A Case of Treated ANCA-Associated Vasculitis with Recurrent Renal Failure

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Case Presentation: Dr. Ruth Pepper, Renal Specialist Registrar, Hammersmith Hospital, Imperial College Healthcare NHS Trust

The patient is a 45-yr-old Caucasian man with no significant past medical history, who in December 2006 developed arthralgias affecting both shoulders and hips and subsequently noticed shortness of breath with a cough, and a lower limb rash. These symptoms did not improve with diclofenac or with a course of anti-inflammatory therapy prescribed by his general practitioner. The patient presented to his local hospital when he developed hemoptysis, epistaxis, and sinusitis, as well as a worsening of his shortness of breath, rash, and arthralgias. He had lost 3.5 kg in weight during the course of his illness. He was on no medication except for amoxicillin. His family history included rheumatoid arthritis and lung cancer in two family members, both of whom were heavy smokers. He was originally from Ireland but had been living in the United Kingdom for the previous 25 yr. He had a partner and three children and was an ex-smoker.

At the local hospital, examination was unremarkable except for a lower limb vasculitic rash. Initial blood tests (Table 1) revealed significant renal impairment with a serum creatinine of 345 μmol/L (normal range 50 to 110 μmol/L) and an acute inflammatory response with a C-reactive protein (CRP) of 204 mg/dl and a serum albumin of 31 g/L. He was treated with antibiotics for a presumed chest infection and with intravenous fluids. On the sixth day of admission, creatinine had increased to 563 μmol/L and he was acidotic with serum bicarbonate 18 mmol/L, at which point he was admitted to the intensive care unit for hemofiltration. Hemoglobin had fallen to 9 from 12 g/L on admission. Further investigations revealed an antineutrophil cytoplasm antibody (ANCA) by immunofluorescence and an anti-PR3 antibody concentration of 358 IU/ml. Antinuclear antibodies and anti–glomerular basement membrane (anti-GBM) antibodies were negative, whereas C3 and C4 complement component levels were normal. Chest radiograph (Figure 1) demonstrated several large, poorly defined opacities with surrounding consolidation in the right upper and middle lobes but no evidence of cavitation. A high-resolution computed tomography (CT) scan of the chest demonstrated patchy consolidation in the anterior and posterior segments of the upper lobes of the right lung (Figure 2). There was patchy airspace shadowing within the left lingula. These changes were consistent with either hemorrhage or infection. A CT scan of the sinuses demonstrated mucosal thickening in the right maxillary sinus.

A clinical diagnosis of Wegener’s granulomatosis (WG) complicated by pulmonary hemorrhage and dialysis-dependent renal failure was made. The patient received further hemodialysis treatment, was commenced on plasma exchange, started high-dose oral corticosteroids, and continued intravenous cyclophosphamide. Plasma exchange treatment was interrupted only to perform a native renal biopsy and resumed after 2 d.

Renal Biopsy: Prof. H. Terence Cook

The renal biopsy (Figure 3) contained 22 glomeruli, all of which showed segmental areas of fibrinoid necrosis. Eight had cellular crescents, and 12 had fibrocellular crescents. There was widespread acute tubular damage. Immunofluorescence showed scanty mesangial IgG, IgM, and C3, but no electron-dense deposits were seen on electron microscopy. The diagnosis was pauci-immune crescentic glomerulonephritis consistent with WG.

Clinical Course

A total of 11 plasma exchange treatments were given over a total of 16 d. The patient received a course of pulsed intrave-
nous cyclophosphamide, with dosage adjustment for renal function and age. A total of 10 pulses of intravenous cyclophosphamide were given. Doses 1 to 3 were 2 wk apart, while the remaining pulses were administered every 3 wk. After receiv-

Table 1. Presenting and day 6 blood test results

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<td>Potassium</td>
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<td>Urea</td>
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<td>Alkaline phosphatase</td>
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<td>CRP</td>
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<td>White cell count</td>
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<td>Neutrophils</td>
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<td>Lymphocytes</td>
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<td>Monocytes</td>
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<td>Eosinophils</td>
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</tr>
<tr>
<td>Fibrinogen</td>
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<td>10.5</td>
<td>9.4</td>
</tr>
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*aPTT, activated partial thromboplastin time.

Figure 1. Chest radiograph upon first presentation demonstrating ill-defined areas of airspace shadowing both in lung fields particularly in the right midzone and at the right base. No obvious cavitation is seen.

Figure 2. High-resolution CT scan upon first presentation demonstrating nonuniform areas of airspace shadowing and consolidation in both lung fields, more so on the right. There are subsegmental areas of consolidation with some volume loss in the right upper and middle lobes. Air bronchograms are evident. No cavitation is present.
ing one further hemodialysis treatment, the patient’s renal function improved, and by day 10, serum creatinine was 327 μmol/L. On discharge (day 20), creatinine had further improved to 232 μmol/L.

Follow-up
During follow-up, the patient’s symptoms resolved completely, and he achieved a clinical remission within 4 wk from the initial diagnosis. The anti-PR3 antibody titer decreased, and ANCA was negative by immunofluorescence within 1 mo (Figure 4). Chest radiography improved, and pulmonary function tests did not demonstrate increased gas transfer coefficient, suggesting no ongoing pulmonary hemorrhage. Steroids were reduced, and his creatinine settled to a new baseline of 170 to 180 μmol/L. By May 2007, the cyclophosphamide course was completed. At this point, the patient was on prednisolone 10 mg, daily cotrimoxazole as Pneumocystis carinii prophylaxis, omeprazole, atorvastatin, irbesartan, and Calcichew. Three weeks after the last cyclophosphamide dose, azathioprine was started at a dosage of 150 mg/d as maintenance immunosuppression.

In June 2007, 5 mo after diagnosis, the patient presented with a short history of rigors. There was no obvious source of infection. He did not describe any vasculitic symptoms, which were a predominant feature of his earlier illness. At this time, his maintenance immunosuppression was prednisolone 10 mg and azathioprine 150 mg, commenced 12 d before presentation to hospital. No other new medications had been started. On examination, he was peripherally cool and hypotensive with BP of 80/40 mmHg. Urine was positive for blood and protein. Blood tests (Table 2) demonstrated an acute deterioration in renal function, with creatinine of 279 μmol/L, having been 147 μmol/L 3 d previously. He was anemic with hemoglobin 10.6 g/dl, and CRP was elevated at 143 mg/dl (Table 2). White cell count was within the normal range but became elevated the following day, with predominant neutrophilia. Urine microscopy showed a large number of white cells (>50/mm³) and red.

Figure 3. All of the glomeruli in the biopsy showed fibrinoid necrosis (A and B; hematoxylin and eosin [H&E]). In some, there were early lesions with segmental fibrinoid necrosis, while many have large cellular crescents (C and D; Jones methenamine silver) with rupture of Bowman’s capsule in some (D).
cells (>50/mm³) but no bacterial growth. Subsequent urine culture also failed to grow any organisms. Urgent renal ultrasound demonstrated normal-sized kidneys (12.7 and 13.2 cm) with no hydronephrosis.

Empirical antibiotic therapy was commenced with vancomycin and Tazocin, together with intravenous hydration. His temperature peaked at 37.7°C. He became more anemic, with hemoglobin dropping to 8.7 g/L, and hypotension persisted. Chest radiograph was normal, and pulmonary function tests demonstrated normal gas transfer coefficient (KCO), excluding significant pulmonary hemorrhage (Figure 5). An urgent ANCA was obtained, which was within the normal range (14 IU/ml; normal range 0 to 25). Since the patient’s renal function did not improve with intravenous hydration and antibiotics, a further renal biopsy was performed.

**Renal Biopsy: Prof. H. Terence Cook**

The biopsy (Figures 6 through 8) contained 12 glomeruli. Three showed global sclerosis, and seven had prominent areas of segmental sclerosis with adhesions to Bowman’s capsule. Two appeared normal. No fibrinoid necrosis was seen. In the interstitium, there was marked edema and a widespread infiltrate of neutrophils and mononuclear inflammatory cells. Many tubules were acutely damaged and showed marked neutrophilic tubulitis. In a few, there were neutrophils within tubular lumens. The appearances were those of a florid neutrophilic tubulointerstitial nephritis (TIN) consistent with a reaction to azathioprine. The glomerular changes were of scarring secondary to the previous episode of crescentic glomerulonephritis.

**Diagnosis and Treatment**

The patient was diagnosed with azathioprine-induced interstitial nephritis. Urine and blood cultures did not grow any microorganisms, in keeping with the biopsy appearances, which were less suggestive of ascending infection than of interstitial nephritis. There was no evidence of recurrent focal segmental necrotizing GN or vasculitis on the biopsy. The azathioprine was stopped, and the dosage of prednisolone was increased to 60 mg/d. Within 2 d of stopping the azathioprine, the serum creatinine had significantly improved to 176 μmol/L with CRP decreasing to 76 mg/L. A week later, the PR3-ANCA concentration had increased to 44 IU/ml (normal range 0 to 25). One month later, mycophenolate mofetil was commenced as maintenance immunosuppression for his vasculitis. The creatinine

<table>
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<td>Urea</td>
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<td>176</td>
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<td>Bilirubin</td>
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<td>Alanine transferase</td>
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<td>Hemoglobin</td>
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<td>1.0 to 3.5</td>
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<td>0.0</td>
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</tr>
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**Figure 4.** Graph demonstrating the response to treatment of serum creatinine, CRP, and PR3-ANCA in our patient over time. The downward arrow demonstrates the time when azathioprine was introduced.

**Table 2.** Blood tests upon re-presentation in June 2007.
remained stable at 137 µmol/L, while the PR3-ANCA concentration fell back into the normal range. The trends in creatinine, CRP, and PR3-ANCA in response to treatment of vasculitis and following the interstitial nephritis are shown in Figure 4.

Conclusions: Dr. Alan Salama, Senior Lecturer and Honorary Consultant Nephrologist, Imperial College London and Imperial College NHS Healthcare Trust

The patient presented with acute dialysis-requiring renal failure, pulmonary hemorrhage, and other clinical features consistent with a diagnosis of WG. He responded to conventional therapy with steroids, cyclophosphamide, and plasma exchange and rapidly entered disease remission. Subsequent to his conversion from cyclophosphamide to azathioprine, he presented with rigors, hypotension, and deterioration in renal function. The differential diagnosis at this stage was between sepsis in an immunocompromised patient, disease relapse, or another cause of shock, such as an allergic reaction. There was no evidence for infection, at the time or subsequently, and no supporting evidence for disease relapse. The diagnosis was established on renal biopsy, which demonstrated acute tubulo-interstitial nephritis with predominant neutrophil infiltration, most consistent with an allergic reaction to the recently introduced azathioprine.

ANCA are associated with three forms of small-vessel vasculitis: Churg-Strauss syndrome, microscopic polyangiitis, and Wegener's granulomatosis.
and exerts its immunosuppressive function through the metabolized in the liver to the active drug 6 mercaptopurine and monitoring (8).

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patients relapsed with a median time of 13 mo. The Chapel Hill

reviewing 246 patients treated in London, reported that 34% of

spanning 10 yr, Harper et al. (5) found that 25% of patients

relapsed at a median time of 17 mo, while Booth et al. (4),

reviewing 246 patients treated in London, reported that 34% of

patients relapsed with a median time of 13 mo. The Chapel Hill

group have shown that in a cohort of 350 patients with AAV, relapse was associated with anti-PR3 antibody positivity as well as upper and lower respiratory disease, although a diagnosis of WG itself was not statistically associated with relapse (9).

Review of our cohort of over 400 patients with AAV fol-

owed at the Hammersmith Hospital for over 30 yr demon-

strates that 37% of patients will have one relapse episode dur-

ing their lifetime, occurring up to 180 mo following diagnosis, emphasizing the careful need for expert long-term follow-up and monitoring (8).

Azathioprine, the current mainstay for maintenance therapy, is metabolized in the liver to the active drug 6 mercaptopurine and exerts its immunosuppressive function through the de novo inhibition of purine synthesis and hence DNA and RNA pro-
duction. It inhibits T lymphocyte cell function and diminishes Ig synthesis. Its metabolites are excreted via the kidneys but in an inactive form. The drug is generally well tolerated, with toxicity occurring as bone marrow suppression, megaloblastic anemia, and hepatic dysfunction. The risk of marrow suppression is increased in patients with low thopurine methyltrans-
ferase activity. Renal impairment with azathioprine is rare. A meta-analysis of more than 500 patients and a postmarketing survey of over 390 patients, all with rheumatoid arthritis, did not identify any with significant azathioprine-mediated renal dysfunction (10,11); however, rarely, as in our patient, an interstitial nephritis may develop. This has been reported in patients with WG, classical polyarteritis nodosa, cryoglobuline-
mia, leukocytoclastic vasculitis, anti-GBM disease and rheuma-
toid arthritis (12–17). Interestingly, it is less commonly reported in transplant recipients, suggesting that there may be a predis-
position in those with certain autoimmune conditions.

Azathioprine-induced reactions may be characterized by al-
lergic symptoms, including rash, fever, myalgias, and arthralgias. Other reports describe profound circulatory collapse as the major symptom following azathioprine introduction, and, as in our patient, they present without evidence of urticaria or anaphylaxis, suggesting that the allergic mediators are not classically histamine related (18,19). Allergic symptoms develop from as early as 1 wk to 1 yr after treatment has started (14). Resolution is rapid on drug cessation, but re-exposure results in more rapid recurrence of symptoms. No obvious patient sus-
ceptibility factors have been identified, although most patients with azathioprine-induced interstitial nephritis have some degree of renal impairment at the time of azathioprine introduc-
tion. Renal biopsy characteristically demonstrates a neutrophil-
rich infiltrate (17), which is an uncommon finding in other drug-induced forms of TIN. A similar case to ours was previ-
ously reported, in which the clinical symptoms following in-
roduction of azathioprine were treated as disease relapse with a further course of cyclophosphamide. Only upon rechallenge with azathioprine was a biopsy obtained and the characteristic biopsy findings discovered (17). We have not rechallenged our patient with azathioprine, as two cases in which this has hap-
pened resulted in severe life-threatening hypotension (18,19), but have maintained him in remission with mycophenolate mofetil (MMF). Whether this is a better drug than azathioprine in preventing relapse will be clarified with the results of the “IMPROVE” EUVAS trial due to report in 2008 (for details, go to http://vasculitis.org/acttrials.htm).

Questions
Dr. Ajay K. Singh, Associate Professor of Medicine, Harvard Medical School: Thank you, Alan, for an excellent discussion. Let me start the Q and A by asking you two questions: First, why you chose to switch the patient to MMF instead of using methotrexate. I ask this because there is some evidence to support efficacy for methotrexate. Second, how about the pos-
sibility of using rituximab for this disease? Would that have been a better option?

Dr. Alan Salama: The evidence that methotrexate is effective
comes from patients with less severe forms of AAV, with mild or no renal impairment (a cutoff serum creatinine of 150 μmol/L was used in the NORAM study) (20). In addition, the bone marrow toxicity of methotrexate in patients with advanced kidney disease makes it more difficult to use effectively. MMF has been used by our group and others with anecdotal success in patients with AAV (21–23), including those with renal failure. Now that our patient’s renal function has improved, methotrexate would be a reasonable alternative; however, as he is in remission on MMF, I see no need to change at the moment. With respect to the anti-CD20 monoclonal antibody rituximab, we and others have found it to be highly effective for the treatment of grumbling or resistant disease (24–26) in patients for whom further doses of cyclophosphamide are contraindicated. We have also used it successfully in induction therapy. Two randomized trials have recently been completed, one in the United States and one in Europe, which should be informative as to whether rituximab is as effective as standard cyclophosphamide regimens in inducing remission and preventing relapse. The main issue with rituximab is what to do once the B cells return, as at this point patients are again at risk of relapse. The role of rituximab as maintenance therapy is yet to be explored.

Prof. Charles Pusey, Professor of Medicine, Imperial College London: Alan, in this patient, intravenous cyclophosphamide was used rather than oral cyclophosphamide. The MEPEX study in patients with severe renal vasculitis used oral cyclophosphamide; what are your thoughts on this?

Dr. Alan Salama: That is correct. We used pulsed intravenous cyclophosphamide with a regimen similar to that used in the CYCLOPS study, due to be published soon, which recruited patients with less severe renal impairment (not requiring dialysis). The recently published MEPEX study (27), comparing plasmapheresis and pulsed methylprednisolone in patients with dialysis-dependent vasculitis, used daily oral cyclophosphamide. Pulsed therapy reduces the total dose of cyclophosphamide and appears to be as effective in the short term as inducing remission in those patients with less impaired renal function (7). There is a balance between achieving disease control and inducing adverse drug events, which, in the case of cyclophosphamide, means trying to inhibit disease successfully with the lowest possible total dosage. Ideally, we should formally compare these regimens in the dialysis-dependent population, although many vasculitis centers have now adopted pulsed intravenous therapy as standard of care.

Dr. Ajay Singh: Alan, in the Hammersmith experience that you presented, most relapses occurred within the first 2 yr. Why not continue the cyclophosphamide for 2 yr?

Dr. Alan Salama: As we discussed earlier, the adverse effects associated with cyclophosphamide are dosage related. The long term National Institutes of Health experience clearly shows that prolonged cyclophosphamide therapy is highly effective but has significant adverse events (3). Two years of therapy may well reduce relapse rates but will do so at a cost in terms of sepsis, gonadal failure, malignancy, and hemorrhagic cystitis. The optimal duration of cyclophosphamide therapy (producing the longest relapse-free survival with the lowest rate of side effects) is really unknown, but we have tended to err on the side of shorter courses of cyclophosphamide and careful follow-up to pick up early signs of relapse.

Prof. H. Terence Cook, Professor of Pathology, Hammersmith Hospital: Alan, in this patient, it was striking that at the time of the second presentation, the ANCA “blipped up” into the 40s. In view of the massive neutrophil infiltrate, the kidneys may have been releasing lots of PR3. Are there other examples of local inflammation inducing PR3 release and an increase in ANCA?

Dr. Alan Salama: The association between infections and episodes of autoimmunity has long been recognized (28), although the precise mechanisms underlying this remain elusive. The suggestion that there is molecular mimicry between an infectious agent and a self-antigen is more firmly established in conditions such as rheumatic heart disease (29). Rarely, C-ANCA has developed in patients with infective endocarditis and in some cases disappeared after clearing of the infection and resolution of the accompanying glomerulonephritis. In transplantation, we recognize that urinary tract infections may precede and promote an episode of graft rejection, and such an association has previously been reported in relapses of nephritis (28). The large renal neutrophil influx in our patient would have exposed PR3 autoantigen to the immune system and could have resulted in the temporary rise in ANCA titer. Certainly, persistence of antigen is a requirement for ongoing immune responses, and if antigen is cleared, sequestered, or in too small a concentration to reach a stimulation threshold for lymphocyte activation, the immune response will diminish.

Prof. Charles Pusey: Terry [Dr. Cook], in this patient, the immunosuppression was also temporarily reduced; this might explain the blip in PR3-ANCA.

Prof. Patrick Maxwell, Professor of Nephrology, Imperial College London: Alan and Terry, why is the TIN so patchy? Also, in looking at the biopsy, the inflammation seems targeted toward the distal rather than proximal tubules. Your thoughts?

Dr. Alan Salama: The reason for this is not clear. Other reported cases of azathioprine-induced TIN and most other cases of drug-induced TIN are also characterized by patchy involvement. I think like many kidney responses, including the nephritis itself, the processes are focal rather than generalized.

Dr. Ajay Singh: Alan, what are your thoughts on the necessity of performing a renal biopsy in a patient like this with rapidly progressive glomerulonephritis and a very high ANCA titer? Isn’t the likelihood that this is a necrotizing small-vessel vasculitis >95%? Why not just proceed expeditiously with plasmapheresis rather than waiting for a biopsy?

Dr. Alan Salama: A kidney biopsy, in my view, is very important, for a number of reasons: The first that there may be another pathology in the kidney. The patient may well have localized WG, and their renal impairment may not be due to vasculitis, as our patient demonstrated the second time around. Moreover, I think there may be additional pathologies, for example in “double-positive” patients, with anti-GBM disease and ANCA, which may not always be obvious from the serology (30). Second, one can gain prognostic information, which may influence the duration or type of therapy; for example, if...
the biopsy were very scarred and there were little early recovery, then one might be tempted to curtail or minimize immunosuppressive therapies. Finally, in centers where the quality of the ANCA assay or the speed of obtaining a result is limited, a biopsy is crucial to confirm the diagnosis. As regards the plasmapheresis, I agree that if the clinical suspicion is AAV and there is a strongly positive ANCA, I would start treatment immediately (as we did) and then fit the biopsy in within the first week of therapy. The desire to obtain a biopsy should not result in treatment delay, especially in patients with pulmonary hemorrhage, who can deteriorate very rapidly.

Prof. Patrick Maxwell: We sometimes defer the renal biopsy; however, we have had several instances where if we had not done a biopsy, we might have missed the diagnosis. Some cases come to mind: A patient with cholesterol embolization and another who had HIV-associated nephropathy; in both cases, the ANCA was positive and initial treatment was for AAV. Admittedly, this was before antigen-specific ELISA were available for myeloperoxidase and PR3. With regards to the timing of the plasmapheresis, generally, for a patient without life-threatening pulmonary hemorrhage, I would not regard it as necessary to start plasmapheresis immediately.

Prof. Charles Pusey: I agree that performing a renal biopsy is very important. I recall a case of infective endocarditis with positive ANCA that might have been missed. Having said that, in this patient, I would have started the plasmapheresis immediately.

Dr. Ajay Singh: Terry, how important do you feel a renal biopsy in patients with Wegener’s is in imparting prognostic information?

Prof. H. Terence Cook: Because WG is usually a focal process, it may be difficult to make firm predictions on outcome from a kidney biopsy. In general, though, I feel that acute changes predict response to therapy and chronic changes bode a poor long-term prognosis.

Prof. Charles Pusey: I agree; however, there have been instances when patients with quite bad scarring on renal biopsy have responded impressively to therapy.

Dr. Ajay Singh: Is there potential value in developing a histologic classification for ANCA-associated vasculitis?

Prof. H. Terence Cook: Currently, there is no classification. Since this a patchy disease, I am not convinced that a formal classification would be helpful in management.

Dr. Ajay Singh: Alan, could you discuss the striking association between the azathioprine-associated TIN and an underlying acute vasculitic process? Coincidence, or is there a pathogenetic link?

Prof. Charles Pusey: I agree; the association hasn’t been widely reported either in transplant recipients or in treating patients with lupus nephritis, where azathioprine is often used.

Dr. Alan Salama: As I mentioned, many patients reported with azathioprine-induced TIN appear to have WG or another form of vasculitis. There are a few cases in the transplant population but significantly fewer considering the numbers of transplant patients who were treated with azathioprine. Additionally, there are, as Charles says, few patients with systemic lupus erythematosus who develop this complication, although more with rheumatoid arthritis. Interestingly, while neutrophil numbers are correlated with high levels of IL-8, the main neutrophil chemokine, in biopsies of patients with AAV, this is also true of other inflammatory forms of nephritis, including lupus. Whether this propensity to produce neutrophil chemokines predisposes to a more neutrophilic TIN is unclear, although neutrophilic TIN is unusual with other drug-induced forms of disease.

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Disclosures
None.

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