GN       | 11 | 30     | None   | None   | 3+ IgM, 1+ C3, 1-2+ C1q, mesangial + capillary loop                             |
| 7  | DiGeorge syndrome                        | Crescentic GN                                 | 17 | <10    | None   | None   | Pauci-immune w/ pos ANCA serology                                                |
| 8  | Chronic granulomatous disease            | Crescentic GN                                 | 43 | 20     | Severe | Moderate| Pauci-immune w/ pos ANCA serology                                                |
| 9  | Job’s syndrome / Hyper-IgE               | Advanced sclerosing glomerulopathy            | 74 | 80     | Severe | Severe | IgA 2+, IgG 3+, IgM 3+, kappa 2+, lambda 2+, mesangial and capillary loop        |
| 10 | Primary immunodeficiency, not otherwise specified | Membranous glomerulopathy                      | 0  | None   | None   | None   | IgG 2+, kappa 2+, lambda 2+ capillary loop deposits                              |
|   | Diagnosis                                                                 | Characteristics                                      | Severity 1 | Severity 2 | Severity 3 |   |
|---|---------------------------------------------------------------------------|------------------------------------------------------|------------|------------|------------|---|
|11 | Primary immunodeficiency, not otherwise specified                        | Focal segmental glomerulosclerosis                    | 0          | None       | None       | C3 2+ mesangial |
|12 | Primary immunodeficiency, not otherwise specified                        | Acute tubular injury                                  | 0          | 10         | None       | Negative within glomeruli |
|13 | Primary immunodeficiency, not otherwise specified                        | Moderate global glomerulosclerosis, IF/TA, and arteriosclerosis | 29         | 40         | Moderate   | None       |
|14 | Primary immunodeficiency, not otherwise specified                        | Mesangial immune complex deposition, increased GGS   | 39         | 10         | Moderate   | Mild       | IgM 3+, C3 1+, kappa 2+, lambda 3+ mesangial |
|15 | IgA deficiency                                                            | Acute interstitial nephritis, mesangial immune complex deposition | 0          | 5-10       | None       | None       | IgG 2+, IgM 2+, C3 1-2+, kappa 2+, lambda 2+ |
|16 | IgA deficiency                                                            | Mild global glomerulosclerosis, IF/TA, and arteriosclerosis | 5          | 20-30      | Mild-moderate | Mild       | None       |
|17 | IgA deficiency                                                            | Minimal change disease                                | 0          | None       | None       | None       | None       |
|18 | IgA deficiency                                                            | Mesangiopathic glomerulopathy with IgG deposits      | 44         | 20         | Severe     | Moderate   | IgG 2+, kappa 1+, lambda 1+ mesangial |
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Figure 1. Membranous glomerulopathy in CVID patients is IgG1 subclass restricted.
Figure 2. Proliferative changes within glomeruli in CVID patients with MG.
Figure 3. CD8$^+$ T cell rich tubulointerstitial nephritis in CVID.
Supplemental TOC

Supplemental Figure 1. Membranous glomerulopathy in CVID patients is PLA2R (A), THSD7A (B), EXT (C), and NELL1 (D) negative for granular capillary loop staining.

Supplemental Table 1. Co-morbid conditions in CVID patients with kidney disease.

Supplemental Table 2. Histopathology and follow-up data from patients with common variable immunodeficiency
Supplemental Figure 1. Membranous glomerulopathy in CVID patients is PLA2R (A), THSD7A (B), EXT (C), and NELL1 (D) negative for granular capillary loop staining.
**Supplemental Table 1.** Co-morbid conditions in CVID patients with kidney disease. Clinical characteristics and co-morbid conditions of CVID patients, including developmental, hematologic, cardiovascular, pulmonary, gastrointestinal, endocrine/metabolic, oncologic, and rheumatologic conditions, are shown. Additional values in parentheses ( ) indicate that in addition to this case series, these manifestations have been reported within the literature for CVID patients with renal disease.

Abbreviations: AIHA=autoimmune hemolytic anemia; ITP=idiopathic thrombocytopenic purpura; T-LGL=T-large granular lymphocytosis; CAD = coronary artery disease; CVA = cerebrovascular accident; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease; OSA = obstructive sleep apnea; GERD = gastroesophageal reflux disease; IBD = inflammatory bowel disease; PUD = peptic ulcer disease; SLE = systemic lupus erythematosus.

| Category         | Disease manifestation | Membranous nephropathy | Tubulointerstitial nephritis | Other |
|------------------|-----------------------|------------------------|-----------------------------|-------|
| **Developmental**| Short stature         | 2                      | 0                           | 0 (+1) |
|                  | Developmental delay   | 2 (+1)                 | 0                           | 0     |
|                  | Failure to thrive     | 2                      | 0 (+1)                      | 0 (+1) |
| **Hematologic**  | Anemia                | 2                      | 0                           | 1     |
|                  | Thrombocytopenia      | 2 (+1)                 | 0                           | 0     |
|                  | Eosinophilia          | 1                      | 0                           | 0     |
|                  | AIHA                  | 0                      | 1                           | 0     |
|                  | ITP                   | 0                      | 1 (+1)                      | 0 (+1) |
|                  | Lymphadenopathy       | 2 (+1)                 | 1 (+1)                      | 0     |
|                  | T-LGL lymphocytosis   | 1                      | 1                           | 0     |
|                  | Non-Hodgkin lymphoma  | 2                      | 0                           | 0     |
|                  | Hemachromatosis       | 0                      | 1                           | 0     |
| **Cardiovascular**| Hypertension          | 7                      | 0                           | 2     |
|                  | Hyperlipidemia        | 1                      | 0                           | 2     |
|                  | Atrial fibrillation   | 1                      | 0                           | 0     |
| Category                  | Condition                          | Count 1 | Count 2 | Count 3 |
|--------------------------|------------------------------------|---------|---------|---------|
| CAD                      |                                    | 1       | 0       | 0       |
| CVA or TIA               |                                    | 2       | 0       | 1       |
| Bicuspid aortic valve    |                                    | 1       | 0       | 0       |
| VSD                      |                                    | 1       | 0       | 0       |
| Pulmonary                | COPD                               | 3       | 1       | 1       |
|                          | OSA                                | 2       | 0       | 1       |
|                          | Granulomatous inflammation         | 1       | 1       | 0       |
|                          | Asthma                             | 5       | 0       | 0       |
| Gastrointestinal         | GERD                               | 1       | 0       | 0 (+1)  |
|                          | IBD                                | 2       | 0       | 0       |
|                          | Liver disease                      | 2       | 0       | 0       |
|                          | PUD                                | 0       | 0       | 1       |
|                          | Autoimmune enteritis / Celiac      | 0       | 1 (+1)  | 0       |
|                          | Eosinophilic esophagitis           | 2       | 0       | 0       |
|                          | Ulcerative colitis                 | 1       | 0       | 0       |
| Endocrine & metabolic    | Obesity                            | 4       | 0       | 0       |
|                          | Hypothyroidism                     | 4       | 0 (+1)  | 1 (+1)  |
|                          | Diabetes                           | 1       | 0       | 1       |
|                          | Hypogonadism                       | 1       | 0       | 0       |
|                          | Gynecomastia                       | 0       | 0       | 1       |
| Oncologic                | Cancer                             | 2       | 2       | 1       |
| Rheumatologic            | Arthritis                          | 0       | 1       | 1       |
|                          | SLE                                | 0       | 1 (+1)  | 1       |
|                          | Srogren’s                          | 0       | 1       | 0       |
|                          | Spondylitis                        | 0       | 1       | 0       |
|                          | Meniere’s disease                  | 0       | 0       | 1       |
| Pt | Diagnosis                                                                 | Age | Sex | Cr  | Prot | Immuno-fluorescence                        | Inflammation                  | Patient medications                  | Treatment for Kidney Disease         | Outcomes                             |
|----|---------------------------------------------------------------------------|-----|-----|-----|------|-------------------------------------------|------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
| 1  | Acute interstitial nephritis, immune complex glomerulopathy              | 25  | F   | 1.5 | 0.2  | IgG 2+, C3 2+, kappa 2+, lambda 2+, subepithelial + mesangial | Mixed T/B, CD4: CD8 = 70:30 | Azithromycin, Augmentin, IVIG      | Splenectomy                          | Cr reduced to 1.2 mg/dL              |
| 2  | Acute interstitial nephritis, immune complex crescentic GN                | 44  | F   | 4.4 | None | IgG 1+, C3 3+, mesangial                  | >95% T cell CD4: CD8 = 40:60 | Antibiotics for pneumonia (not specified) | Prednisone                           | Cr reduced to 0.9 mg/dL              |
| 3  | Chronic active tubulointerstitial nephritis                              | 35  | M   | 3.4 | 2+ on UA | None                                     | >95% T, CD4:CD8 40:60       | Hydralazine, Bystolic, Norvasc, IVIG | Methylprednisolone, followed by prednisone taper | CKD V, Cr = 6.9 mg/dL, BM bx w/ lymphoma |
| 4  | Chronic active tubulointerstitial nephritis                              | 24  | F   | 2.3 | 0.5  | IgG trace, kappa trace, lambda trace      | 100% T, CD4:CD8 70:30        | Esomeprazole, Mycophenolate mofetil, Prednisone, Ondansetron, IVIG | Prednisone, mycophenolate mofetil | CKD3, Cr = 1.7 mg/dL, GFR = 34 mL/min |
| 5  | Ischemic glomerulopathy, Moderate interstitial inflammation             | 39  | F   | 1.3 | 1.2  | None                                      | >90% T, CD4:CD8 80:20        | Infliximab, IVIG                     | Infliximab                           | CKD3, Cr = 2.5 mg/dL, UPC = 1 g/g.    |
| 6  | Chronic active tubulointerstitial nephritis, mild mesangial immune complex deposition | 44  | M   | 2.5 | None | IgG 2+, C3 1+, kappa 2+, lambda 2+, mesangial and | Severe, >95% T cells, CD4:CD8 = 20:80 | Prednisone, Dexilant, Tramadol, IVIG | Prednisone                           | CKD3B, Cr = 2.7 mg/dL, GFR = 26 mL/min, developed Burkitt-like |
| No. | Diagnosis                              | Age | Gender | BMI  | Proteinuria | Pathology                                                                 | Treatment                                                                 | B cell lymphoma                                                                 | Labs                                                                 |
|-----|----------------------------------------|-----|--------|------|-------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------|
| 7   | Chronic active tubulointerstitial nephritis | 24  | F      | 2.6  | 0.495       | None                                                                      | Severe, 100% T cells, CD4: CD8 90:10                                      | Prednisone, Mycophenolate mofetil, IVIG                                    | Prednisone, ID workup ruled out infectious etiology                      | Cr 1.7 mg/dL, GFR 34 mL/min                                               |
| 8   | Membranous glomerulopathy               | 42  | F      | 1.8  | 4.6         | IgA trace, IgG 2+, kappa 2+, lambda 2+                                    | None                                                                      | Lopressor, Norvasc, Cyclobenzaprine, Trazadone, Paxil, Flonase, Hydrochlorothiazide, Xanax, IVIG | IVIG therapy, no immunosuppression.                                     | CKD3, Cr 2.1 mg/dL, GFR = 33 mL/min                                     |
| 9   | Membranous, glomerulomegaly w/ segmental sclerosis | 20  | M      | 1.5  | 0.2         | IgG 2+, kappa 2+, lambda 2+, subepithelial + intramembranous              | None                                                                      | Azithromycin, Levothyroxine, IVIG                                         | No therapy provided.                                                      | Proteinuria remains < 1 g/24 h.                                         |
| 10  | Membranous, glomerulomegaly w/ segmental sclerosis | 38  | F      | 1.9  | 3+ on UA   | IgG2+ C3 trace, kappa 2+, lambda 2+, subepithelial                      | Moderate, mixed                                                          | Amlodipine, Lisinopril, Bacrim, Rituximab, Zevalin, IVIG                   | Rituximab, Lisinopril                                                   | Persistent proteinuria, history of lymphoma in remission.               |
| 11  | Membranous glomerulopathy               | 10  | M      | 0.5  | 0.6         | IgA 1+, IgG 3+, IgM 1+, C3 1+, subepithelial, intramembranous, and mesangial deposits | None                                                                      | Cyclophosphamide, Escitalopram, Montelukast, Mycophenolate mofetil, Omeprazole | IV cyclophosphamide, mycophenolate mofetil for maintenance therapy       | Stable renal function.                                                  |
| Case | Disease Details | Age | Gender | Duration | Clinical Findings | Treatments | Outcome |
|------|-----------------|-----|--------|----------|-------------------|------------|---------|
| 12   | Membranous glomerulopathy | 54  | M      | 1.0      | IgA 2+, IgG 3+, C3 3+, kappa 3+, lambda 3+, subepithelial, subendothelial, mesangial | Lisinopril, Furosemide, Spironolactone, Amlodipine, Levothyroxine, Albuterol, Lexapro, Singulair, Wellbutrin XL, IVIG | Stable renal function, Cr 1.0 mg/dL, proteinuria reduced to 2 g/g, GFR = 81 mL/min. |
| 13   | Membranous glomerulopathy, thrombotic microangiopathy | 68  | M      | 8.7      | IgG 2-3+, IgA 2+, IgM 1+, C3 3+, C1q 2+, kappa 3+, lambda 3+, subepithelial, subendothelial, mesangial | Metoprolol, Unasyn, Prednisone | Patient died soon after biopsy. |
| 14   | Membranous glomerulopathy, focal crescents | 15  | M      | 0.3      | IgG 2+, C3 trace, kappa 2+, lambda 2+, subepithelial and intramembranous | Sirolimus, Budesonide, Mycophenolate mofetil, Rituximab, Amitriptyline, Amlodipine, Gabapentin, Megestrol, Mesalamine, IVIG | Sirolimus, Budesonide, Mycophenolate, Rituximab, Cr 0.4 mg/dL, proteinuria remained (>1000 mg/dL), low albumin (2.2 g/dL) |
| 15   | Membranous glomerulopathy | 70  | F      | 0.8      | IgG trace, IgM trace, C3 trace, kappa trace, lambda trace, subepithelial | Albuterol, Amlodipine, Aspirin, Azelastine, Biotin, Calcium, CoQ-10, Dulera, Duloxetine, Fish oil, Flaxseed Oil, IVIG | None, Cr 0.7 mg/dL, 24 h protein 420 mg, GFR 90 mL/min stable renal function |
|   | Diagnosis                                      | Age | Sex | BMI | Findings | Clinical Features                                                                 | Treatments                                                                                           | Comments                                                                                           |
|---|------------------------------------------------|-----|-----|-----|----------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
|16 | Sclerosing glomerulonephritis                   | 40  | F   | 2.8 | None     | Segmental fibrinogen staining within a single glomerulus                          | Mild, within fibrotic interstitium                                                                   | Unknown, no data available. Not treated, as no active crescents. Serologies consistent with ANCA-associated disease |
|17 | Nodular diabetic glomerulosclerosis            | 69  | F   | 2.6 | 10       | IgM 1+, mesangial                                                                  | Mild, patchy                                                                                         | Coreg, Verapamil, Isosorbide, Bumex, Amaryl, Glipepiride, Linagliptin, Lantus, Aranesp, IVIG        | None. ESKD (biopsy had 90% interstitial fibrosis)                                                      |
|18 | Proliferative glomerulonephritis with monoclonal IgG deposits | 67  | F   | 0.8 | 2        | IgG 3+, IgM 2+, C3 3+, kappa 3+, IgG3 restricted                                   | Mild                                                                                                 | Carvedilol, Aspirin, Cephalexin, Cetirizine, Cyclobenzaprine, Estropipate, Famciclovir, Ferrous sulfate, Fluticasone, Furosemide, Glycopyrrolate, Lansoprazole, Losartan, Mirabegran, Oxybutynin, Phenobarbital, Ranitidine, Sucralfate, Hydralazine. Hematologic workup with no clonal process identified, patient was not treated | Increased proteinuria (2 g→ 6.4 g), stable serum creatinine 0.9 mg/dL, developed hematuria |
|19 | AL amyloidosis, Lambda light chain cast nephropathy, Lambda light chain | 56  | F   | 1.4 | 11.8     | 3+ lambda                                                                         | Dense, patchy infiltrate at corticomedullary junction                                               | NSAIDS, IVIG                                                                                       | Chemotherapy and bone marrow transplant. Cr 1.5 mg/dL, UPCR 0.1 g/g, in remission. |
| Case | Diagnosis                                      | Age | Sex | Cr (mg/dL) | UPCR | GFR (mL/min) | Treatment                                | Outcome                      |
|------|-----------------------------------------------|-----|-----|------------|------|--------------|------------------------------------------|------------------------------|
| 20   | C3 glomerulopathy                             | 19  | F   | 1.9        | 1.4  | None         | Mesalamine, Azathioprine, Amlodipine,    | Lisinopril, ACTHar, Mycophenolate mofetil | Cr 1.9 mg/dL, UPCR reduced to 0.7 g/g, GFR = 30 mL/min |
|      |                                               |     |     |            |      |              | Budesonide, Dicyclomine, Furosemide,    |                              |                              |
|      |                                               |     |     |            |      |              | Lisinopril, Olopatadine, Pentasa,       |                              |                              |
|      |                                               |     |     |            |      |              | Vyvanese, IVIG                           |                              |                              |
|      |                                               |     |     |            |      |              |                                        |                              |                              |
| 21   | Acute tubular injury                          | 64  | F   | 5.5        | None | None         | Loratadine/Pseudoephedrine, Hydrochlorothiazide, Simvastatin, Lisinopril, Aspirin, Calcium w/ vitamin D, Beta-carotene, acetaminophen, NSAIDs, IVIG | Supportive care, patient developed anuria after laminectomy surgery, which resolved. | Came off dialysis. Cr = 3.0 mg/dL. |
| 22   | Thin glomerular basement membranes            | 39  | F   | 0.9        | 0.1  | None         | Unknown, no data available              | None                         | Stable renal function        |