Renal Biopsy: Clinical Correlations
November 15, 4:30–6:30 p.m.
Case 1 from Harsharan Singh, MD – University of North Carolina at Chapel Hill

A 65-year-old woman with a past medical history of recurrent episodes of urticaria, angioedema, irritable bowel syndrome, and hypothyroidism was referred with acute bloody diarrhea and new onset urticaria. A colonoscopy examination was normal 3 years ago.

Physical examination showed the patient was afebrile with a blood pressure of 149/100 mm Hg, numerous erythematous papular skin lesions on the forehead, cheeks, arms, left upper back, and posterior shoulder. Chest examination revealed mild crackles bilaterally. The rest of the physical examination was unremarkable.

Laboratory Data:

- Hemoglobin 7.0 g/dL, platelets 100,000/ml, ESR 65mm/h, CRP 4.5mg/L (upper limit of normal 1.0mg/L), creatinine 0.87 mg/dL.
- Urinalysis revealed dysmorphic hematuria, cellular casts including RBC and tubular epithelial casts. The urine protein-creatinine ratio was 0.207. Complement factor C3 was low at 40 mg/dL (lower limit of normal is 88 mg/dL) and complement factor C4 was undetectable. The rheumatoid factor was significantly elevated at 94 IU/ml. Serologies were negative for ANA, anti-dsDNA, antiphospholipid antibody, lupus anticoagulant and ANCA serologies were all negative. An anti-Ro (SSA) and an SSB antibody were positive.

Colonscopy showed a single ulcer without active bleeding. A skin biopsy from the papular lesions noted showed a leukocytoclastic vasculitis.

Due to the abnormal urine analysis and uncertain etiology of the systemic symptoms, a kidney biopsy was performed.

1. Illustrated are electron micrographic images of glomerular capillary loops.
   The changes show:
   A. Structured deposits and intralysosomal storage products
   B. Intracapillary foam cells and artifacts
   C. Typical amyloid deposits
   D. A glomerulonephritis, likely ANCA associated

2. The biopsy illustrated in question #1 also shows a vasculitis.
   Does this observation change your diagnosis?
   A. Yes
   B. No
DISCUSSION

The constellation of findings in the current case is unusual and not easily subclassified according to standard schemes. The unusual combination of cryoglobulinemic glomerulonephritis and small vessel vasculitis, a clinical syndrome highly suggestive of SLE, a predominant urticarial vasculitis, recurrent bouts of angioedema, presence of hypocomplementemia, negative serologies for ANA and dsDNA, and positive anti-Ro/SSA antibody suggests:

- Hypocomplementemic urticarial vasculitis syndrome (HUVS)
- Anti-Ro (SSA) antibody positive SLE.

Hypocomplementemic urticarial vasculitis syndrome (HUVS) – Definition:
An uncommon immune complex–mediated entity characterized by >6 month history of urticaria and persistent acquired hypocomplementemia. HUVS also can have: leukocytoclastic vasculitis (LCV), severe angioedema, laryngeal edema, pulmonary involvement, arthritis, arthralgia, glomerulonephritis, recurrent abdominal pain, and uveitis.

The diagnostic criteria for HUVS require the presence of both major criteria and at least 2 minor criteria (LCV on skin biopsy, arthralgias or arthritis, glomerulonephritis, ocular inflammation, abdominal pain, and positive C1q-precipitin test with decreased C1q levels). Although not listed in the table below, angioedema, obstructive pulmonary disease, and various neurological findings may also be present. Our patient fulfills both major criteria and more than 2 of the minor criteria listed in the “Diagnostic criteria of hypocomplementemic urticarial vasculitis syndrome” table in Curr Opin Rheumatol, 2000;12(1):24.

Urticarial vasculitis (UV) is considered a clinicopathologic entity consisting of 2 elements: clinical manifestations of urticaria and histopathological evidence of cutaneous leukocytoclastic vasculitis (LCV) of the small vessels. UV likely represents a continuum of disease, ranging from urticaria with minimal vasculitis to life- or organ-threatening systemic vasculitis with minimal urticaria. Hypocomplementemic urticarial vasculitis is associated with more severe disease and with systemic involvement. By comparison, patients with normal complement levels are more likely to have mild disease (sometimes referred to as normocomplementemic urticarial vasculitis). In contrast to patients with hypocomplementemic UV, patients with normocomplementemic UV do not show renal involvement. HUVS has been recognized as a specific autoimmune disorder involving 6 or more months of urticaria with hypocomplementemia in the presence of various systemic findings.
Hypocomplementemic urticarial vasculitis (HUV) is now part of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides as one of the immune complex mediated small vessel vasculitides. Consideration was given to recommending the term anti-C1q vasculitis but preference was given to the term HUV. There was agreement that the link between anti-C1q antibodies and HUV was strong enough to introduce the term into the nomenclature. [ARTHRITIS & RHEUMATISM Vol. 65, No. 1, January 2013, pp 1–11]

HUVS-associated conditions — Although most cases are idiopathic, there are a variety of systemic diseases and exposures associated with HUVS; however, their direct causal role has not been established. Both SLE and Cryoglobulinemic glomerulonephritis have been associated with HUVS.

The most difficult differential diagnosis is distinction of HUVS from SLE. There are overlapping features, and there is speculation that hypocomplementemic urticarial vasculitis syndrome (HUVS) is within the spectrum of SLE. Some overlapping features of HUVS and SLE include arthritis, glomerulonephritis, and the presence of hypocomplementemia. Autoantibodies against C1q can also be found in both HUVS (>90%) and SLE (63%). Some distinguishing features of HUVS which are not typically observed in patients with SLE include angioedema (up to 50%), chronic obstructive pulmonary disease (COPD, up to 50%), and uveitis (30%).

Renal manifestations of HUVS include moderate to heavy proteinuria, hematuria, dysmorphic red blood cells, RBC casts and mild renal failure. The renal disease of HUVS may not be distinguishable from that of other entities and can show many different histological patterns: proliferative glomerulonephritis, focal necrotizing vasculitis, crescentic glomerulonephritis, membranoproliferative glomerulonephritis.

Clinical follow-up
The patient was treated with rituximab: 1 g followed by 1g 2 weeks later. Tapering doses of prednisone were given and most recently decreased to 12.5 mg/day. Two months later, the rash was virtually gone. Urinalysis revealed some blood, no RBC casts, and no dysmorphic RBCs. Follow-up serologies: anti-C1q antibodies were positive.

References
Case 2 from Kerstin Amann, MD – University of Erlangen-Nürnberg

A 30-year-old mildly obese women with slightly reduced general condition presented with nephrotic range proteinuria of 8.7 g/l and microhematuria which were presented for quite some time and were even more pronounced (up to 15 g/day) during pregnancy (until 2 months before). She was pale and had edema and hypercholesterinemia. No macrohematuria.

She had no family history, no known diseases, no diabetes, mild hypertension (150/80 mmHg) of unknown duration. No infection, no malignancies.

No current medication.

Serum findings at presentation:
- Urea: 15 mg/dl
- Creatinine: 0.52 mg/dl
- Cholesterol: 364 mg/dl
- Total protein: 5.2 g/l
- C3: 101 mg/dl
- C4: 29.9 mg/dl
- ANA: <1:80
- ANCA, anti-GBM, ASL antibodies, cryoglobulins: negative.
- No free light chains.

Urine findings at presentation:
- Proteinuria: 3.7 g/g creatinine
- Hematuria: 25 erys/VF
- No leucocyturia.

A kidney biopsy was performed.

HE staining     Silver staining

IgA      IgG
Electron Microscopy:
1. What is the predominant morphological pattern of glomerular changes?
   A. Thickening of glomerular basement membranes with endocapillary proliferation (membranoproliferative pattern)
   B. Thickening of glomerular basement membranes with diffuse to nodular mesangial expansion
   C. Global and Focal glomerulosclerosis
   D. Intracapillary proliferation
   E. Extracapillary proliferation

2. What is the immunohistochemical pattern?
   A. Linear membranous IgG staining
   B. Intensive coarse mesangial IgA and C3c staining
   C. Diffuse coarse granular IgG and C3c deposition along glomerular capillaries as well as in the mesangium
   D. Coarse membranous C3c staining
   E. No specific staining

3. What can be seen on electron microscopy?
   A. Subepithelial osmiophilic deposits
   B. Mesangial osmiophilic deposits
   C. No foot process effacement of podocytes
   D. Microtubular structures in the mesangium
   E. Randomly arranged fibrillar deposits of small size (approximately 15-20 nm in diameter) in the thickened glomerular basement membranes and the mesangium

DISCUSSION

Definition: Fibrillary glomerulonephritis (FGN) is a rare primary glomerular disease first described by Rosenmann and Eliakim in 1977 (1). FGN is encountered in about 0.5 to 1% of native kidney biopsies (2-5) and is defined by the ultrastructural finding of randomly arranged, straight fibrils. Thus, it belongs to the somehow mysterious group of so-called renal diseases with organized deposits (6).

Light microscopy: The light microscopic features are heterogenous; most cases exhibit a membranoproliferative (MPGN-like) pattern with a lobular aspect of the glomerular tuft, mesangial expansion/hypercellularity with or without duplication or splitting of the glomerular basement membranes (GBMs). Less commonly reported morphologic patterns include mesangio- or endocapillary proliferative glomerulonephritis and crescentic glomerulonephritis or pure membranous glomerulonephritis with GBM spikes. Even a characteristic nodular glomerulosclerosis as in diabetic nephropathy is possible. By definition, the glomerular deposits in FGN are Congo red–negative, which distinguishes FGN from Congo-positive fibrils in amyloidosis which stain weekly positive for PAS and silver (7-9).

The tubulointerstitium in FGN shows variable changes such as acute tubular damage, tubular atrophy, interstitial fibrosis depending on the degree of glomerular alterations. The intrarenal vasculature in FGN does not show any specific alterations.

Immunohistochemistry (IH) / Immunofluorescence (IF): The deposits typically predominantly stain for polyclonal IgG (dominance of IgG4 subclass) and C3 complement, indicating immune complex deposition. The staining pattern could be either mesangial or segmentally membranous or a combination of both. In about 50% of cases, additional usually weaker staining of IgA, IgM and C1q can be detected resembling a weak or incomplete full-house pattern raising the suspicion of renal involvement in systemic lupus erythematoses (SLE). Rarely, other staining patterns, i.e. predominant IgA-staining, have been reported (7-9).

Electron microscopy: Deposition of fibrillar material in one or more glomerular compartment with irregularly organized fibrils measuring between 10 and 30 nm in thickness, i.e. somewhat larger than amyloid fibrils which are usually about 10 µm in diameter. However, there is some overlap in size distribution so that the size of the fibrils alone is not sufficient for a definite distinction from amyloid fibrils. The fibrils are either deposited in the mesangium or the GBMs with intramembranous, subepithelial, or even subendothelial location. Of course combinations of all locations can occur. No microtubular structure and no osmiophilic deposits are present. Very rarely fibrillary deposits can also been seen within the tubular basement membranes (7-9).
Etiology: The definite pathogenesis of FGN is not known. There are recent findings indicating that serum precursors such as amyloid P, cryoprecipitated mixed immunoglobulin-fibronectin complexes, can lead to the formation of fibrillary deposits (10).

Most previously reported cases were idiopathic and occurred in the absence of other systemic diseases (2–5). There are, however, in the meanwhile several case reports documenting the coincidence of FGN with a variety of systemic diseases, i.e. diabetes mellitus, hepatitis C, systemic lupus erythematoses. In contrast to immunotactoid glomerulonephritis, however, FGN has not been shown to be associated with lymphoproliferative disorders or monoclonality of deposits.

Clinical presentation: Patients with FGN typically present with proteinuria (usually in the nephrotic range), hematuria, renal insufficiency, and hypertension. Normally, patients do not present any extrarenal symptoms. Mean age at presentation is usually above 50 years with a slight female predominance; there are reports of younger patients (<40 years) in which the prognosis may be slightly better. Of note, however, even children can be affected (11).

Prognosis: poor, with close to 50-60% of patients progressing to ESRD within a few years after diagnosis, despite the administration of steroids and cytotoxic agents. Recently, also rituximab has been used (12).

Of note, early and late recurrence of the disease in the transplanted kidney has been described.

References
Case 3 from Mark Haas, MD, PhD – Cedars-Sinai Medical Center

A 70-year-old white female presented with a cerebrovascular accident and right-sided hemiparesis. Her medical history is remarkable for well-controlled hypertension, hemolytic anemia, and a bout of viral meningitis during the past year. At presentation she was found to have a serum creatinine of 1.2 mg/dL, up from 0.6 mg/dL 6 months earlier. Urinalysis showed 2+ protein, 2-5 RBCs, and >50 WBCs per high power field. Urine protein/creatinine ratio was 1.8. Peripheral blood showed anemia (hemoglobin 8.7 g/dL), thrombocytopenia (platelet count 97,000/L), WBC count of 7300/L. The patient was noted to have a small IgM-kappa spike in the past.

On physical exam the patient was afebrile with blood pressure 134/80. She was mildly tachycardic (heart rate 94). Neurologic exam was consistent with the right-sided hemiparesis. There was no edema.

Medications were Lovenox (enoxaparin), atenolol, and omeprazole.

The patient was started on Cipro for a presumed urinary tract infection and was scheduled for a renal biopsy to identify the cause of the proteinuria and rise in serum creatinine.

Renal biopsy findings:
1. Neoplastic cells in this biopsy are found:
   A. In the interstitium
   B. Within peritubular capillaries
   C. Within glomerular capillaries
   D. All of the above
   E. A and C only

2. The neoplastic cell population:
   A. Is of B lymphocyte lineage
   B. Is a mixture of T and B lymphocytes
   C. Has a low proliferative rate
   D. Consists of cells in the late phase of B cell differentiation
   E. Is typical of chronic lymphocytic leukemia (CLL)

3. The proteinuria in this case is best accounted for by:
   A. Immune complex deposits typical of membranous nephropathy
   B. Amyloid deposits within glomeruli
   C. Infiltration of neoplastic cells into the glomeruli
   D. A proliferative glomerulonephritis
   E. Monoclonal immunoglobulin deposition disease with glomerular involvement

4. The anemia and thrombocytopenia in the case are most likely to be related to:
   A. A thrombotic microangiopathy involving the kidney
   B. The hemolytic anemia noted in the clinical history
   C. A viral-related hemophagocytic syndrome
   D. Infiltration of the bone marrow by the same neoplastic cells present in the kidney
   E. None of the above
Renal Biopsy Diagnosis:
1. Large B Cell Lymphoma with an intravascular component (involvement of glomerular and peritubular capillaries) and interstitial involvement
2. Mild associated acute tubular injury
3. Mild arteriosclerosis

Comment: Co-expression of Bcl-2 and c-Myc has been reported to be associated with an inferior prognosis in cases of diffuse, large B cell lymphoma (DLBCL); as with this case the majority of such cases are associated with a high proliferative rate as evidenced by >70% Ki-67 staining of the neoplastic cells [1]. CD-5 positive DLBCL is most often seen in females over the age of 65, is associated with poorer overall survival than CD-5 negative DLBCL [2,3], although prognosis may be improved by treatment with rituximab [3]. Approximately 20% of cases of CD5-positive DLBCL have an intravascular component, although renal involvement in such cases is unusual [2,3].

DISCUSSION

The kidney is a frequent site of involvement by leukemias and lymphomas, at least in autopsy series. In such series, the frequency of renal involvement, detected microscopically, can vary from ~30% to as high as 90%, with the highest rates in acute and chronic lymphocytic leukemia (ALL, CLL) [4,5]. However, these neoplasms usually do not cause mass lesions in the kidneys or directly cause renal impairment, although it is well known that systemic lymphoproliferative disorders may indirectly cause renal failure and/or proteinuria by inducing paraprotein-associated lesions and paraneoplastic glomerulopathies. Renal pathologists may unexpectedly encounter lymphomatous or leukemic infiltrates in native renal biopsies, and although this is not common a high index of suspicion for such infiltrates is advisable as most renal pathologists have had very limited exposure to hematopathology since their residency training, and the consequences to the patient of failing to properly identify such infiltrates can be severe.

There are only a limited number of published case series of renal involvement by hematologic neoplasms diagnosed by renal biopsy. Kowalewska et al [6] identified 18 such cases among 3889 native renal biopsies (0.5%) examined at their center in Seattle between January, 2002 and June, 2007. Of these 18 cases, all showed interstitial infiltration of neoplastic mononuclear leukocytes or plasma cells (CLL in 7), and 10 showed a glomerular lesion related to the neoplasm (although none showed neoplastic cells within glomeruli): a membranoproliferative (MPGN)-type glomerulonephritis (GN) in 4 (all with immune complex deposits, 3 kappa-restricted), 1 case each of light chain deposition disease and AL-amyloid, and 4 with paraneoplastic-related glomerulopathies (2 minimal change, 1 membranous, and 1 pauci-immune crescentic GN; see ref. [7] for evidence supporting the latter association). In all but 1 of the 18 cases, the serum creatinine at the time of biopsy was elevated. Nine of the 18 patients did not have an established diagnosis of a hematologic neoplasm, although 3 of these 9 did have a monoclonal gammapathy of unknown significance.

Li et al [8] reported 20 Chinese patients with non-Hodgkin lymphoma and evidence of renal impairment (renal failure, proteinuria, or both) who underwent a renal biopsy. Of these patients, 9 had lymphomatous infiltrates within the biopsy: 1 with DLBCL involving both glomerular and tubulointerstitial compartments similar to our case, 1 intravascular large B cell lymphoma with malignant cells within glomeruli but not in the interstitium, and 7 with patchy interstitial infiltrates of neoplastic B cells (CLL or DLBCL). Not including the patients with intravascular lymphoma, 14 had glomerular lesions, the most common of which (7 cases), as in the series of Kowalewska et al [6], were MPGN-like lesions. All were associated with B cell neoplasms, although only 2 were light-chain restricted. Three patients had minimal change nephropathy, 2 had pauci-immune crescentic GN, 1 an immune complex-mediated crescentic GN, and 1 anti-GBM nephritis with IgG-lambda staining in glomerular capillary walls.

At our center, Christine VanBeek [9] studied 41 native renal biopsies directly infiltrated by a hematologic neoplasm. These 41 biopsies represent 0.3% of over 14,000 such biopsies examined over a 7-year period (2004 – 2010). The most common lesions seen were CLL (16), non-CLL low-grade B cell lymphomas (7), and DLBCL (6); our case is not included as it did not occur during the study period. Two intravascular large B cell lymphomas were present among the cases, however only 1 other case (a T/NK large granular cell lymphoma) showed direct glomerular involvement by the neoplastic cells.

Not including plasma cell lesions, there were 23 low-grade lymphomas and 10 intermediate or high grade lymphomas, and these differed considerably in their presentation. Most notably:

1. Cases of intermediate and high grade neoplasms most often presented with acute renal failure and typically involved the majority of the interstitial area present (in most cases at least 80%). By contrast, low grade neoplasms, including CLL, were typically associated with a slow rise in serum creatinine and focal interstitial involvement (usually <30%).
2. ~80% of patients with low grade neoplasms were known to have a hematologic malignancy at the time of renal biopsy. By contrast, only 3 of the 10 patients with intermediate and high grade neoplasms were known to have this at the time of biopsy.
3. Most (87%) of the cases with low grade neoplasms had significant co-existing pathology in the biopsy, either related or unrelated to the hematologic malignancy. By contrast, only 1 of the 10 patients with an intermediate or high grade neoplasm had significant co-existing pathology (membranous nephropathy).

4. Of the patients with CLL, 6 had an immune complex GN; all were light chain restricted (5 kappa, 1 lambda), and 5 contained IgG with negative IgA and negative or trace IgM. Five of these 6 glomerular lesions had an MPGN pattern.

Both cases of intravascular large B cell lymphoma (IVLCL) were in older (>60 years) females with no prior history of malignancy and no mass lesions radiographically, who each presented with renal insufficiency, proteinuria, microscopic hematuria, and lower extremity edema. In each biopsy, no more than 50% of glomeruli were involved, and in most of these glomeruli the involvement was segmental. In 1 of the 2 biopsies neoplastic cells were also noted in peritubular capillaries. These 2 cases represent less than 0.02% of the native renal biopsies received at our center, consistent with reports that renal involvement by IVLCL is quite uncommon (e.g., 2/96 cases of IVLCL reported by Murase et al; ref [10]). However, there are a small number of reported cases of renal-limited IVLCL [11]. These cases generally present with renal insufficiency and varying levels of proteinuria, ranging from very mild to nephrotic range. Interestingly, several of these patients have been successfully treated with chemotherapy (most often cyclophosphamide, doxorubicin, vincristine, and prednisolone; CHOP), which contrasts with the generally poor prognosis of IVLCL involving other organ systems [11].

References
Case 4 from Samih Nasr, MD – Mayo Clinic

A 66-year-old Mexican female presents for follow up on CKD and worsening proteinuria. She denied any recent changes of medications, NSAID use, or flank tenderness. Urine output has not changed without dysuria, gross hematuria, or increased frequency.

Past medical history: longstanding diabetes with retinopathy, hypertension, hyperlipidemia, lower urinary tract infection, CKD stage 3 (GFR 30-59).

Family history: Unremarkable; no family history of kidney disease.

Social history: Widowed; former smoker; no history of drug or alcohol use.

Current outpatient medications: Doxazosin (Cardura), enalapril (Vasotec), ergocalciferol, hydrochlorothiazide (Hydrodiuril), insulin glargine (Lantus), pravastatin (Pravachol).

Physical examination and review of systems: Unremarkable; no skin rash, edema, or hepatosplenomegaly.

Vital signs: BP: 118/30, pulse: 76; weight: 70.8 kg.

Imaging studies: Renal ultrasound: kidney size: 12.2 cm (L) x 10.3 cm (R); no hydronephrosis, stones or masses; normal echogenicity.

Laboratory work-up:
- Hemoglobin: 11.2 g/dl; hematocrit: 33.6%; hemoglobin A1C: 8.5%; WBC count: 9.8 k (normal range 4.4-10.4); platelet count: 216 k (normal range 130-400).
- BUN: 22 mg/dl; serum creatinine 1.3 mg/dl; normal serum calcium, total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, and CO2; total protein: 7.7 g/dl (normal range 6.4-8.3); serum albumin: 3.2 g/dl (normal range 3.4-5.0); serum C3 and C4: within normal range; serum protein electrophoresis with immunofixation: negative for paraprotein; urine protein to creatinine ratio: 9.8 g (up from 3.7 g/day 5 months prior).
- Urinalysis: protein: >600, trace blood, neg leukocyte esterase; Ph: 6.0, spec gravity: 1.015, glucose: 70 mg/dl, ketones: trace, 5 WBCs/hpf, 2 RBCs/hpf, rare bacteria, 11-20 hyaline casts, no RBC casts.

1. The least likely biopsy finding is:
   A. Diabetic Nephropathy alone
   B. Diabetic Nephropathy + nondiabetic renal disease
   C. Nondiabetic renal disease alone

2. What is the best cytochemical stain to do on this biopsy?
   A. von Kossa
   B. AFB
   C. Congo red
   D. Mucicarmine
   E. Sudan Black B

3. What is the best way to type amyloid in this patient?
   A. Immunohistochemistry
   B. LMD/MS
   C. Genetic testing
   D. Morphology alone
Diagnosis: Renal leukocyte chemotactic factor 2-associated amyloidosis

**DISCUSSION**

Amyloidosis is an uncommon group of diseases characterized by extracellular deposition of insoluble fibrils which result from abnormal folding of proteins. Amyloid deposits characteristically stain Congo-red-positive and show apple-green birefringence under polarized light. 30 precursor proteins of amyloid have been identified so far. The kidney is the most commonly affected organ in systemic amyloidosis. The 2 most common types of renal amyloidosis are immunoglobulin (Ig) light chain-derived amyloidosis (AL) and reactive (secondary) amyloidosis (AA). The kidney may also be affected by several rare hereditary forms of amyloidosis, such as those derived from fibrinogen A (AFib), transthyretin, gelsolin, lysozyme, apolipoprotein AI (AApo AI), apolipoprotein AII (AApo AII), and apolipoprotein AIV (AApo AIV). 1

In 2008, Benson et al.2 discovered a new form of amyloidosis derived from leukocyte chemotactic factor 2 (ALECT2) in a nephrectomy specimen from a patient who presented with nephrotic syndrome and renal insufficiency. ALECT2 now accounts for 2.7 to 10% of cases of renal amyloidosis in the U.S.1,3,4 In a recent series of 474 cases of biopsy-proven renal amyloidosis form the Mayo Clinic, 86% were Ig-derived, 7% AA, 3% ALECT2, and 1% AFib.1 In another series from Nephropath, of 414 cases, 83% were Ig-derived, 10% ALECT2, and 5% AA.3 ALECT2 has now been established as an important cause of ESRD in Hispanics. In the above mentioned study from Nephropath, ALECT2 accounted for >50% of renal amyloidosis cases from Southwestern U.S. which have a high concentration of Hispanics.3 Of the 40 patients with ALECT2 in this series, 88% were Hispanics.3 In another recent series of 72 patients with renal ALECT2 by Said et al. from the Mayo Clinic, 92% of patients were Hispanics.3 Notably, in the Mayo Clinic series, all 34 Hispanic patients who disclosed their origin were Mexican. As Mexican Americans constitute the largest group of U.S. Hispanics, it is still unknown if they are more likely to develop ALECT2 than U.S. Hispanics originating from other countries. Aside from Hispanics, Punjabs, First Nations people in British Columbia, Arabs, Israeli, and Native Americans are more prone to develop ALECT2 than Caucasians.3,5,6

ALECT2 mainly affects the kidney followed by the liver, but several other organs can be affected. Of the 120 ALECT2 cases diagnosed by laser microdissection/mass spectrometry (LMD/MS) at the Mayo Clinic between 2007-2012, 72 affected the kidney, 36 liver, 5 spleen, 3 prostate, and 1 each from gallbladder, pancreas, small bowel, and parathyroid gland.6 ALECT2 is now the second most common type of liver amyloidosis after AL, detected in 25% of 130 cases typed by LMD/MS at the Mayo Clinic,7 which was frequently incidentally discovered during the work up for chronic hepatitis or steatohepatitis.7 There have been no autopsy-based studies on patients with ALECT2 so far; thus, it is still unclear if ALECT2 is a systemic form of amyloidosis as in AL and AA, or, as in AFib, an amyloidosis type with dominant renal involvement and clinically insignificant extrarenal involvement.

The typical clinical presentation of renal ALECT2 is an elderly Hispanic patient with chronic renal insufficiency and bland urinary sediment. The median age at biopsy in the series by Said et al.5 was 66 years; only 2 patients (3%) were younger than 50 years of age. The indication for kidney biopsy in the series by Said et al.5 was unexplained chronic renal insufficiency with or without proteinuria. The mean serum creatinine at biopsy in the study by Larsen et al. (Larsen, 2014 #9) was 2.8 mg/dl.3 In the study by Said et al.5, 91% of patients had a serum creatinine >1.2 mg/dl at biopsy (median 2.8). Rarely, ALECT2 is an incidental pathologic finding found in the non-neoplastic parenchyma of nephrectomy specimens performed for resection of renal cell carcinoma in patients without renal insufficiency or proteinuria.6 ALECT2 is now accounted for in 2.7% to 10% of renal amyloidosis cases.8 In contrast to other forms of renal amyloidosis, proteinuria is an inconsistent finding in ALECT2. In the series by Said et al., 21% of patients had no proteinuria, 46% subnephrotic proteinuria, and 33% nephrotic range proteinuria. In the Larsen et al.3 study, 40% of patients had no proteinuria. Full nephrotic syndrome is rare (10% of patients).8 Microscopic hematuria is uncommon, encountered in 16% of patients in one study.8 Chronic hypertension is present in up to two-thirds of patients and diabetes mellitus in up to a third.3,5

There is currently no specific therapy for ALECT2. Unfortunately, a minority of reported patients with ALECT2 received chemotherapy with/stem cell transplant for erroneous presumed diagnosis of AL as 8-10% of patients had clinical evidence of plasma cell dyscrasia.3,5 Patient survival in ALECT2 is significantly better than that of AL and AA, likely due to the lack of cardiac involvement in ALECT2. In the series of 72 patients mentioned above, only 6% of patients died after a median follow up of 22 months.5 The renal survival on the other hand is guarded; 39% of patients in the above mentioned study progressed to ESRD.5 The average deterioration in renal function is 0.5 ml/min/1.73 m² per month. Independent predictors of renal survival in renal ALECT2 are serum creatinine at diagnosis, with a value of 2.0 mg/dl being the best cutoff for predicting ESRD, degree of glomerulosclerosis, and presence of diabetes.5 Renal amyloid load and degree of proteinuria do not predict outcome. Preliminary data suggest that renal transplantation is a reasonable therapeutic option for those with advanced disease. In the series by Said et al., the disease recurred in 1 of 5 patients transplanted, but the short-term outcome was good: after a mean duration of 20 months of post-transplant follow up, no patient had graft loss and 2 had normal final serum creatinine.

Histologically, ALECT2 shows preferential and universal interstitial involvement. This is different from AL, AA, and AFib in which glomerulot (AL, AA, AFib) and vessels (AA and AL) are the prime sites of amyloid deposition.1,3,5,8 Although glomerular and vascular amyloid deposits are seen in most cases of ALECT2, they are mild in most cases.5 In contrast to AApo AIV which mainly affects the medullary interstitium, ALECT2 shows a predominant involvement of cortical interstitium.3,5 The deposits in ALECT2 tend to be strikingly congophilic3 and show...
the characteristic apple-green birefringence under polarized light. Similar to other forms of amyloidosis, the fibrils ultrastructurally appear randomly oriented with a mean diameter of 7-12 nm. Glomerular amyloid spicules however are far less common than in AL.\textsuperscript{1} Immunofluorescence is usually negative, although false positive staining for IgG with/without staining for IgM, IgA, kappa, and lambda may rarely occur\textsuperscript{8} albeit with a lesser frequency than in AA deposits.\textsuperscript{1} Importantly, concurrent renal disease is present in about a quarter of renal ALECT2 cases\textsuperscript{3,5} with diabetic nephropathy being the most common followed by IgA nephropathy and membranous nephropathy.\textsuperscript{3,5} These concurrent diseases likely contribute to the proteinuria in patients with ALECT2.\textsuperscript{3,5}

Typing amyloid deposits by LMD/MS is currently the best tool to diagnose ALECT2 and other forms of amyloidosis, due to its high sensitivity and specificity and because it is a single test that can detect the culprit protein in contrast to immunohistochemical typing of amyloidosis which requires staining for multiple antibodies using several tissue sections. Unfortunately LMD/MS is available only in few selected centers such as the Mayo Clinic. There is now a commercially available antibody for immunohistochemical detection of LECT2 which appears to be highly sensitive; however, weak false positive staining may occur particularly in AL\textsuperscript{9} which may result from aggressive antigen retrieval. Therefore, it is crucial that this antibody is carefully validated and optimized for the diagnosis of ALECT2. In cases that exhibit only weak staining, confirmation by LMD/MS is recommended.

The pathogenesis of ALECT2 is still unknown. LECT2, mainly synthesized by hepatocytes, is involved in chemotaxis, inflammation, immunomodulation, and the damage/repair process.\textsuperscript{10,11} Its serum levels are increased in liver diseases. Mereuta et al.\textsuperscript{7} found that hepatocytes in patients with liver ALECT2 strongly and uniformly expressed LECT2 mRNA while hepatocytes of normal individuals and patients with AL were negative. There was variable expression in hepatocellular carcinoma. They did not detect any mutation in the LECT2 gene (tested in 1 patient with liver ALECT2 and 6 patients with renal ALECT2). However, all patients were homozygous for the G nucleotide in exon 3 of the mature protein which is a common polymorphism with a frequency of 0.21 in individuals of Mexican ancestry.(Larsen, 2014 #9) The authors proposed that ALECT2 could be due to constitutive or compensatory LECT2 overexpression by hepatocytes.\textsuperscript{7} Notably, serum levels of LECT2 tested previously in few patients with ALECT2 were not increased and hence the disease is unlikely to be a result of consistently elevated serum LECT2 levels.\textsuperscript{8} The strong ethnic bias, the homozygosity for the G allele found in all patients tested so far, and the occurrence in two siblings in one report\textsuperscript{8} suggest a genetic basis for the disease. Larsen et al.\textsuperscript{3} hypothesized that ALECT2 is a digenic disorder induced by a combination of G polymorphism in the LECT2 gene and a yet to be discovered gene mutation(s). Further studies are needed to determine if ALECT2 is in fact a genetic disorder. It is unlikely that renal ALECT2 is a complication of malignancy, autoimmune disease, or liver disease, as the prevalence of these conditions in patients with renal ALECT2 is comparable to older individuals in general.\textsuperscript{3,5}

References
Case 6 from H. Terence Cook, MBBS – Imperial College of London

The patient is a 67-year-old white male. Seven years ago he underwent excision of a 3mm melanoma on his leg. Sentinel node biopsy was positive. Four years later he developed a recurrent melanoma on his leg, and 8/10 obturator nodes contained tumour. Seven months ago imaging showed progressive disease in para-aortic nodes. MRI showed a cerebellar infarct. He was entered in a phase 3 clinical trial of Nivolumab vs Ipilimumab vs combination of both. In addition to his trial medications he was taking simvastatin and lansoprazole.

He was referred for a nephrology opinion because of gradually increasing creatinine from 1.5 to 1.9 mg/dl over 4 months. On examination, there were bibasal fine crepitations at both lung bases. PR examination revealed a smoothly enlarged prostate.

CT scan of the lung was reported as showing grade 1 pneumonitis.

Urine dip stick showed protein ++ Blood +++

Labs:

Blood: Haemoglobin 11.2 g/dl, WBC 10.3 x 10^9/L, PLT 374 x 10^9/L.

Serum: Na 136 mmol/L, K 4.6 mmol/L, Creatinine 1.9 mg/dl, Glucose 88 mg/dl, Alk Ph 68 U/L, Gamma glutamyl transferase 32 U/L, Total bilirubin 0.82 mg/dl, Total protein 7.4 g/dl, Albumin 3.3 g/dl, Ca 9.32 mg/dl, Mg 1.8 mg/dl

1. In which compartment of the kidney is the main abnormality?
   
   A. Glomeruli
   B. Tubules
   C. Arteries
   D. Interstitium
   E. Peritubular capillaries

2. Which of the following is the glomerular lesion?

   A. Mesangial expansion
   B. Endocapillary and extracapillary hypercellularity
   C. Necrosis
   D. Nodular glomerular sclerosis
   E. Focal and segmental glomerulosclerosis

3. Antibodies to which of the following proteins will stain the atypical cells in glomeruli?

   A. CD68
   B. HMB-45
   C. CD3
   D. PD-1
   E. S100
Diagnosis:
The kidney shows glomerular involvement by metastatic malignant melanoma

**DISCUSSION**

The clinical suspicion in this case was that the renal impairment was drug-related. Lansoprazole is a protein pump inhibitor and these drugs are associated with acute tubulointerstitial nephritis [1]. The patient was in a trial of two anti-tumour drugs. Nivolumab is a fully human IgG4 monoclonal antibody that acts as an immunomodulator by blocking ligand activation of the programmed cell death 1 (PD-1) receptor on activated T cells. If programmed cell death 1 ligand 1 (PD-L1), binds to PD-1, the T cell dies. Since many cancer cells make PD-L1, the cancer cells can disarm the T cells and inhibit them from attacking the tumour. Nivolumab blocks PD-L1 from binding to PD-1. The European Journal of Cancer considered Programmed Death-1 receptor/Programmed Death-1 Ligand-1 receptor monoclonal antibodies to be the cancer 'Drug of the Year' in 2013. Common adverse events with nivolumab included fatigue, rash, diarrhea, decreased appetite, nausea, and pruritus. Grades 3-4 toxicity occurred in 41 of 296 patients, with 3 deaths attributed to treatment-related pneumonitis [2]. No renal adverse effects have been reported.

Ipilimumab is a fully humanized monoclonal antibody that binds CTLA-4, a protein receptor that down regulates the immune system. The drug is thought to prevent the down-regulation of cytotoxic T cells by dendritic cells within the tumour. Ipilimumab treatment has been associated with severe and potentially fatal immunological adverse effects due to T cell activation and proliferation. It is associated with colitis, hepatitis and dermatitis endocrinopathies; uveitis, iridocyclitis, neuropathies, and inflammatory myopathy. In the kidney there are reports of granulomatous tubulointerstitial nephritis and a lupus-like glomerulonephritis [3].

However, the pathology in the kidney was unrelated to therapy and in fact was involvement of the glomeruli by metastatic malignant melanoma. Intraglomerular metastasis of solid tumours is rare and most cases are detected at autopsy rather than by biopsy In one study intraglomerular metastases were at autopsy found in 3% of cases of disseminated malignancy [4]. Intraglomerular metastasis has been reported with malignant melanoma [5] and in that case the presentation was with acute renal failure.

He subsequently developed progressive pneumonitis. He exited the clinical trial and received prednisolone with good clinical improvement. Nine months after the biopsy he is being considered for further chemotherapy as part of a clinical study (NEMO trial (NRAS melanoma and MEK inhibitor): A randomized Phase III, open label, multicenter, two-arm study comparing the efficacy of MEK162 versus dacarbazine in patients with advanced unresectable or metastatic NRAS mutation-positive melanoma.

**References**