A 63-year-old man was diagnosed with urothelial carcinoma. Treatment consisted of neoadjuvant therapy with Gemcitabine/Paclitaxel, followed by radical cystoprostatectomy. During his fourth dose of adjuvant chemotherapy with Gemcitabine/Docetaxel, his creatinine increased to 6.25 mg/dL from a baseline of 1.6 mg/dL. He had 4.5 g/24 h of proteinuria, 0–3 red blood cells (RBCs) on urinalysis, normal complement levels, and negative serologies [anti–nuclear antibody (ANA), anti–double stranded (ds) DNA, ANCA, SPEP/UPEP]. Additional laboratory values included a platelet count of $330 \times 10^3/\mu L$ on the date of the biopsy (reference range, $140–420 \times 10^3 \mu L$) and a peripheral smear showing abnormal red blood cell morphology (anisocytosis, polychromasia with basophilic stippling, macrocytes, schistocytes, tear drop cells, etc.). He also had diarrhea (positive *Clostridium difficile* culture) and bilateral deep vein thromboses. Serum lactate dehydrogenase trended upward to markedly increased levels (Figure 1). A kidney biopsy was performed.

The biopsy showed up to 49 glomeruli, of which 34 were globally sclerotic. Patent glomeruli showed diffuse congestion and mesangiolysis with prominent endothelial swelling of the corresponding preglomerular arterioles (Images 1 and 2). Rare intraparenchymal arteries showed similar findings characterized by luminal congestion, endothelial swelling, and fibrin deposition (Image 3). Electron microscopy showed findings compatible with acute thrombotic microangiopathy characterized by subendothelial, electron lucent expansion with a flocculent quality (Image 4).
1. Which is the main pathogenic mechanism of thrombotic microangiopathy regardless of its etiology?
   A. Anti–endothelial antibodies
   B. Endothelial injury
   C. Malignant hypertension
   D. Decreased serum ADAMTS-13 levels
   E. Shiga toxin exposure

Answer: B – Endothelial injury is the common denominator in thrombotic microangiopathy. All of the listed answer choices can secondarily lead to endothelial injury by a variety of different mechanisms.

2. A group of medicine residents come to the pathology department after rounds and are interested in seeing the biopsy on their patient. Their clinical impression is that the patient experienced acute renal failure due to a complication associated with a drug that the patient was taking. Which is a pathogenic mechanism of drug-induced nephrotoxicity?
   A. Postrenal obstruction
   B. Thyroidization
   C. Tubular cell toxicity
   D. Congenital cystic disease

Answer: C – Tubular cell toxicity is one of several mechanisms of drug-induced nephrotoxicity. Others include thrombotic microangiopathy, rhabdomyolysis, inflammation, and crystalloid nephropathy. "Thyroidization," or atrophic tubular dilatation with prominent intratubular proteinaceous material, is a finding associated with ESRD/severe CKD. Postrenal obstruction (i.e., lower urinary tract obstruction) is not associated with drug-induced nephrotoxicity. Last, congenital cystic disease is not associated with drug-induced nephrotoxicity.

3. A 67-year-old man with a medical history of diabetes mellitus II, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), and atrial fibrillation presents to the emergency room with malaise and back pain. He had been prescribed high-dose nonsteroidal anti-inflammatory drugs (NSAIDS) approximately 3 months prior to presentation after sustaining a fall in his home. Laboratory data reveal a creatinine level of 4.5 mg/dL and increased urinary eosinophils. Which statement regarding drug-induced nephrotoxicity is TRUE?
   A. Drug-induced nephrotoxicity is less common today than it was at least 30 years ago
   B. Prompt clinical correlation of the findings on renal biopsy with a medication history can aid in efficient treatment of drug-induced nephrotoxicity
   C. The etiology of a thrombotic microangiopathic (TMA) pattern on kidney biopsy is often limited to thrombotic thrombocytopenic purpura
   D. The mechanism of action of sunitinib is microtubule stabilization

Answer: B – Prompt correlation of the findings on renal biopsy with the patient's medication history (which is not always available on the requisition) can lead to efficient withdrawal of the offending drug in many cases and preserve renal function. Drug-induced nephrotoxicity is much more common in current times than it was decades ago, as patients are living longer and more subject to polypharmacy. A pattern of TMA on a kidney biopsy has a wide variety of etiologies including thrombotic thrombocytopenic purpura (TTP), (atypical) hemolytic uremic syndrome (HUS), pregnancy-associated renal disease, malignant hypertension, scleroderma renal crisis, drug toxicity, radiation nephritis, and many more. Sunitinib is a tyrosine kinase inhibitor. Paclitaxel is directed at the microtubular architecture.
Discussion

It is reported that drugs cause approximately 20% of community-based and hospital-acquired cases of acute renal failure (1–4). The finding is more common among older adults. Compared with decades ago, patients survive longer to be older, with a higher incidence of diabetes and cardiovascular disease requiring multiple medications and exposure to more diagnostic and therapeutic procedures (5). In many cases of drug-induced nephrotoxicity, renal impairment is reversible if the offending drug is discontinued; rendering the medication history that accompanies a renal biopsy of paramount importance.

This case details the histopathologic findings in a 63-year-old man that had been receiving gemcitabine with taxanes, a chemotherapeutic agent commonly used to treat a variety of malignancies, but very commonly used in the treatment of urothelial carcinoma. The kidney biopsy revealed evidence of thrombotic microangiopathy, a disease pattern with more common etiologies that include TTP, atypical HUS (aHUS), and malignant hypertension-associated diseases like scleroderma renal crisis. Mechanisms of renal injury secondary to drug-induced thrombotic microangiopathy most commonly include an immune-mediated reaction or direct endothelial surface toxicity; however, all forms thrombotic microangiopathy are essentially related to endothelial injury of some form, which can be due to a wide variety of causes (6). One report indicated the novel finding of new onset or exacerbation of existing hypertension in association with gemcitabine associated TMA (7). Another documented the onset of acute TMA in a group of patients that recently used a crush-resistant formulation of oxymorphone hydrochloride (8). In some cases, the TMA event is “renal limited” and may not be associated with systemic symptoms of thrombosis or a significantly decreased platelet count. Some of the more common drugs associated with nephrotoxicity of any form include clopidogrel, ticlopidine, cyclosporine, mitomycin-C, and quinine (6, 9).

After the diagnosis of TMA was made in this patient, a hematology-oncology consult confirmed the abnormal red blood cell morphology on peripheral smear, and a trial of Eculizumab was recommended while the patient was undergoing hemodialysis therapy. The drug was approved and purchased; however, the patient was lost to follow-up and did not receive it. As of this report, the patient is no longer dialysis dependent and has creatinine levels that range from 3.4 to 4.3 mg/dL.

In summary, drug-induced nephrotoxicity is a much more common source of AKI than many medical professionals realize. When acute TMA is identified on a kidney biopsy and does not clinically correlate with the more commonly associated entities of (atypical) HUS or TTP, a medication or illicit drug investigation may aid in the discovery of the etiology. The importance of identification of the histopathologic patterns associated with drug-induced injury, correlation of the pattern with the patient's medication history (which is not always provided), and prompt communication of the findings to the referring nephrologist so that withdrawal or dose reduction of the offending agent can ensue cannot be understated.

References

A 65-year-old white man with a history of hepatitis B initially presented to his hematologist for evaluation of long-standing microcytic anemia, proteinuria, and chronic back pain. Workup revealed elevated serum free kappa light chains, as well as increased urine kappa to lambda light chain ratio. He underwent a bone marrow aspiration biopsy, which revealed findings consistent with a B-cell lymphoproliferative disorder/lymphoplasmacytic lymphoma. At the time of diagnosis, a serum protein electrophoresis revealed monoclonal protein gammopathy, which immunofixation identified as IgM kappa monoclonal protein. The free kappa:lambda ratio was 5:1. Ultrasound of the patient’s kidneys revealed enhancement of the bilateral kidneys, suggestive of an infiltrative process involving the kidneys. A kidney biopsy was performed.
1. What is the BEST differential diagnosis regarding the kidney biopsy findings in this patient?
   A. Membranoproliferative GN (MPGN) versus membranous GN
   B. Light chain cast nephropathy versus Acute Tubular Injury
   C. Interstitial nephritis versus neoplastic infiltrate
   D. Light chain deposition disease versus amyloidosis

2. Which renal manifestation is MOST common in patients with Waldenstroem's macroglobulinemia?
   A. Subendothelial IgM deposits and capillary thrombi
   B. Amyloidosis
   C. Discrete renal mass
   D. Interstitial Infiltrate

3. Which therapy is rarely used to control renal manifestation of Waldenstroem's macroglobulinemia?
   A. Rituximab
   B. Plasmapheresis
   C. Chlorambucil
   D. Stem cell transplant

In view of the clinical history, the following differential diagnosis for a possible renal lesion can be entertained: light chain deposition disease, AL-amyloidosis, cryoglobulinemic GN, secondary membranous nephropathy, MPGN, light chain cast nephropathy, involvement by neoplastic lymphoproliferative disease, and secondary FSGS.

Kidney biopsy findings: Seven glomeruli are present, one of which is globally sclerosed. One glomerulus shows pericapsular fibrosis. Glomeruli are negative for endocapillary proliferation, necrosis, or thrombi. The mesangium of nonscarred glomeruli shows increased cellularity and matrix deposition. There is focal interstitial scarring with proportional tubular atrophy involving 20% of the biopsy tissue. There is a focal interstitial lymphocytic infiltrate involving 10% of the biopsy tissue. The tubules show focal, mild acute tubular injury characterized by focal dilated lumina, cytoplasmic vacuolization, and sloughing of the brush border. Proteinaceous casts within the tubules are occasional identified. The vessels show moderate intimal sclerosis and medial thickening. Immunohistochemistry shows that the interstitial lymphocytic infiltrate is positive for CD20 and IgM, and rare CD138-positive cells are also seen.

Immunofluorescence microscopy reveals 1+ IgM and 2+ kappa staining of cells in interstitium and in peritubular capillaries. Immunofluorescence stains for IgG, IgA, C3, C1q, lambda, and fibrinogen are all negative.

Electron microscopy demonstrates irregular thickening of the glomerular basement membranes with segmental effacement of the foot processes. The tubules showed mild injury and dilated mitochondria. The endothelial cells show normal fenestrations. The mesangium shows a mild increase in matrix and cellularity. Subepithelial, intramembranous, subendothelial, and mesangial electron dense deposits are not identified.

Biopsy diagnosis: Involvement of kidney by neoplastic IgM+ B-cell-predominant Infiltrate.

Clinical follow-up: The patient was offered several treatment options. Initially, the patient elected to be treated with the monoclonal anti-CD20 antibody, rituximab, in combination with an alkylating agent, bendamustine. However, due to a persistent hepatitis B viral load, he has been unable to receive rituximab thus far. He has undergone a total of four cycles. He is tolerating the treatment without significant side effects, except for mild fatigue and mild weight loss, which has now stabilized. The patient is receiving entecavir to treat the hepatitis B, and rituximab will be instituted once the hepatitis B viral load has been cleared. Over the course of 2 months of treatment, the patient’s quantitative IgM levels have decreased from 2030 to 1130 mg/dL.
Waldenström macroglobulinemia (WM) is a rare lymphoplasmacytic lymphoma characterized by proliferation of B lymphocytes in the bone marrow with a circulating monoclonal IgM gammopathy in the serum (1). The MYD88 L265P gene mutation has been shown to support the growth and survival of WM cells (2). MYD88 acts as an adaptor molecule in Toll-like receptor and interleukin-1 receptor signaling (3). Recurrent somatic CXCR4 gene mutations have also been identified in approximately 30% of WM patients (4).

The clinical manifestations include hepatomegaly (20%), splenomegaly (15%), and lymphadenopathy (15%) (5). The disorder has an incidence of three per million cases per year. The median age at diagnosis is 63–68 year (2, 5, 6). WM is more common in whites and has a slight male predominance (7).

The clinical manifestations of WM are associated with the direct tumor infiltration of various organs by the IgM proteins, which form complexes, leading to hyperviscosity syndrome. Serum hyperviscosity is only observed in 15% of patients at diagnosis and is characterized by oro-nasal bleeding, retinal hemorrhage, and a wide array of neurological abnormalities (8). Pulmonary, cutaneous, and gastrointestinal manifestations have also been documented. Renal involvement by WM is a rare occurrence (9).

Patients with monoclonal IgM in their serum do not necessarily develop WM. In one review, only 17% of these patients developed WM (10). It is the ability of the IgM paraproteins to form intravascular complexes that results in vascular occlusion, leading to the disease.

Approximately 15% of patients with WM show signs of renal impairment, which typically manifests with glomerular abnormalities. On light microscopy, the most commonly described glomerular alteration is voluminous periodic acid Schiff (PAS)-positive subendothelial deposits or intracapillary protein thromb (11). Cryoglobulins may be present in the capillary thrombi. In rare cases, amyloidosis has been associated with WM (11). Uncommonly, WM involvement of the kidney has been described to form a discrete renal mass (12, 13). The mass was comprised of a diffuse infiltration of the renal parenchyma by aggregates of neoplastic lymphoplasmacytic cells.

Acute renal failure is rare and is a result of extensive vascular occlusion by IgM complexes, dehydration, massive renal infiltration by neoplastic cells, or distal nephron obstruction (13).

Immunofluorescence microscopy reveals glomerular granular or amorphous deposits, which stain for IgM and quite frequently IgG, as well. Staining for C3 and C4 in the peripheral capillary wall can also be seen. In some cases, there is also light chain restriction (10).

Electron microscopy shows electron dense deposits located in various renal compartments, such as the subendothelium, glomerular capillary spaces, or in the extraglomerular vasculature (14).

Treatment of WM is aimed at clearing the circulating IgM paraproteins. First-line therapy generally consists of monoclonal anti-CD20 antibody, rituximab, alone or preferably in combination (15). Other front-line therapy options include alkylating agents (i.e., chlorambucil, cyclophosphamide, and bendamustine), nucleoside analogues (i.e., fludarabine or cladribine), or combination therapy (7).

Renal manifestations rarely may require dialysis. In patients in whom an immediate control of the disease is warranted, such as symptomatic hyperviscosity, coagulopathy, cryoglobulinemia, or cold agglutinin disease, a rapid reduction of the IgM paraprotein can be achieved with plasmapheresis (2). Stem cell bone marrow transplantation, while rarely used, is a feasible therapeutic alternative (16).

The median survival for patients has varied in studies from 5 to 11 years (16). The main cause of death includes disease progression, transformation to high-grade lymphoma, or complications of therapy (17). If amyloidosis is found complicating the clinical picture, survival decreases to about half the period (18). Gastrointestinal hemorrhage is the most common cause of death (19).

References


Case 3 from Kammi J. Henriksen, MD – University of Chicago

A 30-year-old Hispanic woman with metabolic syndrome and hypertension was initially referred to nephrology at the 11th week of her second pregnancy for heavy proteinuria (5.8 g/24 h). Of note, she had had a history of preeclampsia during her first pregnancy 3 years earlier and had delivered a small for gestational age preterm infant. Workup now revealed a serum creatinine of 1.2 mg/dL and normal serologic studies. A renal biopsy was strongly encouraged, but the patient declined. At 25 weeks of gestation, she became severely hypertensive and proteinuric (12 g/24 h), and she underwent an emergency Caesarian section. A premature baby boy was delivered in respiratory failure and died of sepsis 5 days later.

The patient was lost to follow-up for several months and then returned with progressive renal insufficiency and persistent proteinuria. Physical examination was notable for morbid obesity, BP of 138/94 mmHg, a depressed affect, and 2+ peripheral edema. A renal ultrasound showed normal-sized kidneys with normal echogenicity. Laboratory findings were as follows:

**Serum findings:**
- Creatinine: 1.83 mg/dL
- Albumin: 2.3 mg/dL
- C3: 53.5 mg/dL (normal range: 71.3–184.5 mg/dL)
- Normal/negative studies: C4, ANA, ANCA, anti-GBM, hepatitis B and C, HIV

**Urine findings:**
- 24-hour urine collection: 12.8 g protein
- Red blood cells: 2–15 monomorphic red cells/high-power field (hpf)
- White blood cells: None

The patient was begun on lisinopril (40 mg daily) and agreed to a renal biopsy. Representative images are shown below.
1. **What are the morphologic pattern(s) of glomerular injury?**
   A. Pure mesangial proliferation
   B. Membranoproliferative pattern (accentuated lobulation, mesangial expansion and proliferation, and thickening/duplication of the GBMs)
   C. Acute exudative GN
   D. Focal and segmental glomerular sclerosis
   E. B and D

2. **Based on the immunofluorescence findings, what disease(s) should be considered in the differential diagnosis?**
   A. Resolving postinfectious GN
   B. C3 GN
   C. Dense deposit disease (MPGN type II)
   D. Atypical postinfectious GN
   E. All of the above

3. **What is the pathognomonic ultrastructural finding illustrated above?**
   A. Subepithelial deposits and “humps”
   B. Subendothelial “wire loop”–type deposits
   C. Hyperdense intramembranous deposits in a discontinuous “ribbon-like” distribution
   D. Mesangial fibrils
   E. Podocyte foot process effacement

4. **The patient’s hypocomplementemia is most likely related to:**
   A. Complement activation by immune complex deposition
   B. Autoantibodies that bind and stabilize C3 convertase
   C. Liver disease
   D. Mutations in complement inhibitors
   E. Inherited deficiency of complement control proteins
Renal biopsy revealed findings diagnostic of dense deposit disease, and subsequent testing revealed the presence of C3 nephritic factor. The patient was treated with maximal doses of lisinopril; attempts were made to administer eculizumab, but the patient’s insurer would not authorize payment. Ten months after biopsy, the patient became pregnant, at which point her renal function again started to decline; at 6 months of gestation, she was diagnosed with intrauterine fetal demise, became anuric, and has been dialysis dependent ever since.

Discussion

Dense deposit disease (DDD) is a rare nephropathy manifested by extremely electron dense deposits and complement accumulation in the glomerular and tubular basement membranes, initially described by Berger and Galle in the early 1960s (1–3). Formerly known as MPGN type II, DDD is now classified as a “C3 glomerulopathy.” This recently coined group of diseases is characterized by C3 deposition in the paucity or absence of glomerular immunoglobulin and is associated with dysregulation of the alternative complement pathway (4–7).

C3 glomerulopathy includes both C3 glomerulonephritis (C3GN) and DDD, which are distinguished from one another by the ultrastructural appearance and location of glomerular deposits. Most patients with DDD (>80%) are positive for serum C3 nephritic factor (C3NeF), an autoantibody that binds to and stabilizes C3 convertase (or its components) and therefore results in continuous activation of the alternative complement pathway and massive C3 consumption (8–11). Genetics also contribute to the development of DDD, as mutations in several genes encoding complement regulators have been identified including complement factor H (CFH). It has been proposed that infections may trigger disease onset in genetically predisposed individuals (12).

DDD affects both children and adults, although it usually presents in childhood (mean age at diagnosis: 19 years). The disease is equally represented among sexes. Clinical findings at presentation typically include hematuria, proteinuria (sometimes with nephrotic syndrome), and varying degrees of hypertension and renal insufficiency. Most patients have hypocomplementemia, specifically low C3. Features of partial lipodystrophy or the development of ocular drusen can accompany the renal manifestations of DDD in a minority of patients. There is an association with underlying monoclonal gammopathy in adult patients. The disease tends to be steadily progressive, with approximately 50% of patients developing ESRD within 10–15 years of diagnosis. DDD usually recurs in renal allografts. Most therapy for DDD is ineffective, including steroids and other immunosuppression. However, several recent studies have indicated a potential role for complement inhibitors such as Eculizumab in a subset of patients (13,14).

The light microscopic features of DDD are heterogeneous (15,16). Some cases (25%–45%) exhibit a classic MPGN-like pattern with accentuated lobulation of the glomerular capillary tufts, mesangial expansion and hypercellularity, and thickening and duplication of the GBMs. A similar proportion of cases (30%–50%) exhibit mild mesangial proliferation with or without endocapillary hypercellularity. Focal crescent formation or an exudative glomerulonephritis can also be seen. Regardless of the pattern of glomerular injury, the glomerular and tubular basement membranes show segmental thickening in areas of complement deposition by eosinophilic, refractile deposits, which are strongly PAS positive. These deposits are fuchsinophilic by trichrome and stain poorly with Jones methenamine silver stain. Progressive glomerular and tubulointerstitial scarring develops later in the disease.

The immunofluorescence/immunohistochemical findings in DDD are characterized by intense “ribbon-like” deposition of complement C3 in a segmental distribution along the GBMs and coarse mesangial granules or spherules. Broad linear C3 deposits can also be seen in the tubular basement membranes and Bowman capsules. Ig and C1q deposition is sparse to absent; focal Ig deposits are present in a minority of cases, but at least two levels of fluorescence intensity less than C3 (17). There is also a DDD variant with C4d deposition rather than C3, which is associated with activation of the lectin pathway (18).

Ultrastructural evaluation reveals pathognomonic, highly osmiophilic “ribbon-like” dense deposits along the lamina densa of the GBMs, resulting in a very electron dense appearance. These deposits lack organized substructure. The GBM deposits are frequently seen in a segmental/discontinuous distribution, resulting in a “sausage string” pattern. Similar deposits can be seen in the mesangium, along Bowman capsules, and in the tubular basement membranes. Occasional cases show subepithelial deposits resembling subepithelial “humps,” which are less dense than the intramembranous deposits. Studies using laser capture microdissection and mass spectrometry analysis have shown that the glomerular deposits contain components of the alternative and terminal complement pathway including C3, C5, C8a, C9, CFH-related protein 1, clusterin, vitronectin, and apolipoprotein E (19).

The primary differential diagnostic consideration is C3GN, which can show overlapping histologic features with DDD. Immunofluorescence microscopy in C3GN tends to show bright granular C3 staining predominantly in the mesangial areas and occasionally along the glomerular capillary walls, in contrast to DDD, which shows prominent ribbon-like capillary wall staining and coarse mesangial granules or “spherules.” By electron microscopy, C3GN typically shows discrete amorphous deposits in mesangial and occasional subendothelial and/or subepithelial locations, which are less electron dense than those of DDD. Postinfectious glomerulonephritis (PIGN) with resolving or atypical features is another diagnostic consideration. PIGN frequently demonstrates an acute, “exudative” pattern of glomerular injury with neutrophilic inflammation. There may be some glomerular Ig deposition by immunofluorescence microscopy in PIGN, although C3 can persist longer than Ig. Subepithelial “humps” can be seen by ultrastructural evaluation in both PIGN and DDD, but again the deposits of PIGN are less electron dense than those of DDD.
References

A 76-year-old man presents with a history of hypertension, CKD stage 3 (creatinine, 3.6 mg/dL), and nephrotic range proteinuria.

Patient had been admitted with AKI and posterior reversible encephalopathy syndrome in the setting of severe hypertension during the last year. Previous creatinine had been normal, with elevation to 3.0 mg/dL on admission. Creatinine stabilized to 2.5 mg/dL by discharge, but there was residual proteinuria (5 g). SPEP/UPEP is negative for monoclonal protein. PLA2R negative. The patient has no history of diabetes.

The patient underwent kidney biopsy for continued nephrotic-range proteinuria. BP: 160/70 mmHg. Serologies are all negative. Urinalysis shows 0–2 RBCs/hpf and 6–10 white blood cells (WBCs)/hpf. Complements normal. Platelets, 245,000.
1. What feature in the biopsy correlates with the nephrotic-range proteinuria?
   A. Mesangial expansion
   B. Acute tubular injury
   C. FSGS
   D. Arteriosclerosis

2. In which other compartment(s) of the kidney is/are there abnormal findings?
   A. Arteries
   B. Tubules
   C. Interstitium
   D. All of the above

3. Is there evidence of microangiopathic injury from the previous episode of malignant hypertension?
   A. Yes
   B. No

Discussion
Pathologic Features
Light microscopy demonstrates FSGS with hyalinosis, located primarily at the vascular pole, correlating with the clinical proteinuria. The tubules show thinning and simplification, with occasional cell sloughing, consistent with acute tubular injury. A few small foci of tubular atrophy and interstitial fibrosis are present. Several small arteries show cleft-shaped lumens consistent with cholesterol embolization. Larger arteries have mild to moderate intimal fibrotic thickening. In addition, several arteries and glomeruli contain lamellated basophilic material that is PAS and silver negative. The material appears to be located in vascular lumens and mesangium in the glomeruli and within the lumen and/or wall of arteries and arterioles. The material is nonrefractile and did not polarize. Immunofluorescence studies could not be performed due to lack of glomeruli. Electron microscopy demonstrates moderate to severe podocyte injury, correlating with the proteinuria. No definitive foreign material was identified ultra-structurally.

Differential Diagnosis
Follow-up clinical information revealed that the patient had undergone repair of an abdominal aortic aneurysm in January 2015, with use of an unknown graft material. The procedure is believed to have been an open surgical procedure, rather than endovascular, and that the repair was suprarenal.

Hydrophilic polymer emboli have been reported secondary to the use of this material in intravascular devices. In a report of nine cases, polymer material was identified in the lungs, brain, and lower extremities (1). A similar material was demonstrated in a transplant kidney following repair of an abdominal aortic aneurysm, associated with acute kidney failure (2). A foreign body giant cell reaction is sometimes seen; however, in most instances, there is no inflammatory response.

Other possible sources include foreign material from injected substances, contrast media, and other surgical gels or materials. This patient is well known to the nephrologist and has no known intravenous drug abuse (IVDA) or injection of other substances. No recent contrast studies had been performed, and no other surgical procedures were done.

The material on H&E resembles Tamm-Horsfall protein, which has been shown to retrograde into the glomerulus/Bowman’s space with severe obstruction. However, other features of obstruction are absent.

Given the history of hypertensive crisis with AKI, the possibility of angiopathic injury was considered. Myxoid change secondary to endothelial injury can appear basophilic and be present within the wall of arteries/arterioles and glomeruli.
References


The patient is a 67-year-old white man with a history of ESRD presumed secondary to diabetes and hypertension. He underwent a cadaveric renal transplant approximately 21 months ago with an uncomplicated postoperative course. The kidney was a 1A, 2B, 1DR mismatch. Both the donor and recipient were cytomegalovirus (CMV) negative. His creatinine baseline is 1.1–1.3 mg/dL. His creatinine has risen to 1.6–1.8 mg/dL over the last 3 months. He is reportedly compliant with his medications. The patient’s medical history is significant for gastric bypass surgery approximately 11 years ago, followed by a 150-lb weight loss, hypertension, diabetes complicated by retinopathy and peripheral neuropathy, and CAD. The patient is currently taking tacrolimus and prednisone for immunosuppression, Bactrim, rosuvastatin, metoprolol, amlodipine, and metformin. Routine labs show a normal WBC count, hemoglobin of 11.8 g/dL, hematocrit of 36.4%, and a platelet count of 147 10^3/μL. A complete metabolic panel shows an elevated creatinine of 1.77 mg/dL and BUN of 36 mg/dL and is otherwise unremarkable. Urinalysis is negative. Blood polymerase chain reaction (PCR) testing for BK virus is negative, and donor-specific antibody testing is negative. Tacrolimus level is 7.8 ng/mL.

Which of the following are causes of secondary oxalosis?
A. Gastric bypass surgery
B. Pancreatic insufficiency
C. Excessive vitamin C intake
D. Inflammatory bowel disease
E. All of the above

Primary hyperoxaluria is most commonly due to autosomal recessive mutations of which of the following hepatic genes?
A. AGXT: encodes alanine glyoxylate aminotransferase
B. GRHPR: encodes glyoxalate reductase
C. HOGA1: encodes 4-hydroxy-2-oxoglutarate aldolase
D. OX1: hereditary oxalosis enzyme cofactor 1
3. Oxalate crystals have the following light microscopic appearance:
   A. Brown, fan-shaped polarizable crystals
   B. Clear fan-shaped nonpolarizable crystals
   C. Clear fan-shaped polarizable crystals
   D. Purple irregular-shaped nonpolarizable crystals

Discussion

Oxalate nephropathy may be primary or secondary. Primary hyperoxaluria (PH) is due to autosomal recessive inheritance of defects in hepatic genes responsible for glyoxalate metabolism including AGXT, GRHPR, and HOGA. Primary disease is most commonly caused by deficiency of alanine glyoxylate aminotransferase (AGXT; 70%–80% of cases). PH type II is due to deficiency of glyoxalate reductase (GRHPR; ~10% of cases) and results in a milder variant. PH type III is due to dysfunction of 4-hydroxy-2-oxoglutarate aldolase (HOGA1; ~10% of cases). Although PH is more commonly diagnosed in children, 20%–40% of cases are diagnosed as adults. Patients with PH most commonly present with nephrolithiasis, hematuria, and abdominal pain. Secondary oxalosis may present with acute or chronic renal failure, depending on the etiology. Patients who have undergone gastric bypass surgery may present years following their operation with a slowly progressive rise in serum creatinine. Acute toxicity may occur following ingestion of substances with high levels of oxalate such as ethylene glycol.

The pathologic findings of oxalate nephropathy are identical regardless of etiology. Numerous calcium oxalate crystals are seen scattered throughout the tubulointerstitium. The crystals have a clear/translucent appearance and are arranged in both irregular and fan-like shapes. Calcium oxalate is readily visualized using polarized light. The crystals preferentially deposit in the cortex in tubular lumens, tubular epithelium, and interstitium. The tubules may show signs of injury: dilatation, epithelial simplification, cell sloughing, and loss of the proximal tubular brush border. Granulomatous inflammation may sometimes be seen in association with calcium oxalate crystals.

Secondary oxalate nephropathy (secondary oxalosis) is caused by multiple mechanisms: increased intake of oxalate, increased absorption of oxalate, changes in intestinal microorganisms, diminished oxalate excretion, or vitamin deficiency of thiamine or pyridoxine. Increased intake may be related to ingestion of oxalate rich foods including spinach, coffee, rhubarb, star fruit, black tea, peanuts, strawberries, chocolate, and soy products. Vitamin C and ethylene glycol intake may also lead to secondary oxalate nephropathy. Increased oxalate absorption occurs in the setting of fat malabsorption. Oxalate, absorbed in the small intestine, binds to dietary calcium, which limits its absorption. In fat malabsorptive states such as chronic pancreatitis, the free calcium is bound by the excessive small intestinal fat, leading to elevated levels of free oxalate, which is now able to be absorbed by the intestinal mucosa. Furthermore, elevated intestinal fat and bile acids increase intestinal permeability to oxalate. Gastric bypass surgery, inflammatory bowel disease, and gastrointestinal lipase inhibitors may all lead to fat malabsorption and oxalate nephropathy. The anaerobic bacterium, Oxalobacter formigenes, converts oxalate to formate as a means to produce energy. Colonization of the gut with this bacterium is likely protective against excessive oxalate absorption. Prolonged antibiotic use may alter gut flora, placing patients at higher risk for development of oxalate nephropathy. Studies suggest that roux-en-Y gastric bypass may diminish gut levels of O. formigenes, adding additional risk to this procedure.

Oxalate crystals are commonly seen early in the post-transplant period due to a release of accumulated oxalate. Because the kidney is the primary site of oxalate removal, oxalate builds up in patients with CKD. In a normally functioning allograft, oxalate crystals are rare or absent 3 months after transplant and should be investigated further.

References