Kidney Case Conference: Nephrology Quiz and Questionnaire

A Case of ANCA-Associated Vasculitis

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Case

A 70-year-old man with a past medical history of hyperlipidemia presented with migrating polyarthritis involving both shoulders and his right wrist. His x-rays showed evidence of degenerative joint disease. He was prescribed ibuprofen and his pain improved. Four weeks later he developed acute bilateral shoulder pain and dyspnea on exertion. His exam was notable for hypertension (146/84 mg Hg), normal oxygen saturation on room air, mild bilateral shoulder pain with rotation, and bilateral expiratory wheezing on his pulmonary exam. Laboratory studies revealed a serum creatinine of 1.4 mg/dl (baseline 0.8 mg/dl), uric acid level of 4.9 mg/dl (normal 4.8–8.7 mg/dl), and erythrocyte sedimentation rate (ESR) of 102 mm/h (normal 0–15 mm/h). A urinalysis revealed 2+ protein, 3+ blood, 10–20 white blood cells (WBCs), and five to ten red blood cells (RBCs) per high-power field (hpf). Tests for C3, C4, rheumatoid factor, and antinuclear antibody were normal.

His shoulder pain worsened and he developed a purpuric rash on his lower and upper extremities, prompting admission to the hospital, where his serum creatinine was 6.7 mg/dl and urinalysis showed 2+ protein, 3+ blood, 10–20 WBCs, and 20–50 RBCs/hpf. A random urine protein-to-creatinine ratio was 700 mg/g. ANCA enzyme immunoassay revealed a diffuse, cytoplasmic staining pattern and serum anti-protease 3 antibody of 182 units/ml (normal <20 U/ml), whereas anti-myeloperoxidase and serum anti-glomerular basement antibody levels were normal. Computed tomography of the chest and sinuses without intravenous contrast showed bibasilar ground glass opacities. He had no hemoptysis or epistaxis.

He underwent a kidney biopsy that showed pauci- immune, crescentic GN with moderate to severe glomerular and interstitial fibrosis and tubular atrophy (Figure 1).

Which of the following treatment strategies is appropriate in this case?

A. Induction treatment with plasma exchange therapy and high-dose corticosteroids.
B. Induction treatment with rituximab and high-dose corticosteroids.
C. Induction treatment with mycophenolate mofetil and high-dose corticosteroids.
D. Prepare for dialysis, no immunosuppression recommended.

Correct Answer: B

This patient has features that are associated with poor outcomes in ANCA-associated vasculitis including severe kidney insufficiency on presentation, a high percentage of globally sclerotic glomeruli, and severe interstitial fibrosis on kidney biopsy. The 2010 Histopathologic Classification of ANCA-Associated Glomerulonephritis, which classifies patients on the basis of the percentage of glomeruli involved and severity of glomerular damage, has now been validated as a prognostic tool in multiple cohorts (1).

In question 1, only choice B contains a first-line regimen that would be appropriate for the treatment for ANCA-associated vasculitis and kidney involvement, that is, corticosteroids in combination with cyclophosphamide or rituximab (2,3). Although other dosing schemes have been described, the US Food and Drug Administration–recommended dose of rituximab for ANCA-associated vasculitis is four weekly doses of 375 mg/m².

The data supporting the use of rituximab-based regimens for the treatment of patients with severely decreased eGFR remains controversial. Retrospective case series data describe high rates of remission, improvement in eGFR, and dialysis independence for patients with eGFR <20 ml/min per 1.73 m² treated with rituximab-based regimens (4,5). Although many of these patients also received cyclophosphamide and/or plasma exchange therapy, the role of adjunctive plasma exchange therapy in severe ANCA-associated vasculitis is also controversial. The Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis found higher rates of dialysis independence at 12 months for patients with serum creatinine >5.8 mg/dl who were treated with cyclophosphamide, oral prednisolone, and plasma exchange dialysis versus those treated with intravenous methylprednisolone, cyclophosphamide, and oral prednisolone (without plasma exchange) (43% versus 19%). However, no short-term survival benefit was observed, nor was there long-term improvement for the composite end point of ESKD or death (6).

Preliminary results of the International Randomized Controlled Clinical Trial Assessing Plasma Exchange and Steroid Dosing in the Treatment of ANCA-Associated Vasculitis show no difference in ESKD or death with adjunctive plasma exchange (ClinicalTrials.gov Division of Nephrology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania).

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Mythophenolate mofetil is not first-line therapy for severe ANCA-associated vasculitis.

Case Continued

He was treated with intravenous methylprednisolone 1000 mg daily for 3 days, prednisone 60 mg/d, and four weekly doses of rituximab 375 mg/m². Six months later, his prednisone had been tapered to 5 mg/d. His rash had resolved, he had no joint pain or shortness of breath, his serum creatinine was 3.5 mg/dl, his ESR was 23 mm/h, and his anti-protease 3 antibody titer was 35 U/ml. A urinalysis showed 2+ protein, trace heme, 2–5 WBCs, and 2–5 RBCs/hpf. His urine protein-to-creatinine ratio was 1500 mg/g. A repeat computed tomography of the chest revealed improving ground glass opacities.

What is the most appropriate assessment and recommendation for managing this patient?

A. He is entering remission, prescribe rituximab maintenance therapy.
B. He is entering remission, prescribe azathioprine maintenance therapy.
C. His proteinuria is increasing, prescribe a second course of induction therapy with cyclophosphamide and high-dose corticosteroids.
D. He is entering remission and has proteinuria, start renin-angiotensin system blockade and taper prednisone to off.

Correct Answer: A

On the basis of his Birmingham Vasculitis Activity score, our patient had improving disease activity parameters. However, maintenance therapy is often required to prevent relapse, particularly for those with risk factors such as anti-protease 3 antibody–positive disease, lung or upper respiratory involvement, rising or persistently elevated ANCA titers, or prior relapse. The Rituximab versus Azathioprine for Maintenance in ANCA-associated Vasculitis study found that for patients in remission after cyclophosphamide-based therapy, rituximab maintenance therapy was associated with a lower frequency of relapse (29% versus 5%; hazard ratio for relapse, 6.61; 95% confidence interval, 1.56 to 27.96), with similar adverse event rates (7). The Rituximab Vasculitis Maintenance Study, examining rituximab versus azathioprine as therapy for maintenance of remission for ANCA-associated vasculitis, is comparing these treatments after rituximab induction therapy (Clinicaltrials.gov identifier NCT01697267).

The ideal maintenance rituximab schedule has yet to be determined. The Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis 2 study found that fixed (intravenous, 500 mg on days 0 and 14, then 6, 12, and 18 months) dosing was not associated with a lower relapse rate versus individually tailored dosing (on the basis of testing for peripheral CD19-positive B cell recovery and ANCA reappearance/rise in titer every 4 months; 17.3% versus 9.9%; P=0.22) (8). An important observation of this study was that CD19-positive B cell recovery and ANCA titer levels were not reliable predictors of relapse because peripheral B cells were not detected in 45% of relapses, and 18% relapses were both peripheral B cell negative and ANCA cell negative. The ideal duration of maintenance therapy remains unknown, as are the risks of long-term maintenance rituximab therapy in the ANCA-associated vasculitis population.

In ANCA-associated GN, microscopic hematuria is an important marker of disease activity and risk of relapse. A recent study has confirmed that persistent proteinuria is not an independent risk factor for relapse (9), and there is...
also no data to support renin-angiotensin-aldosterone system blockade in ANCA-associated vasculitis.

**Case Continued**

He was started on maintenance therapy with rituximab 500 mg every 6 months and prednisone 5 mg daily. Because of the concern that a kidney relapse could lead to ESKD and that his age would make him a poor kidney transplant candidate, he has continued on rituximab maintenance therapy every 6 months. Four years after his initial presentation, his last serum creatinine was 2.8 mg/dl, his ESR was 10 mm/h, and his anti-protease 3 titer was 2 U. A urinalysis showed negative protein, negative heme, no WBCs, and no RBCs/hpf.

**Disclosures**

Dr. Hogan reports personal fees from Dimerix, Variant, GSK, Aurinia, and Retrophin, outside the submitted work.

**References**


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