ASN KIDNEYWEEK 2018

San Diego, CA • Oct 23 – 28

Renal Biopsy: Clinical Correlations

October 27, 2018
4:30-6:30 p.m.

Case 1 from J. Charles Jennette, MD, University of North Carolina at Chapel Hill

Two months before a kidney biopsy, a 14-year-old girl developed suicidal ideation, began cutting herself, and ran away from home. She was admitted to a psychiatric hospital for 10 days and started receiving bupropion, trazadone, and lamotrigine for bipolar disorder.

Two weeks prior to biopsy, she developed lymphadenopathy, dysphagia, and an erythematous non-pruritic rash across her chest. All medications were stopped, and she received erythromycin for 5 days for "strep throat." The rash resolved.

One day after the erythromycin was discontinued, she developed a diffuse rash, fever to 104°F, and joint pain. Lab data included increased liver function test results (LFTs); negative hepatitis panel, HIV, Epstein–Barr virus (EBV), and cytomegalovirus (CMV) results; and creatinine 1.18 mg/dL. She was given risperidone for her bipolar disorder.

Ten days before the biopsy, she developed pharyngitis, fever, and erythematous rash. Lab data revealed additional increases in LFTs and creatinine 1.12 mg/dL; her antinuclear antibody (ANA), anti-double-stranded (ds) DNA, and antistreptolysin O results were all negative. The rash and pharyngitis improved, and she became afebrile.

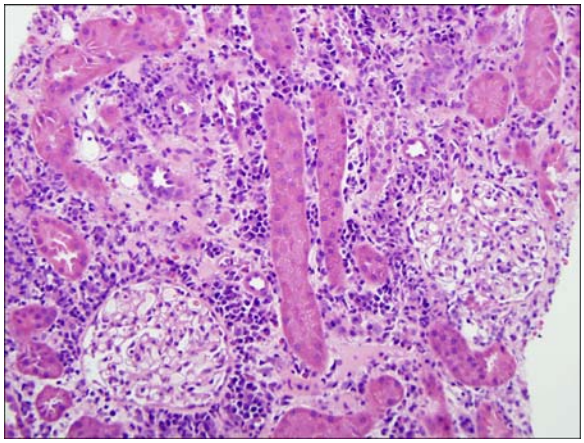
Two days prior to biopsy, the patient developed severe glossitis and pharyngitis and was found to have improved LFTs, creatinine 2.21 mg/dL, and eosinophil count 16%. She was admitted to University of North Carolina Hospitals.

Examination revealed a temperature of 102.9°F, BP 140/80 mm Hg, glossitis and pharyngitis, cervical lymphadenopathy, and no skin rash. Laboratory data included creatinine 2.67 mg/dL, blood urea nitrogen 19 mg/dL, trace proteinuria, urine protein/creatinine ratio 0.444, 29 white blood cells per high-power field (hpf), 5 red blood cells per hpf, numerous urine eosinophils detected with a Hansel stain, and blood eosinophil count 18%.

A kidney biopsy was performed.

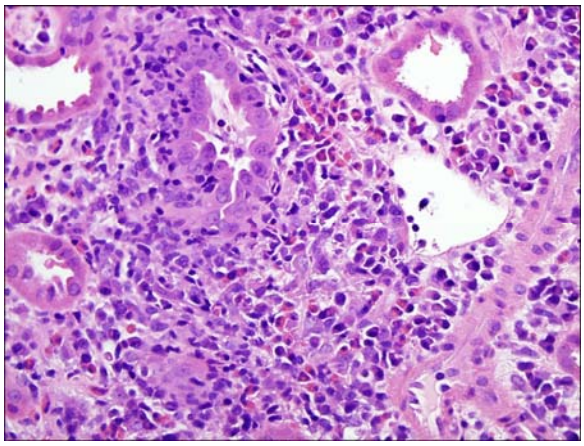
Questions for Case 1

1. Given the pattern of injury below (Case 1, Image 1), which is the most likely etiology?
   A. Lymphoproliferative neoplasm
   B. Infection
   C. Drug nephrotoxicity
   D. Drug hypersensitivity reaction
   E. Chronic glomerulopathy or vasculopathy with secondary chronic inflammation



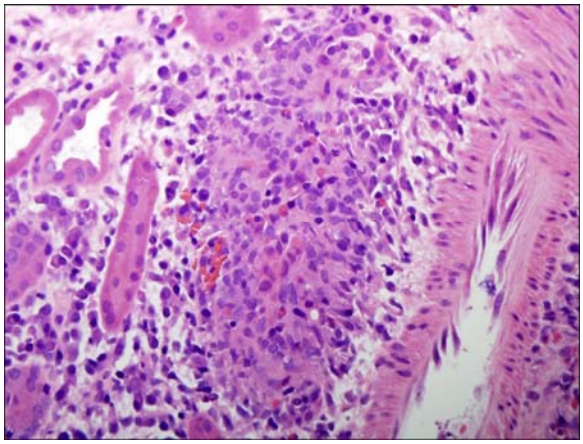
The photomicrograph has marked interstitial edema with prominent interstitial infiltration of predominantly mononuclear leukocytes (mostly lymphocytes) with admixed eosinophils that are difficult to see at this magnification. The variability among cells, looseness of the cell infiltrates, and interstitial infiltration rather than pushing replacement of parenchyma do not suggest lymphoproliferative neoplasm. The relatively normal architecture of the tubular epithelial cells does not suggest nephrotoxicity. The absence of segmented polymorphonuclear leukocyte is evidence against acute bacterial infection (pyelonephritis). Some other infection (e.g., viral) cannot be completely ruled out by the histology, but this pattern of injury is much more often caused by hypersensitivity than infection. Chronic glomerulopathy or vasculopathy with secondary chronic inflammation can cause extensive interstitial infiltration by mononuclear leukocytes but is always accompanied by interstitial fibrosis and tubular atrophy.

2. Which histologic feature is shown in the image below (Case 1, Image 2) and helps narrow the differential diagnosis?
   A. Absence of interstitial fibrosis
   B. Absence of tubular atrophy
   C. Presence of tubulitis
   D. Presence of numerous eosinophils
   E. All of the above



An essential teaching point of this question is that not only the presence, but also equally important the absence, of specific observations is necessary in making a pathologic diagnosis. The absence of interstitial fibrosis and tubular atrophy indicated that this is an acute rather than a chronic process. The tubulitis (seen best in the tubule left of center in the upper half of the image) confirms that the inflammation is attacking tubules. The numerous eosinophils (e.g., in the upper right quadrant of the image) support a hypersensitivity pathogenesis.

3. The elongated oval lesion in the center of the image below (Case 1, Image 3) is a granuloma. Which histologic feature is required to conclude that this is a granuloma?
   A. Multinucleated giant cells
   B. Focal accumulation of predominantly macrophages
   C. Both A and B
   D. Only B



A granuloma is a focal compact accumulation of predominantly macrophages. Giant cells (which result from the fusion of multiple monocytes into a large multinucleated macrophage) may be present in granulomas but are not required to make a diagnosis of granulomatous inflammation.

Diagnosis

This patient had drug-induced acute granulomatous tubulointerstitial nephritis, consistent with DRESS (drug reaction with eosinophilia and systemic symptoms), also called drug-induced hypersensitivity syndrome (DIHS).

Discussion

The whole-slide images and photomicrographs demonstrate marked interstitial edema with prominent interstitial infiltration of predominantly mononuclear leukocytes (mostly lymphocytes) with prominent admixed eosinophils, focal tubulitis, and granulomatous inflammation. The variability among cells, looseness of the cell infiltrates, and interstitial infiltration rather than pushing replacement of parenchyma do not suggest lymphoproliferative neoplasm.

The relatively normal architecture of the tubular epithelial cells does not suggest nephrotoxicity. The absence of segmented polymorphonuclear leukocyte is evidence against acute bacterial infection (pyelonephritis). Some other infection (e.g., viral) cannot be completely ruled out by the histology, but this pattern of injury is much more often caused by hypersensitivity than infection. Chronic glomerulopathy or vasculopathy with secondary chronic inflammation can cause extensive interstitial infiltration by mononuclear leukocytes but is always accompanied by interstitial fibrosis and tubular atrophy.

A granuloma is a focal compact accumulation of predominantly macrophages. This specimen has numerous well-defined granulomas. Giant cells are rare and small in the granulomas in this case. Giant cells (which result from the fusion of multiple monocytes into a large multinucleated macrophage) may be present in granulomas but are not required to make a diagnosis of granulomatous inflammation.

Not only the presence, but also equally important the absence, of specific observations is necessary in making a pathologic diagnosis. The absence of interstitial fibrosis and tubular atrophy indicates that this is an acute rather than a chronic process. The tubulitis confirms that the inflammation is attacking tubules. The numerous eosinophils support a hypersensitivity pathogenesis.

The pathologic findings alone support a diagnosis of acute granulomatous tubulointerstitial nephritis. The numerous eosinophils suggest a hypersensitivity reaction. The clinical data are required to conclude that the tubulointerstitial nephritis is a component of DRESS.

Based on the pathology alone, the diagnosis is limited to the observed pattern of injury, i.e., acute granulomatous tubulointerstitial nephritis. However, integration of the clinical and laboratory data allows a more informative and actionable clinicopathologic diagnosis of acute granulomatous tubulointerstitial nephritis as a component of DRESS.

DRESS is a drug-induced systemic inflammatory syndrome that can be caused by aromatic anticonvulsant drugs including lamotrigine. Manifestations include rash, fever, eosinophilia, and systemic manifestations, including hepatitis, myocarditis, and tubulointerstitial nephritis. DRESS with granulomatous tubulointerstitial nephritis has been reported secondary to lamotrigine, which is the likely cause in the patient described in Case 1.

DRESS syndrome is one of the severe cutaneous adverse reaction syndromes, which also includes Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis.

DRESS is characterized by severe diffuse erythematous skin eruption that can progress to exfoliative dermatitis, fever, eosinophilia, atypical lymphocytosis, and systemic organ involvement (especially lung, liver, kidney, and heart). Allopurinol, anti-epileptic drugs, and sulfonamides are the most frequent causes of DRESS. DRESS usually has a longer latency period (3–8 weeks) between the drug exposure and onset of symptoms compared with other drug-induced hypersensitivity reactions.

DRESS has been considered a rare syndrome occurring in approximately 0.5 individuals per 1 million population; however, a recent study using an electronic health record allergy keyword search module indicated an occurrence rate of 2/100,000.[6] The 69 DRESS cases identified had liver (42%) or renal (42%) injury; 11 (16%) had both liver and renal injury. Thus, 58% had renal disease. Causes included antibiotics (74%) (vancomycin [39%], β-lactams [23%], fluoroquinolones [4%], tetracyclines [4%], and sulfonamides [3%]) and anticonvulsants (20%).

One report of acute granulomatous interstitial nephritis and colitis in anticonvulsant hypersensitivity syndrome associated with lamotrigine treatment was similar to Case 1.[8] The authors described a 17-year-old girl with a history of bipolar disorder who developed fever, lymphadenopathy, skin rash, diarrhea, and acute renal failure requiring dialysis after the use of lamotrigine. Renal biopsy showed acute tubulointerstitial nephritis with focal granulomas.

There are rare case reports of DRESS with acute tubulointerstitial nephritis and renal-limited necrotizing vasculitis)[3,4]; however, glomerulonephritis and vasculitis are not typical features of DRESS. Drug withdrawal and corticosteroid therapy usually result in resolution of the systemic and renal manifestations; however, relapse of tubulointerstitial nephritis may occur after corticosteroid discontinuation without re-exposure to the initiating drug.

Anti-epileptic drugs (AEDs) can cause DRESS. This reaction usually develops 1–12 weeks after initiation of an aromatic anticonvulsant drug.[9] In a study of AED-induced DRESS in eight consecutive patients, all had dermatological manifestations, eosinophilia, and systemic (hematological and hepatic) manifestations that could be attributed to treatment with carbamazepine (two patients), lamotrigine (three patients), and phenytoin (three patients). Therapeutic management included removal of the drug, symptomatic management, life support, and use of corticosteroids.[7]

The pathogenic mechanisms causing DRESS are poorly understood. DRESS caused by anticonvulsant hypersensitivity is thought to have three components: (1) deficiency or abnormality of the epoxide hydroxylase enzyme that detoxifies the metabolites of aromatic amine anticonvulsants; (2) associated reactivation of herpes-type viruses, such as human herpesvirus 6, CMV, and EBV; and (3) ethnic predisposition related to certain HLA subtypes.[1] Arene oxides, toxic intermediaries in the metabolism of anticonvulsant drugs, can bind to macromolecules, causing cell death and acting as haptens. They then activate T cells, resulting in an immune response that releases cytokines, which mediate local and systemic inflammatory events, including recruitment of eosinophils (e.g., via IL-5 release).

In summary, Case 1 pathologic findings alone support a diagnosis of acute granulomatous tubulointerstitial nephritis. The numerous eosinophils suggest a hypersensitivity reaction. Knowledgeable integration of the pathologic findings with the clinical and laboratory data is required to discern the most precise and actionable clinicopathologic diagnosis of acute tubulointerstitial nephritis as a component of DRESS.

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Case 2 from Tibor Nadasdy, MD, Ohio State University

The patient is a 60-year-old white woman with ductal adenocarcinoma of the tail of pancreas diagnosed in January 2016. She underwent distal subtotal pancreatectomy and splenectomy. The tumor invaded the peripancreatic tissue, but no lymph node metastases were noted. She was treated with gemcitabine and radiation. In August 2016, she was diagnosed with peritoneal metastasis, and she received nab-paclitaxel and napabucasin in addition to gemcitabine.

On May 7, 2017, she presented with hypertensive crisis; her BP was up to 214/96 mm Hg. Her serum creatinine was 2.2 mg/dL (baseline serum creatinine was 0.6–0.8 mg/dL). After her BP was normalized, she was discharged; however, her serum creatinine value remained elevated. Her platelet count dropped to 66,000/μL. Her hemoglobin was 6.8% and hematocrit 20%–23% (she was anemic before with a hemoglobin of 10% and hematocrit 29%). Her haptoglobin value was <30 mg/dL and lactate dehydrogenase elevated at 881 U/L. She had numerous schistocytes in her peripheral blood. Serum complement levels were normal (C3 148 mg/dL, C4 28 mg/dL, CH50 <60 U/mL). Complement biomarker studies revealed elevated serum levels of BB at 1449 ng/mL (range 244-961 ng/mL) and C5a at 61 ng/mL (range 19-48 ng/mL). Serum C4d and C5B-9 levels were within normal ranges. Her ADAMTS13 level was normal. Lupus serologies were negative. The patient did not have monoclonal gammopathy. Because of the clinical suspicion of thrombotic microangiopathy (TMA), her chemotherapy, including gemcitabine, was stopped. A kidney biopsy was performed on May 31, 2017.

Biopsy Findings

The tissue for light microscopy contained 26 glomeruli; most of them had an ischemic and “bloodless” appearance. Arterioles and interlobular arteries showed prominent mucoid intimal thickening with obliteration of the lumen and fragmented red blood cells embedded in the thickened intima. There was evidence of acute tubular injury as well as mild interstitial edema.

Thirteen glomeruli were available for immunofluorescence; other than focal segmental smudgy fibrinogen staining in the glomeruli and arteriolar walls, no specific immunofluorescence findings were noted.

Two glomeruli were examined under the electron microscope. There was prominent diffuse subendothelial widening along the glomerular capillary loops with electron-lucent to amorphous material between the swollen endothelium and the GBM. Scattered electron densities were noted in the widened subendothelial space. Focally, platelet aggregates were noted in the glomerular capillary lumina. Endothelial tubuloreticular inclusions were not seen.

Follow-Up

After the renal biopsy, the patient started receiving eculizumab on June 6, 2017, with weekly doses of 900 mg IV. Her last gemcitabine dose of 1200 mg was given July 18, 2017. Her serum creatinine concentration decreased to 1.9 mg/dL by August 15 and to 1.4 mg/dL by October 2017. In August 2017, she started receiving FOLFIRI (leucovorin, 5-fluorouracil, and irinotecan). Since then, her serum creatinine has been stable, 1.3–1.6 mg/dL, until now. Recently, she was found to have a few pulmonary nodules suspicious for metastatic tumor.

Questions for Case 2

1. The glomerular changes are secondary to which of the following?
   A. Metastatic pancreas carcinoma
   B. Ischemia
   C. Endothelial injury
   D. Hypercoagulability
   E. Combination of B, C, and D

The patient developed thrombotic microangiopathy (TMA) secondary to gemcitabine treatment. Glomerular changes in TMA usually develop because of endothelial injury (endothelial swelling with loss of fenestration and subendothelial widening along the glomerular capillaries), hypercoagulability (fibrin or platelet thrombi), and ischemia (glomerular capillary wrinkling) secondary to obliterative changes in the arteries and arterioles.

2. The glomerular capillary in Image 9 contains which of the following?
   A. Platelets
   B. Polymorphonuclear leukocytes
   C. Tumor cells
   D. Fungi
   E. Fibrin

   The glomerular capillary in Image 9 is occluded by a platelet aggregate.

3. The morphologic findings are secondary to which of the following?
   A. Severe uncontrolled hypertension
   B. Gemcitabine treatment
   C. Metastatic pancreas carcinoma invading the renal vasculature
   D. C3 glomerulonephritis
   E. Vasculitis

   This patient has TMA. Gemcitabine is one of the most common causes of drug-induced TMA. The severe hypertension in this white woman was secondary to the TMA.

Discussion

Gemcitabine is a pyrimidine analog, which is commonly used to treat pancreatic cancers, some other gastrointestinal cancers, and lung carcinoma. Gemcitabine is now a well-recognized cause of TMA.[6,7] The incidence of gemcitabine-associated TMA was initially estimated to be 0.015%, but recently incidence as high as 0.4% was reported.[5] This could be the result of increased drug use as well as improved recognition of TMA. In our renal biopsy database, we encountered 20 cases of gemcitabine-induced TMA in the last 10 years (out of approximately 10,000 native kidney biopsies). Our experience is the same; during the last years, we have seen increasing numbers of renal biopsies with gemcitabine-induced TMA.

TMA does not appear immediately following the initiation of gemcitabine treatment, and there is usually several months of lag time (1–19 months in the literature) between starting the drug and the development of TMA.[5] It appears that the cumulative dose of gemcitabine plays a role in the pathogenesis. All patients present with worsening renal function, and most of them develop severe hypertension at the same time. Microangiopathic hemolytic anemia (MAHA) is common. However, MAHA is not present in all patients, and it may be completely absent in some of them. Reviewing our 20 cases, 13 patients had laboratory signs of MAHA; in seven patients, MAHA was not evident.

The pathogenesis of gemcitabine-induced TMA is unclear. It is likely that there is some degree of direct endothelial drug toxicity; however, recent data implicate the role of complement activation as well. Although most patients do not have low serum complement levels, serum levels of complement biomarkers (such as C5a, C4d, BB, and C5b-9) are frequently increased.[8] Therefore, more and more centers started to use the C5-inhibitor monoclonal antibody eculizumab to treat patients with gemcitabine-induced TMA.[9-11] Although larger series are not available yet, most of the case reports and case series indicate surprisingly good results. This reflects our experience as well. Two patients were published from our center who recovered after eculizumab treatment,[10] and we have other successfully treated patients since this publication. It appears that complement activation plays a role not only in obvious complement-mediated forms of TMA (forms of TMA associated with congenital or acquired abnormalities of the alternate complement activation pathway), but also in many other forms of TMA that were originally not felt to be associated

with abnormal complement activations, such as drug-induced TMA, antiphospholipid antibody syndrome, other autoimmune diseases (we have seen scleroderma renal crisis resolving after eculizumab treatment), transplant-associated TMA, and even thrombotic thrombocytopenic purpura (TTP). It is likely that complement activation plays a crucial role in the pathogenesis of severe vascular injury in TMA disregarding the underlying etiology. Also, most forms of TMA likely represent a multifactorial disease. There is likely a genetic predisposition (such as abnormalities in the genes regulating alternate complement pathway activation) as well as environmental factors, including drugs, and superimposed diseases, such as malignancies, autoimmune diseases, inflammatory diseases, and severe hypertension. At our institution, eculizumab is given to patients with TMA if abnormal complement activation is suspected before the results and workup for alternate complement pathway abnormalities are back. Our patient, presented here, did not undergo genetic workup for alternate complement pathway abnormalities, but other patients did with negative results.[10]

Differentiating between antineoplastic drug-associated TMA (such as from gemcitabine) and cancer-associated TMA can be quite difficult.[5] However, this distinction is important because of therapeutic implications. In cancer-associated TMA, the antineoplastic treatment should not be stopped. Cancer-associated TMA usually occurs in patients with widespread metastatic disease, the renal involvement is less prominent than in chemotherapy-associated TMA, signs of disseminated intravascular coagulopathy are more common than in chemotherapy-induced TMA, and the clinical presentation in cancer-associated TMA is frequently that of TTP rather than atypical hemolytic uremic syndrome.

References

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Case 3 from Ritambhra Nada Duseja, MD, MBBS, Postgraduate Institute of Medical Education and Research, Chandigarh, India

A 48-year-old male patient presented with fever and vomiting he'd been experiencing for 10 days. He was diagnosed as hepatitis C virus (HCV+) positive (genotype 1a, 2,993,036 IU/mL) and given the direct-acting antivirals (DAAs) sofosbuvir and ledipasvir. Within a week of starting DAAs, he developed rapidly progressive renal failure and a papulosquamous rash on his palms; a skin biopsy confirmed leukocytoclastic vasculitis.

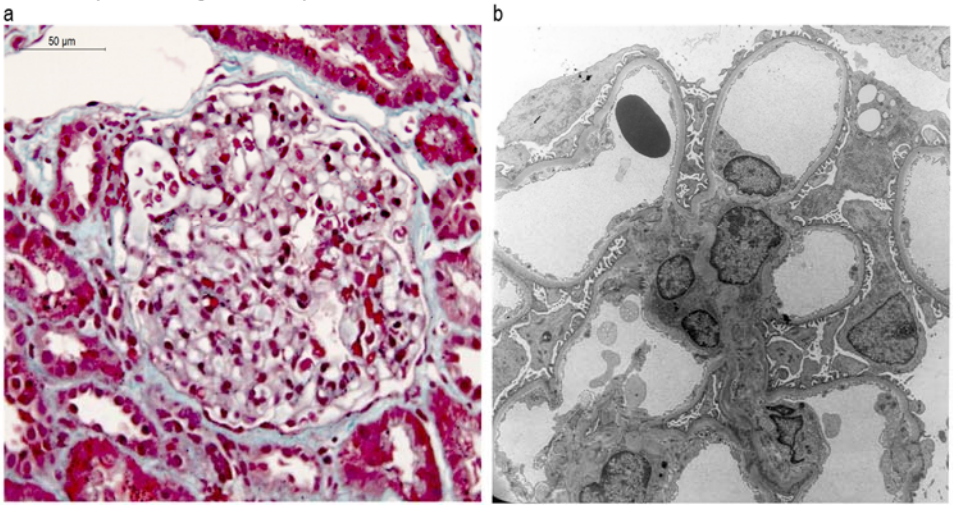
The patient had no history of cola-colored urine, decreased urine output, froth in the urine, pedal edema, facial swelling, or hematuria. There was no other pertinent history associated with review of systems, including diabetes mellitus or hypertension. His mother had hepatitis C–positive chronic liver disease with esophageal varices; she had completed treatment with DAAs and was HCV RNA negative. Physical exam results for the patient were essentially normal, and his BP was 130/90 mm Hg. Laboratory tests yielded the following:

Hemoglobin	12 g/dL
White blood cell count	8100/mL
Platelets	306,000/µL
Vitamin D	44 ng/mL
PTH	8.9 pg/mL
Ratio of blood urea nitrogen to creatinine	105/2.39 mg/dL
Calcium	11.7–10.9 mg/dL
Total protein	6.8 g/dL
Albumin	3.59 g/dL
Total bilirubin	0.45 mg/dL

Urinalysis was normal with no significant proteinuria and negative for paraproteinemia. Levels of C3 and C4 were normal; test results were negative for cryoglobulins and malarial parasite. An ultrasound of the abdomen revealed a fatty liver, mildly raised renal echogenicity, right kidney 12.9 cm, left kidney 11.2 cm, and bilateral acute parenchymal disease.

Liver enzymes were within normal limits. A kidney biopsy was performed.

Question 2 (Case 3 Image 1 a and b)



(a) Glomeruli showed normal histology. (b) Immunofluorescence was negative, which was confirmed by absence of immune complexes on electron microscopy. No tubulo-reticular inclusions were seen.

Questions for Case 3

1. In a patient who is HCV positive, which renal biopsy finding could be expected?
   A. Glomerular lesions, i.e., immune complex–mediated membranoproliferative glomerulonephritis (MPGN)/cryoglobulinemia and IgA nephropathy
   B. Hypovolemic AKI
   C. Embolic from infective endocarditis
   D. Drug-induced injury
   E. All of above

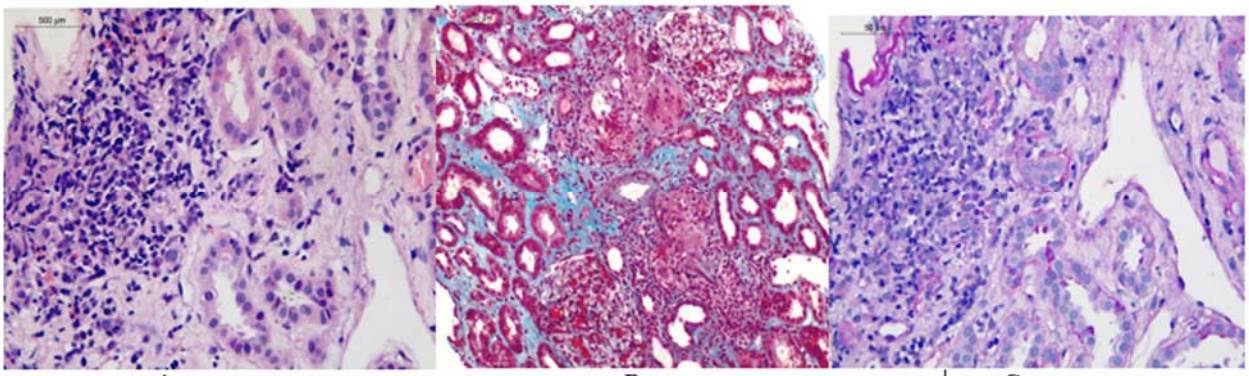
   In HCV-positive patients, renal biopsies can have glomerular, tubulointerstitial, and vascular involvement. Glomerular involvement can be in the form of immune complex–mediated MPGN, which may have hyaline thrombi of cryoglobulins. Membranous nephropathy and IgA nephropathy with mesangioproliferative pattern or HCV-associated thrombotic microangiopathy are other possibilities. In chronic disease states, patients can have nonbacterial thrombotic endocarditis, which is a common source of emboli resulting in focal necrotizing glomerulonephritis or mesangiolytic glomerulopathy. Pre-renal acute tubular injury due to volume depletion is a common cause of renal dysfunction in patients with liver diseases. Tubular injury due to bile cast nephropathy in settings of acute or acute-onset chronic liver failure also needs to be considered. Because these patients are receiving treatment for HCV and related complications, drug-induced injury can appear in renal biopsies. Cryoglobulinemic MPGN can have accompanying cryoglobulinemic vasculitis.

2. Which does the renal biopsy show?
   A. Interstitial nephritis suggestive of drug-induced injury
   B. Granulomatous tubulointerstitial nephritis and acute tubular injury
   C. Tubulitis with interstitial nephritis
   D. All the above

   Figure A reveals the presence of interstitial nephritis with eosinophils and edema. Figure B shows the presence of non-necrotizing epithelioid cell granuloma with giant cells distributed along the small artery. The giant cells do not show asteroid bodies or any other inclusions. Figure C reveals the presence of tubulitis and edema. There is no evidence of nephrocalcinosis.

   Overall features based on non-necrotizing naked granulomas, the absence of nephrocalcinosis, and inclusions in the giant cells were suggestive of drug-induced granulomatous tubulointerstitial nephritis (GTIN).

   Dominant findings in the renal biopsy were as seen in Case 3 - Images 2a, 2b, and 2c (Question 2).



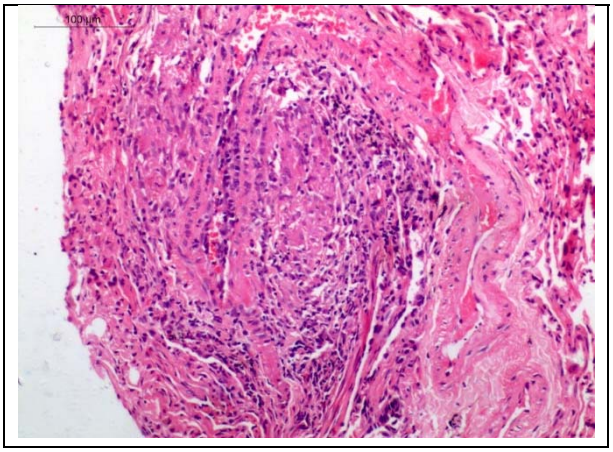
A B C

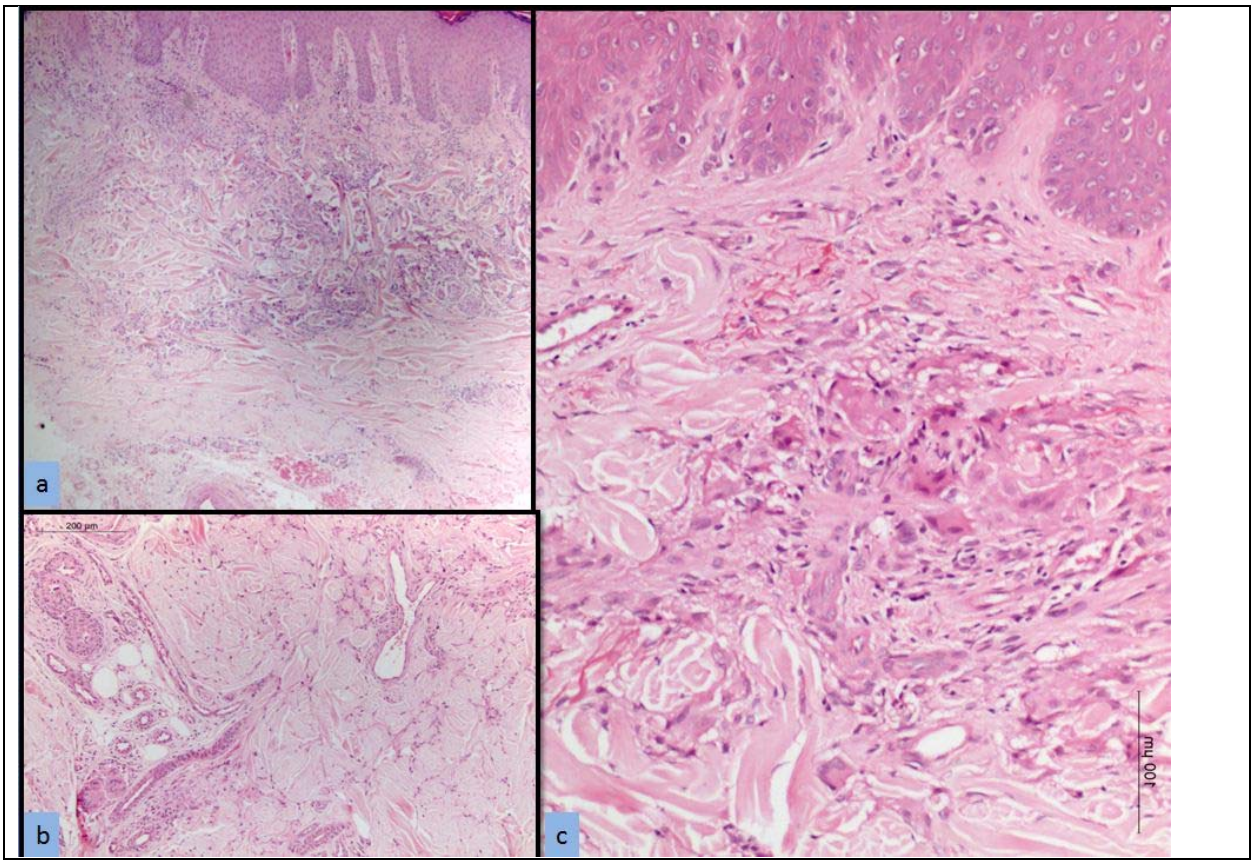
3. Which effect does the direct-acting antiviral drugs used in this case have?
   A. Do not cause AKI
   B. Can cause acute tubulointerstitial nephritis
   C. Can cause granulomatous tubulointerstitial nephritis (GTIN)
   D. Can cause glomerular lesions

   According to available literature, AKI is reported in 1%-15% of patients with HCV who are treated with sofosbuvir. Histology shows acute interstitial nephritis; GTIN has not been reported,[1-2] even though granulomas can be seen in any drug-induced interstitial nephritis. The temporal correlation of the onset of AKI after initiation of treatment with DAAs was so compelling that sofosbuvir was stopped after 13 days (after the biopsy report of drug-induced granulomatous inflammation). This meant long-term harm to the patient because it resulted in denial of treatment for presently curable HCV. The amoxicillin and paracetamol that the patient had taken for fever do not cause GTIN.

4. Which morphological feature is not correct in terms of GTIN?
   A. Tubercular granulomas are ill-defined granulomas with caseous necrosis.
   B. Sarcoid granulomas are compact non-caseating epithelioid.
   C. Granulomas tend to be along vessels in granulomatous polyangiitis.
   D. Drug-induced granulomas do not have epithelioid cells.

   Drug-induced granulomas can have loose collections of epithelioid cells. In fact, other than demonstrable organisms, no morphologic clues seem to be diagnostic of GTIN. Compact sarcoid-like granulomas can be seen in tuberculosis, and non-caseating granulomas in an immunosuppressive setting can show tubercular bacilli. DAAs were stopped, but his fever did not respond, his serum creatinine concentration increased, and his skin lesions also progressed. Further investigations were done to find out the cause of his persistent fever. High-resolution CT (non-contrast) revealed mediastinal and bilateral hilar lymphadenopathy with pulmonary nodules. There were no pulmonary symptoms. A transbronchial biopsy and repeat skin biopsy were done. A lung biopsy showed compact non-caseating epithelioid cell granuloma with giant cells in the interstitium. No organism could be demonstrated by special stain.





Diagnosis

The patient had GTIN associated with sofosbuvir treatment for hepatitis C infection.

Discussion

Overall features based on non-necrotizing naked granulomas, the absence of nephrocalcinosis, and inclusions in the giant cells were suggestive of drug-induced GTIN.

Drug-induced granulomas can have loose collections of epithelioid cells. In fact, other than demonstrable organisms, no morphologic clues seem to be diagnostic of GTIN. Compact sarcoid-like granulomas can be seen in tuberculosis, and non-caseating granulomas in the immunosuppressive setting can show tubercular bacilli.[1] In our index case, because there was significant temporal correlation of the onset of renal dysfunction with treatment with the DAAs sofosbuvir and ledipasvir, drug-induced GTIN was considered.

According to available literature, AKI is reported in 1%-15% of patients with HCV who are treated with sofosbuvir. Histology shows acute interstitial nephritis; GTIN has not been reported,[2-3] even though granulomas can be seen in any drug-induced interstitial nephritis. Drug-induced sarcoid-like reactions (DISRs) have been reported with other drugs, especially immune checkpoint inhibitors, highly active antiretroviral therapy, interferons, and tumor necrosis factor-α antagonists.[4] They have not been reported with the DAAs sofosbuvir and ledipasvir. DISRs are clinically indistinguishable from sarcoidosis, mainly manifesting as pulmonary or cutaneous lesions. It usually occurs within months of initiation of these drugs and improves after the offending drugs are discontinued. In life-threatening situations, the offending drug can be continued despite DISRs and treatment given for sarcoidosis.

Stopping sofosbuvir after 13 days (after the biopsy report of drug-induced granulomatous inflammation) meant long-term harm to the patient because it resulted in denial of treatment for presently curable HCV. The amoxicillin and paracetamol that the patient had taken for fever do not cause GTIN.

Follow-Up

DAAs were stopped, but his fever did not respond, his serum creatinine concentration increased further, and his skin lesions also progressed.

Further investigations were done to find out the cause of his persistent fever. As part of a workup for granulomatous inflammation, high-resolution CT (non-contrast) revealed mediastinal and bilateral hilar lymphadenopathy with pulmonary nodules. There were no pulmonary symptoms. A transbronchial biopsy was done. A lung biopsy showed compact non-caseating epithelioid cell granulomas with giant cells in the interstitium. No organism could be demonstrated by special stain.

A skin biopsy revealed the presence of epithelioid cell collections along with giant cells in the upper dermis and perivascular giant cells in the lower dermis.

There was granulomatous inflammation in kidney, lungs, and skin, but a Ziehl–Neelsen stain for tubercular bacilli in all these tissues was negative. A Mantoux test result was not reactive; sputum for acid-fast bacilli was negative. GeneXpert results from a lung biopsy for tubercular bacilli were also negative. The patient had hypercalcemia and elevated levels of angiotensin-converting enzyme. High-resolution CT had shown mediastinal lymphadenopathy with pulmonary nodules. Hence, it was a case of sarcoidosis, which first manifested as AKI in the form of GTIN precipitated by coexisting volume depletion–associated tubular injury resulting from vomiting. The patient was given steroids, his fever subsided, and his creatinine value showed a downward trend. DAAs were restarted, and complete remission of HCV was achieved. The patient was saved from further denial of HCV treatment.

Cases of GTIN comprise 0.5%-0.9% of all native kidneys and 0.6% of allograft biopsies.[3] Associated causes differ according to region; infections are more often seen in developing counties.[5-6]

GTIN due to sarcoidosis is underreported because of a lack of guidelines for investigating other organs in pulmonary sarcoidosis.[7] Renal involvement in sarcoidosis significantly adds to morbidity. On systematic investigation of extrapulmonary organs, renal involvement has been evaluated in only three large series.[8-10] These series reported renal sarcoidosis in a wide range varying from 1% to 30%-50% of patients. In an autopsy series, 7%-30% patients had renal involvement, which may be clinically silent.[11-12]

The most common renal manifestation is gTIN; other manifestations can be nephrocalcinosis, renal mass, and secondary AA amyloidosis.[7] Patients with GTIN tend to present with advanced stage (CKD stage 5) in contrast with those with non-GTIN, who present with CKD stage 1 or 2.[10]

Most patients with sarcoidosis with GTIN present with extra-renal manifestation, which can be pulmonary, ocular, or dermatologic.[13-16] Only few series report GTIN without extrarenal involvement.[17-18] Some cases diagnosed as GTIN were subsequently diagnosed as sarcoidosis, as in our index case.[13,19-21]

GTIN can be the first manifestation of systemic diseases like sarcoidosis, and early diagnosis is important.[22] In addition to contributing to a diagnosis, renal biopsy in sarcoidosis also helps in prognostication because the granulomatous presentation accompanies higher creatinine values and advanced tubulointerstitial fibrosis.[7]

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Case 4 from Steven Salvatore, MD, Weill Cornell Medicine, New York

A 65-year-old white woman with a 35-year history of rheumatoid arthritis (RA) and hypothyroidism was referred to a nephrologist when her rheumatologist noted her serum creatinine was elevated at 1.7 mg/dL; the value had been trending up from 1.4 mg/dL 7 months previously and 1.5 mg/dL 2 months ago. Prior laboratory values were not available.

The patient noted chronic joint pains from her RA, which was currently well maintained. She denied usage of nonsteroidal anti-inflammatory drugs, but over the years, she received multiple regimens, including methotrexate for a number of years. More recently, she took adalimumab for the past year and a half, and it was managing her symptoms well. She also took levothyroxine and zolpidem.

On examination, she was found to have stiff wrists with a decreased range of motion. The remainder of her exam was unremarkable. She did not have rash or significant edema. Her BP was elevated at 150/70 mm Hg, and she was not previously known to be hypertensive.

Laboratory findings at the time of her office visit included the following:

White blood cell count	6500/µL
Hemoglobin	8.9 g/dL
Platelets	476,000/µL
Creatinine	1.66 mg/dL
Glucose	91 mg/dL
Albumin	3.6 g/dL

A urinalysis revealed large blood (with red blood cell casts) and 100 mg/dL protein. Quantification of proteinuria was approximately 2 g/24 h.

Additional serologies included the following: rheumatoid factor positive, antinuclear antibody (ANA) positive (1:640), double-stranded (ds) DNA positive, complements normal, negative for hepatitis B (HBV) and hepatitis C (HCV), perinuclear ANCA (pANCA) positive (anti-myeloperoxidase [MPO] 38), cytoplasmic ANCA (cANCA) positive (anti-proteinase 3 [PR3] 64).

A kidney biopsy was performed.

Biopsy Findings

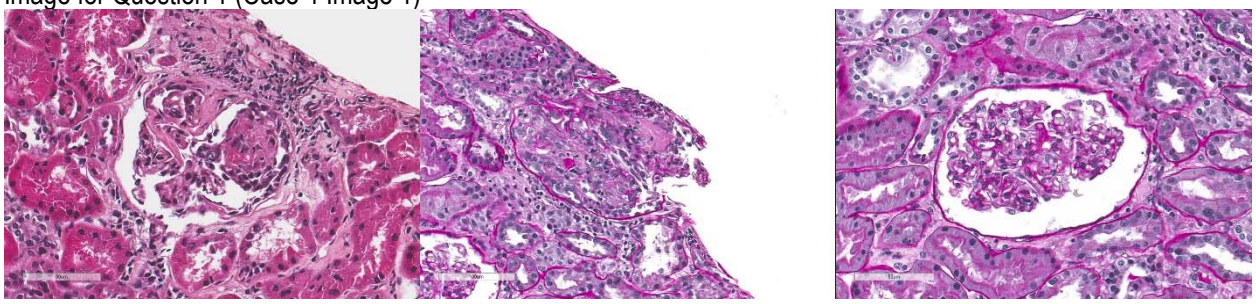
The biopsy showed two cores of cortex and deep cortex with up to 12 glomeruli, 2 of which had fibrinoid necrotizing lesions with cellular crescents, 2 cellular crescents, 3 fibrocellular crescents, and 1 fibrous crescent. The remaining glomeruli did not show significant hypercellularity, and the immunofluorescence (IF) and electron microscopy (EM) findings were negative for deposits.

Questions for Case 4

1. Based on the glomeruli seen in the biopsy (three shown in Image 1), in a patient with a complex clinical presentation that includes multiple positive serologies (ANA, dsDNA, rheumatoid factor, ANCAs), which statement must be true?
   A. With a positive ANA and segmental crescents, the patient has focal lupus nephritis (International Society of Nephrology/Renal Pathology Society [ISN/RPS] class III) with crescents.
   B. With some normal glomeruli and a negative IF study, the patient has pauci-immune crescentic glomerulonephritis.
   C. Because both cANCA and pANCA are positive, they can both be ignored as false positives and are not related to the pathology seen.
   D. Anti-GBM antibody should be tested in this patient because of the focal nature of the crescents.

   The images show acute crescents in two glomeruli (one of which has active necrosis) and a normal glomerulus in the third image. This is a case of pauci-immune crescentic glomerulonephritis (CrGN) despite some positive lupus serologies. The point of the question is to differentiate between etiologies of CrGN using the biopsy pathology; specifically, the fact that uninvolved glomeruli are normal combined with no staining on IF would make the diagnosis pauci-immune CrGN. The other choices are distractors.

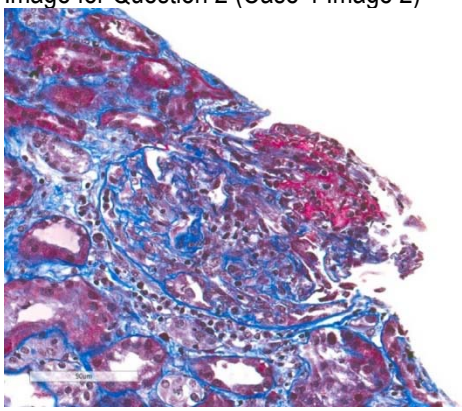
   Image for Question 1 (Case 4 Image 1)



2. In a patient with the glomerular disease depicted in Image 2 and positive cANCA, pANCA, ANA, and dsDNA with no history of systemic lupus, what additional history should be considered as a possible cause of the renal injury?
   A. History of recent PD-1 inhibitor chemotherapeutic usage
   B. History of recent antibiotic use, especially cephalosporins
   C. History of recent mycobacterial, nocardia, or listeria infection
   D. History of recent usage of tumor necrosis factor α (TNF-α) inhibitor, cocaine, or hydralazine

   The glomerulus shows an acute necrotizing crescent. In a patient without lupus who presents with positive pANCA, cANCA, and lupus serologies, you should consider and inquire about drug-induced vasculitis or lupus. Answer D includes medications or adulterants in illicit drugs that may induce these serologies.

Image for Question 2 (Case 4 Image 2)



3. Which kidney biopsy finding may be seen in a patient with RA?
   A. Crescentic glomerulonephritis
   B. Mesangial proliferative glomerulonephritis
   C. Secondary amyloidosis
   D. Membranous glomerulonephritis
   E. All the above

   All of the patterns of glomerular disease mentioned above may be seen in the setting of RA, with mesangial proliferative GN and secondary AA amyloidosis being the most common renal lesions.

Diagnosis

This patient had acute, subacute, and chronic crescentic glomerulonephritis (CrGN), pauci-immune type, pANCA and cANCA positive, in the setting of a tumor necrosis factor α (TNF-α) antagonist.

Discussion

In the kidney biopsy, the pathologic differential diagnosis is relatively straightforward. By light microscopy, there is an active necrotizing CrGN in a patient who presented with nephritic syndrome. Pathologically, CrGN can be divided into three main types, immune complex–mediated, pauci-immune, or anti-GBM etiology, which can then be differentiated by IF findings. In this case, the lack of immune complexes or linear IgG staining leads to the diagnosis of pauci-immune type, which is further supported by positive ANCA serologies. The larger implications for our case concern both a clinical perspective (what is leading to the underlying etiology?) and a biopsy to differentiate between drug-induced vasculitis and lupus nephritis (because of overlapping serologies).

Inhibitors of TNF-α have proven to be effective at managing symptoms related to RA as well as other autoimmune conditions. However, an increased use of these agents has led to an increased detection of adverse effects, which in rare cases may include kidney disease. Clinical vigilance by the rheumatologist and nephrologist, as well as knowledge of the relevant adverse effects, is important to detect potential iatrogenic, medication-induced renal injury and reverse the course at an early stage.

To date, there are five agents currently marketed to block TNF-α. Etanercept (Enbrel) is a soluble TNF-α receptor blocker that competitively inhibits TNF-α. The other agents, infliximab (Remicade), adalimumab (Humira), and newer drugs golimumab (Simponi) and certolizumab (Cimzia), are all monoclonal antibodies to TNF-α. By inhibiting an important immunology cytokine in the native immune system, TNF-α agents may increase the risk of infection or reactivation of latent infection such as mycobacteria tuberculosis, which is a well-described adverse effect. At the same time, dysregulation of the immune system may lead to induced autoimmunity and potential renal disease, which have been described in the literature.

Several case reports and series, briefly summarized in Table 1, have been published to date on patients, mostly with RA as well as inflammatory bowel disease, who developed positive serologies and subsequent clinical manifestations: positive ANA/dsDNA and low complements clinically resembling systemic lupus erythematosus (SLE), positive ANCA serologies, and vasculitic symptoms. Many patients develop positive serologies in the absence of clinical renal or systemic symptoms, with positive ANA in up to 29%-77% of patients and positive dsDNA and ANCAs in lower frequency. The importance of identifying the offending medication is critical because withdrawal of the medication typically causes resolution of the auto-antibody; however, in about half of the cases, the patients' renal failure is irreversible.

Report	Patient and Medications	Serology	Kidney Biopsy
Doulton 2004	32-year-old F, etanercept	MPO-ANCA and ANA	CrGN
Ashok 2008	31-year-old M, infliximab	PR3-ANCA and ANA	CrGN
Saint Marcoux 2006	39 patients; etanercept, infliximab, or adalimumab	ANA (22), low complements (6), ANCA (5)	CrGN in 3
Simms 2008	62-year-old F, adalimumab	ANA and cANCA	CrGN
Fournier 2009	58-year-old F, adalimumab for 4 y	MPO-ANCA	CrGN
Kaneko 2010	2 patients, etanercept	MPO-ANCA, ANA	CrGN
Hirohama 2010	33-year-old F, infliximab	MPO-ANCA	CrGN
Reitblat 2013	2 patients, etanercept and infliximab for 7 and 5 years	PR3-ANCA (1) and MPO-ANCA (1)	CrGN (1) and skin vasculitis only (2)
Stokes 2005	5 patients; etanercept, infliximab, and adalimumab	ANA (4), low C3/C4 (2), ANCA (2)	2 LN, 2 CrGN, 1 MGN
Mor 2005	22-year-old F, etanercept for 4 y	ANA/dsDNA, low complements	Class IV LN
Shakoor 2002	4 patients, etanercept for 6 wk to 14 mo	ANA, dsDNA	No renal disease
Mohan 2002	16 patients, etanercept	ANA, dsDNA	No renal disease
Sokumbi 2012	8 patients; etanercept, infliximab, or adalimumab	NR	Mostly cutaneous, 1 kidney biopsy with IgAN
Debandt 2003	3 patients with RA; 2 etanercept, 1 infliximab	All ANA, 2 dsDNA	No renal disease (skin and joints only)
ANA, antinuclear antibody; CrGN, crescentic glomerulonephritis; ds, double-stranded; F, female; LN, lupus nephritis; M, male; MGN, membranous glomerulonephritis; MPO, myeloperoxidase; NR, not reported; PR3, proteinase 3; RA, rheumatoid arthritis.			

Table 1: Published reports of anti–TNF-α–associated vasculitis or autoimmune diseases. The CrGNs listed all related to pauci-immune.

In our biopsy practice at Weill Cornell Medicine, we have had a similar experience in kidney biopsy findings from patients who are taking TNF-α inhibitors. Over the past 15 years, we have seen biopsies for 48 patients who were known to be taking TNF-α antagonists. Five patients (including this case) were diagnosed with pauci-immune CrGN. Four of the five cases have had positive MPO-ANCA serologies, one case of which also had PR3-ANCA, and one case was ANCA negative. Of these cases, three additionally had positive ANAs, including two that also had positive dsDNA. We have seen one biopsy revealing ISN/RPS class III plus class V lupus nephritis in a patient who developed a positive ANA and dsDNA but normal complements while taking etanercept. Of note, in this same cohort, four patients also developed active or chronic thrombotic microangiopathy, which is not widely reported in the literature but may also have some connection to induced autoimmunity such as that to antiphospholipid antibodies.

TNF-α is a cytokine with an important role in the inflammatory response and host defense, but as such, it also has a deleterious role in autoimmune conditions such as RA with an increased inflammatory response. Therefore, inhibition

of TNF-α is a prime target for treating these patients. Inhibition of TNF has also been reported in induced autoimmune diseases, including SLE and vasculitis. A postulated explanation is that an impaired balance between CD4+ T-helper cells from Th1 to Th2 leads from an RA to an SLE phenotype and is potentially responsible for various autoantibody development—but further work is still needed in this area.

Clinical Considerations in This Case

In addition to those caused by TNF-α inhibitors, other drug-induced autoimmune diseases may become clinically apparent with renal presentation in patients who are taking hydralazine, minocycline, propylthiouracil, or levamisole. Hydralazine can induce serologies and occasionally diseases resembling both SLE and ANCA, particularly in patients who are "low acetylators." Minocycline has been known to induce a positive ANA and ANCA. Propylthiouracil treatment may lead to positive pANCA but usually not ANA. Levamisole, an anti-helminthic agent, has received more recent attention in the literature because of its rather ubiquitous inclusion in various preparations of cocaine. The adulterant, not the cocaine itself, may cause patients to develop positive serologies, including to one or both ANCAs, ANA, and antiphospholipid antibodies. As a general rule, a patient who does not have SLE and develops positive serologies in later adulthood, particularly with both positive ANCAs, should trigger a clinical investigation of an implicated drug-induced autoimmunity.

Other Kidney Lesions in RA

Nephrologists, rheumatologists, and pathologists must be cognizant of other renal diseases in patients with RA. Several glomerular diseases are known to exist in RA with various patterns of injury including mesangial proliferative glomerulonephritis (including the possibility of mixed connective tissue disease overlap or IgA-dominant deposits), secondary AA amyloidosis from recurrent inflammation, or in some cases even ANCA-positive pauci-immune CrGN. Because patients with a known autoimmune disease, RA, are at risk of developing other autoimmune conditions, such as lupus-like glomerulonephritis or ANCA antibodies even in the absence of a drug-induced trigger, it becomes more difficult to clearly and definitively implicate a TNF-α inhibitor as causative. Studies such as the ones above, which demonstrate a temporal relationship to the medication and renal disease, induction of serology, and resolution of auto-antibodies after cessation of the medication are useful at implying a causal association.

Follow-Up on This Patient

After a biopsy, the adalimumab was discontinued, and the patient was given pulse steroids and rituximab. At 6 months, her BP had normalized, the dsDNA was negative, and the ANA was at 1:160. Her anti-PR3 was negative and anti-MPO decreased from 38 to 28. The patient's creatinine had decreased from a maximum of 2.4 mg/dL to 1.48 mg/dL. She was last seen in clinic 3 years after her initial presentation with a creatinine value of 1.24 mg/dL. Her urinalysis was bland and ANA, dsDNA, and ANCAs were all negative. Rheumatoid factor remained positive.

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Case 5 from Guillermo A. Herrera, MD, FASN, Louisiana State University Health Sciences Center, Shreveport

A 45-year-old muscular man with hypercholesterolemia and hypertension controlled with diet presented to the emergency department "feeling bad and weak" and was found to be in renal failure of unknown etiology. No history of systemic disorders was elicited. No family history of renal diseases was discovered. The patient denied use of illicit drugs. The only medication he was taking was atorvastatin (40 mg/d). He had been taking atorvastatin for 83 days.

Laboratory workup showed increased levels of blood urea nitrogen (35 mg/dL) and serum creatinine (9 mg/dL). His GFR was 25 mL/min/1.73 m^2. Urinary sediment revealed numerous casts, microscopic hematuria without dysmorphic red blood cells, and leukocyturia. The patient's creatine phosphokinase (CPK) value was in the upper limits of normal, and no myoglobin was found in the urine. A urine screen for drugs was negative.

A renal biopsy was performed.

Questions for Case 5

1. Which is not a cause of acute myoglobinuric renal failure?
   A. Medications
   B. Cocaine use
   C. Strenuous exercise
   D. Genetic mutations in myoglobin
   E. Trauma

   Causes of acute myoglobinuric renal failure include strenuous exercise, cocaine use, skeletal muscle trauma, and certain medications, in all these situations related to muscle damage. Normally, myoglobin is loosely bound to plasma proteins and only small amounts are delivered to the kidneys. When massive amounts of myoglobin are released, the binding capacity of the plasma protein is exceeded. As a result, myoglobin reaches glomeruli, is filtered through peripheral capillary walls, and is delivered to the tubules, where it may obstruct distal nephrons and lead to renal failure. Direct proximal tubular damage by myoglobin degradation products may also contribute to renal failure. Renal ischemia, volume depletion, and hypotension can potentiate acute myoglobinuric renal failure.

2. Which is not a light microscopic feature of acute myoglobinuric renal failure?
   A. Pigmented tubular casts in distal nephrons
   B. Necrotizing glomerular changes
   C. Tubular injury
   D. Patchy interstitial inflammation that may include eosinophils
   E. Interstitial edema

   Glomeruli are spared in acute myoglobinuric renal failure. They may reveal nonspecific reactive changes but are most commonly essentially normal.

3. Myoglobin casts may exhibit characteristic ultrastructural features best described as which of the following?
   A. Fracture planes in casts and surrounding tubular cell reaction
   B. Markedly electron-dense material, often with rounded edges
   C. Polymorphonuclear cells and cellular debris
   D. Crystalline material
   E. Fine electron-dense material with striations

The myoglobin tubular casts are rather characteristic. They are markedly electron-dense and typically display rounded edges. They show no crystals, lack fracture planes (as in "myeloma" casts), and do not contain polymorphonuclear cells.

4. Which factor is related to the reason for statins' association with acute myoglobinuric renal failure?
   A. Administration of a high-dose statin
   B. Low serum levels of acetylcholinesterase
   C. Level of hypercholesterolemia when treatment is started
   D. Obesity
   E. Hypertension

   The association of statins with acute myoglobinuric renal failure has been a subject of scrutiny. Individuals taking high-dose statins may develop acute myoglobinuric renal failure. This potential is accelerated when other coexisting conditions exist, such as use of contrast. In a large study, those individuals who took higher doses of statins were more likely to be hospitalized for AKI during the first 120 days of treatment, compared with those taking lower dosages. Risk remained elevated 2 years after starting treatment.

Diagnosis

This patient had acute myoglobinuric renal failure; we discuss the importance of clinicopathologic correlation and pathogenesis.

Discussion

The typical clinical presentation is acute renal failure. Approximately 5%–10% of patients with acute renal failure have rhabdomyolysis and myoglobinemia or myoglobinuria. The renal pathologist must have a high index of suspicion to make the diagnosis of myoglobinuric renal failure. The clinical presentation is generally that of acute renal failure of unknown etiology, though in some cases, an increased serum CPK or the finding of myoglobin in the urine may suggest underlying rhabdomyolysis. It should be pointed out that the actual CPK level may be quite variable in these patients depending on the degree of muscle damage and how much time it takes to measure the CPK from the episode that led to the renal failure. Some cases have a normal CPK. In many cases, the clinical history may not include any hints to the underlying process, and the renal pathologist must carefully find clues to pursue this diagnosis and then investigate possible etiologies by reviewing the clinical history with the nephrologist.

It has been reported that rhabdomyolysis is the underlying cause of acute renal failure in as many as 7%–15% of all cases in the United States. The increased circulating myoglobin may directly produce proximal tubular damage or may be delivered to the distal nephron where cast formation occurs. The latter mechanism of renal damage is favored. The myoglobin-containing casts induce the release of free radicals may lead to vasoconstriction, resulting in additional ischemic insults to the proximal tubular epithelium.

The specific significance of proximal tubular damage due to myoglobin remains unclear, though the majority of the cases exhibit some degree of detectable tubular damage and myoglobin can be localized to the cytoplasm of proximal tubular cells in a significant number of cases. Myoglobin degradation products have been found to be toxic to the tubular epithelium.

Rhabdomyolysis is the main underlying condition associated with this entity. There are a number of underlying etiologies and preexisting conditions, such as medication use (including illicit drugs like cocaine, heroin, opium, and opioids and polydrug use), trauma, multiorgan failure, dehydration, HIV, pancreatitis, sepsis, infection, obtundation (being found unconscious), chemotherapy, myopathies, intense strenuous physical activity, malignant hypertension, postsurgery complications, and wasp stings, among others. To link the renal biopsy findings to these underlying or preexisting conditions, extensive questioning of the patients may be necessary.

The findings in the renal biopsies may be subtle or confusing, eliciting other diagnosis. The presence of tubular casts with pigmentation (often yellow to brown tinged), or with other “unusual” colors such as red or pink, should alert the pathologist to order an immunohistochemical stain for myoglobin to determine the nature (content) of the casts. Myoglobin casts are not associated with fracture planes or reaction of the surrounding tubular cells or multinucleated giant cells in the adjacent interstitium. No polymorphonuclear cells are present in these casts. Furthermore, the tubular casts may be only a focal finding in the biopsy specimens, and in small biopsies only a couple of casts may be found.

It is also common to see in these cases a mild and patchy interstitial inflammatory infiltrate composed predominantly of mononuclear cells and sometimes eosinophils associated with focal tubulitis and tubular injury. Glomeruli are either unremarkable or slightly reactive with segmental mesangial expansion, and the biopsy may reveal findings related to vascular nephrosclerosis but no findings directly related to the myoglobinuric process responsible for the acute renal failure in any of these two other renal compartments.

Immunofluorescence is entirely negative in most cases, and in some there may be granular C3 mesangial staining.

Ultrastructurally typical myoglobin casts are markedly electron-dense and exhibit rounded edges, but because of fragmentation and other interactions with Tamm-Horsfall protein, they may reveal other less diagnostic appearances. The appearance of the tubules casts is so classical that when found, they can be trusted to indicate the presence of myoglobin in them.

The differential diagnosis can be quite extensive. In some cases, because of the prominent tubular damage, a diagnosis of acute tubular necrosis is rendered if the myoglobin casts are not detected. In other cases, because of the inflammatory changes, a diagnosis of acute tubulointerstitial nephritis is rendered, and in those cases with eosinophils, a drug reaction is suspected. There are also cases where the renal pathologist does not see enough changes in the biopsy to explain the acute renal failure, failing to link the importance of myoglobin in the pathogenesis of the renal failure. This link becomes more important when, as is true in only a minority of the cases, there is an increase in CPK or myoglobin in the urine. The classic clinical triad of muscle pain, weakness, and dark urine is often absent in these cases. Some pathologists do not fully recognize the value of using the immunohistochemical stain for myoglobin essentially as a screening test.

A variety of clinical interventions are documented in the literature to treat this condition. These include IV volume expansion to prevent hypotension and renal hypoperfusion and promote brisk urine flow, correction of any electrolyte disturbances that may be present, and urine alkalinization. These measures should help destruction of existing tubular casts and prevention of additional ones. Loop diuretics have also been used if the patients develop hypervolemia.

Anecdotally, the majority of the patients affected recover renal function as the tubules regenerate and return to baseline (in terms of serum creatinine concentration and GFR), but chronic renal failure has been documented in a significant number of cases. Recovery depends on the nature of insult, preexisting conditions (including degree of vascular nephrosclerosis and other renal diseases), and time from insult to therapeutic intervention. It should be noted, however, that in one study, 45% of the patients fully recovered renal function while an identical percentage was left with some degree of chronic renal failure. The remainder of the patients in the study died, presumably as a result of complications of the underlying disease, not necessarily acute myoglobinuric renal failure, though it likely contributed to the outcome.

In the case presented here, statins were immediately discontinued and after 2.5 weeks, the patient recovered renal function, with a serum creatinine of 1.3 mg/dL documented on day 17 after admission. The patient required dialysis for 10 days because he was markedly oliguric. Follow-up 2 years later revealed a serum creatinine of 1.1 mg/dL and a GFR >60 mL/min/1.73 m^2.

Statins have been shown to benefit in the prevention of cardiovascular disease. The documented risks associated with the use of statins most notably include liver damage, muscle pain, and weakness. Renal damage in the form of acute renal failure has been somewhat controversial. There are publications highlighting a beneficial role for statins in patients with chronic renal failure.

There has been a trend to increase the potency of statin treatment by using larger doses of simvastatin or atorvastatin (40-80 mg), or using even more potent statins such as rosuvastatin, to achieve better control of hypercholesterolemia. Potency is equaled with the ability of the drug to reduce absolute LDL cholesterol. Increased use of higher-potency statins stemmed from the outcomes of clinical trials during which they improved cardiovascular outcomes more than the lower-potency statins did. From statins, the AKI has been attributed to rhabdomyolysis, though this hypothesis requires more investigation. It has been reported that individuals taking higher doses of statins were 34% more likely to be hospitalized for AKI during the first 120 days of treatment, compared with those taking lower doses. The risk remained increased 2 years after starting treatment.

In summary, based on the information available today, it is prudent for physicians to use low-potency statins whenever possible to provide cardiovascular benefits without the risk of AKI.

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