Nephroquiz 7: Novel Treatments for Antineutrophil Cytoplasmic Antibody-associated Pauci-Immune Glomerulonephritis

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CASE
A 45-year-old woman was admitted because of weakness, anemia, hematuria, proteinuria, and acute kidney failure. On physical examination, the pulse was 72 per minute, the blood pressure was 155/80 mm Hg, respiratory rate was 18 per minute, oxygen saturation was 96%, and body temperature was 37.2°C. There was no rash or oculopathy, but periorbital edema was seen. The thyroid gland was estimated in normal size and no nodules were palpated. The patient did not have any complaints of rhinorrea or sinusitis. No lymphadenopathy was detected. There were normal heart and lung sounds. On both flanks, she had moderate tenderness. Examination of the joints and neurologic system revealed no abnormalities. In her lower limbs, 3+ pitting edema, without any erythm or tenderness was detected.

Laboratory studies were performed and she did not have any previous laboratory studies (Table 1). A repeat chemistry panel confirmed the elevated creatinine, which rose further to 4 mg/dL by the following day and the repeat urinalysis confirmed the presence of hematuria and proteinuria. Urine protein excretion in 24 hours was 1886 mg and the C-antineutrophil cytoplasmic antibody titer was positive. Chest radiography, computed tomography of the sinuses, and electrocardiography were normal. An ultrasonography of the genitourinary tract revealed normal-sized kidneys with increasing both kidney echogenicity and no evidence of hydronephrosis. Serum protein electrophoresis showed polyclonal gammapathy.

Kidney biopsy was urgently obtained and showed 9 glomeruli that 2 of them were globally sclerosed and the other revealed prominent mesangial proliferation associated with foci of obliteration of the Bowman space by proliferation of epithelial cells or formation of fibrous matrix. There was prominent interstitial inflammatory cell infiltration, which were mixed in nature and associated with tubular atrophy and epithelial destruction. A few of the vessels were involved with inflammatory cells. Immunofluorescence of the biopsy showed pauci-immune pattern and finally our definite diagnosis was renal limited pauci-immune crescentic glomerulonephritis (Figures 1 and 2). The patient was immediately pulsed with solumedrol 500 mg per 3 days and continued on prednisolone, 1 mg/kg/d. Cyclophosphamide, 500 mg, was administered as

Figure 1. The arrow shows crescentic necrotic lesion in the glomerulus in light microscopy
intravenous infusion and was repeated every month for 6 months. In her follow-up after 7 months, she had no recurrence and had no other new symptoms and her serum creatinine was stable around 1.6 mg/dL. Urine sedimentation was inactive, but her proteinuria persisted around 1g/24 h; thus, cyclophosphamide was switched to azathioprine, 100 mg/d, prednisolone was tapered to 10 mg/d, and other hypertensive agents were continued.

**QUIZ**

But what is a new treatment of renal-limited pauci-immune crescentic glomerulonephritis?

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises 3 different disease entities: Churg-Strauss syndrome, microscopic polyangiitis, and Wegener granulomatosis. A renal-limited AAV is an autoimmune disease with complex pathophysiology. Antineutrophil cytoplasmic antibodies with specificity for proteinase-3 or myeloperoxidase are hallmarks of AAV and have a pivotal role in disease development. In addition to ANCA, the cellular immune system contributes to the pathogenesis of the disease. The ANCA-mediated degranulation of neutrophils causes vasculitic damage; T cells drive granuloma formation, promote vasculitic damage by several different pathways, and enhance autoantibody production by B cells. Recently, complementary proteinase-3 and lysosomal membrane protein-2 were suggested as novel autoantigens in AAV. New findings also indicate the importance of complement, danger-

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Admission Time</th>
<th>6 Month</th>
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<tbody>
<tr>
<td>Protein</td>
<td>Trace-positive</td>
<td>...</td>
</tr>
<tr>
<td>Sediment, per low-power field</td>
<td>Many erythrocytes, 8 to 10 leukocytes</td>
<td>...</td>
</tr>
<tr>
<td>24-hour volume, mL</td>
<td>2500</td>
<td>...</td>
</tr>
<tr>
<td>24-hour protein, mg</td>
<td>1866</td>
<td>...</td>
</tr>
<tr>
<td>24-hour creatinine, mg</td>
<td>1075</td>
<td>...</td>
</tr>
</tbody>
</table>

**Blood**

- Hemoglobin, g/dL: 12.2... 
- Leukocyte count, × 10^9/L: 9...
- Differential count, %: ...
- Neutrophils: 60...
- Band forms: 1...
- Lymphocytes: 34...
- Eosinophils: 2...
- Platelet count, × 10^9/L: 267...
- Erythrocyte sedimentation rate, mm/h: 60...
- Reticulocyte count, %: 2...
- Prothrombin time: Normal...
- Partial thromboplastin time: Normal...
- Serum protein, g/dL: 8...
- Serum albumin, mg/dL*: 3.8...
- Gamaglobulin†: 4.2...
- Urea nitrogen: 29.6 25.0...
- Serum creatinine: 4.0 1.6...
- Serum bilirubin: Normal...
- Serum conjugated bilirubin: Normal...
- Electrolytes: Normal normal
- Serum aspartate aminotransferase: Normal ...
- Alamine aminotransferase: Normal ...
- Alkaline phosphatase: Normal ...
- Perinuclear antineutrophil cytoplasmic antibody: Negative ...
- Antimyeloperoxidase antibodies: Positive ...
- Total complement: Normal ...
- Complement C3: Normal ...
- Complement C4: Normal ...
- Hepatitis B surface antigen: Negative ...
- Hepatitis C antibody: Negative ...
- Rheumatoid factor: Negative ...
- Antiglomerular basement membrane antibodies: Negative ...
- C-reactive protein: Negative ...
- Antibodies to double-stranded DNA: Negative ...
- Antinuclear antibodies, U/mL¹: 0.84 ...
- Venereal disease research laboratory: Negative ...
- Serum protein electrophoresis: polyclonal gammopathy ...

*The normal range is 3.6 to 4.8.
†The normal range is 0.7 to 1.3.
‡Normal values are less than 0.9.
associated molecular patterns, and dendritic cells in AAV.

Table 2 reviews the novel treatment for AAV and puts them into context with the current understanding of disease mechanisms.1 Understanding the pathogenesis of AAV allows application of targeted therapy. As autoantibodies have a key role in AAV, depletion of B cells or interfering with maturation of these cells might ameliorate disease. Blocking adhesion and activation of neutrophils might also dampen or even prevent vasculitic damage. Vasculitic damage needs to be repaired and endothelial progenitor cells are regarded as an important factor of vascular repair. Endothelial progenitor cells mobilization and function might be enhanced by additional treatment with erythropoietin or statins. T cells drive the disease as well and could be targeted. For this purpose, T-cell activation could be limited by interfering with the costimulatory molecules and it might be beneficial to deplete subsets of effector T cells. Next, migration of T cells to tissue sites or T-cell-driven granuloma formation might be inhibited by biologics already available. Finally, treatment with antibiotics might prevent disease flares triggered by bacteria.1

CONFLICT OF INTEREST
None declared.

REFERENCES

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Table 2. Treatment Strategies for Antineutrophil Cytoplasmic Antibody-associated Vasculitis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
<th>Medication</th>
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</thead>
<tbody>
<tr>
<td>Depletion of effector T cells</td>
<td>Antibodies against CD25 deplete activated T cells</td>
<td>Basiliximab, Daclizumab</td>
</tr>
<tr>
<td>Regulation of effector T cells</td>
<td>Blockade of CD28/CD80 dependent T-cell activation</td>
<td>Abatacept, Belatacept</td>
</tr>
<tr>
<td>Block adhesion of neutrophils</td>
<td>Blockade of CD11b/ICAM-1-mediated adhesion to endothelium</td>
<td></td>
</tr>
<tr>
<td>Limit activation/recruitment of neutrophils</td>
<td>Inhibition of C5 cleavage. Blockade of C5a receptor on neutrophils</td>
<td>Eculizumab, Pexelizumab</td>
</tr>
<tr>
<td>Enhance vascular repair</td>
<td>Promote EPC mobilization and function</td>
<td>Erythropoietin, Statins</td>
</tr>
<tr>
<td>Inhibition of migration</td>
<td>Blockade of α4-integrins on T cells</td>
<td>Natalizumab</td>
</tr>
<tr>
<td>Interfere with granuloma formation</td>
<td>Blockade of TNF-α</td>
<td>Infliximab, Adalimumab</td>
</tr>
<tr>
<td>Depletion of B cells</td>
<td>Neutralization of BLys and blockade of BLys-receptors on B cells</td>
<td>Belimumab, Atacicept</td>
</tr>
<tr>
<td>Antimicrobial treatment</td>
<td>Reduction of microbial flora that might trigger disease flares</td>
<td>Cotrimoxazole</td>
</tr>
</tbody>
</table>

1ICAM-1 indicates intercellular adhesion molecule-1; EPC, endothelial progenitor cell; TNF-α, tumor necrosis factor-α; and BLys, B lymphocyte stimulator.