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

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IJKD 2012;6:314-6
www.ijkd.org

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 proteine 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 polycolonal gammapathy.

Kidney biopsy was urgently obtained and showed 9 glumeruli that 2 of them were globally sclerosed and the other revealed prominent mesengial 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 crecsentic glomerulonephritis (Figures 1 and 2). The patient was immediately pulsed with solumedrol 500 mg per 3days and continued on prednisolone, 1 mg/kg/d. Cyclophosphamide, 500 mg, was administered as

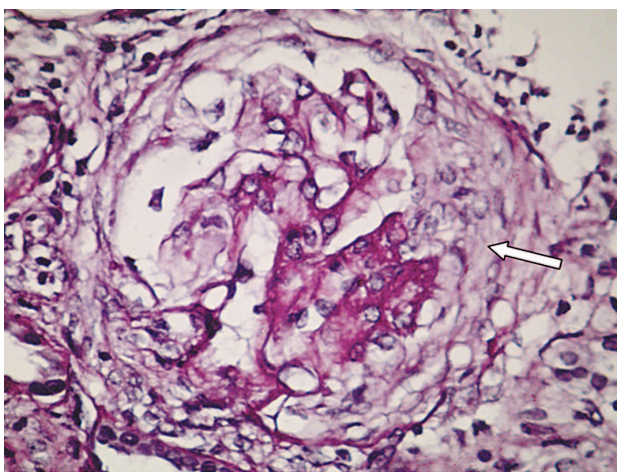

Figure 1. The arrow shows crescentic necrotic lesion in the glomerulus in light microscopy

Table 1. Laboratory Findings and Results of Urinalysis

Parameter	Value	
	Admission Time	6 Month
Urine		
Protein	Trace-positive	…
Sediment, per low-power field	Many erythrocytes, 8 to 10 leukocytes	…
24-hour volume, mL	2500	…
24-hour protein, mg	1866	…
24-hour creatinine, mg	1075	…
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	…
Protrombin 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	…
Alanine 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/mL‡	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.

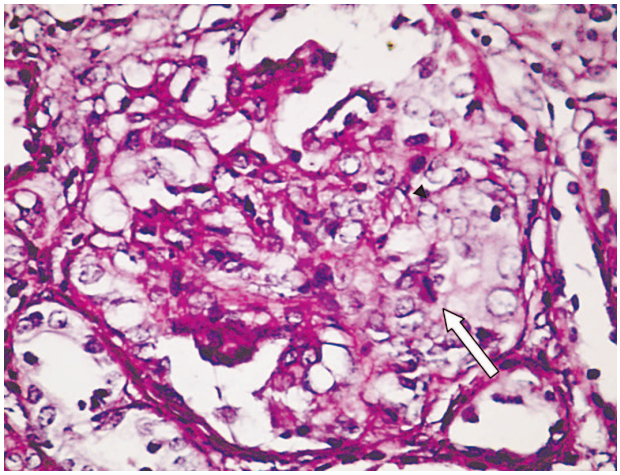

Figure 2. In light microscopy, decreasing mesential matrix and cellular pattern was shown. Destroying of capillary loops are seen.

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 persis ted 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 2. Treatment Strategies for Antineutrophil Cytoplasmic Antibody-associated Vasculitis

Treatment	Mechanism	Medication
Depletion of effector T cells	Antibodies against CD25 deplete activated T cells	Basiliximab, Daclizumab
Regulation of effector T cells	Blockade of CD28/CD80 dependent T-cell activation	Abatacept, Belatacept
Block adhesion of neutrophils	Blockade of CD11b/ICAM-1-mediated adhesion to endothelium	…
Limit activation/recruitment of neutrophils	Inhibition of C5 cleavage. Blockade of C5a receptor on neutrophils	Eculizumab, Pexelizumab
Enhance vascular repair	Promote EPC mobiliztion and function	Erythropoietin, Statins
Inhibition of migration	Blockade of a4-integrins on T cells	Natalizumab
Interfere with granuloma formation	Blockade of TNF-α	Infliximab, Adalimumab
Depletion of B cells	Neutralization of BLys and blockade of BLys-receptors on B cells	Belimumab, Atacicept
Antimicrobial treatment	Reduction of microbial flora that might trigger disease flares	Cotrimoxazole

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

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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