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Rapidly progressive renal failure followed by respiratory failure in an elderly woman

Rubina Naqvi*, Muhammed Mubarak

Departments of Nephrology and Histopathology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan

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Implication for health policy/practice/research/medical education:
Patients with dual positive antibodies of anti-GBM antibody and ANCA antibody, have a poor prognosis and behave more like anti-GBM disease than vasculitis. The prognosis of such patients is poor.

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Nephropathology quiz

1. Case Presentation

A 65-year-woman, housemaid, was in perfect health 2 months ago, when she developed intermittent fever with rigors and malaise. She was treated symptomatically by local doctors and given lots of parenteral fluids. She developed peripheral and periorbital swelling gradually over the last 2 weeks. She was referred to us because of deranged renal functions. On arrival, her vitals were; body temperature, normal; blood pressure, 160/100 mm Hg; pulse, 76/min; peripheral pulses, normal. She was mildly anemic, edema was 3+ (pedal, periorbital), no palpable lymph nodes, and no rash were found. Systemic examination revealed clear lungs, hyperdynamic heart sounds with gallop and flow systolic murmur of 3/6. Abdominal examination was unremarkable. Chest X-ray during initial evaluation is shown in Figure 1A.

Her laboratory investigations showed; hemoglobin, 8.3 g/dL; total leukocyte count, 11.5 $\times 10^9$/L (N=75%, L=15%, E=1.7%, M=9%, B=0.3%); platelets, 261$\times 10^9$/L; erythrocyte sedimentation rate (ESR), 110 mm/1st h; urea, 189 mg/dL; serum creatinine, 21.3 mg/dL; sodium, 135 mEq/L; potassium, 6.1 mEq/L; chloride, 99 mEq/L; and venous bicarbonate, 13 mEq/L; blood sugar, fasting, 97 mg/dL; and random, 105 mg/dL; serum total proteins, 5.6 g/dL; albumin, 1.9 g/dL; globulins, 3.7 g/dL; calcium, 7.7 mg/dL, creatine phosphokinase (CPK), 94 U/L, and lactic dehydrogenase (LDH), 292 U/L. Liver function tests were normal. Urinalysis revealed pH of 8; specific gravity, 1015; proteins, 3+; RBCs, numerous; WBCs, numerous; and no casts. Renal biopsy was performed and the representative light microscopy and immunofluorescence (IF) images are shown in Figure 1B-D.

Relevant serological markers were as; anti-nuclear antibodies (ANAs), weak positive (titer; 1:40); anti-dsDNA, negative; anti-neutrophil cytoplasmic antibodies (ANCA), both anti-proteinase 3 (PR3) and anti-myeloperoxidase (MPO), positive, anti-PR3, IgG, 5.4 (>3.5 is positive); anti-MPO, IgG, 27(>9 is positive); and anti-glomerular basement membrane (GBM) antibody, >30 U (moderate to strong positivity).

Ultrasound (US) abdomen was normal except for gall bladder which showed a single stone and sludge. Right and left kidneys measured 11.5 and 11.6 cm, with slightly increased echogenicity. X-Ray skull and pelvis were unremarkable.

She was given pulse steroids, 750 mg/d for three days, followed by oral prednisolone, 1 mg/kg/d. Pulse cyclophosphamide was given, 750 mg 13 days after admission. Plasmapheresis was started two days

*Corresponding author: Prof. Rubina Naqvi, Email address: rubinanaqvi@gmail.com

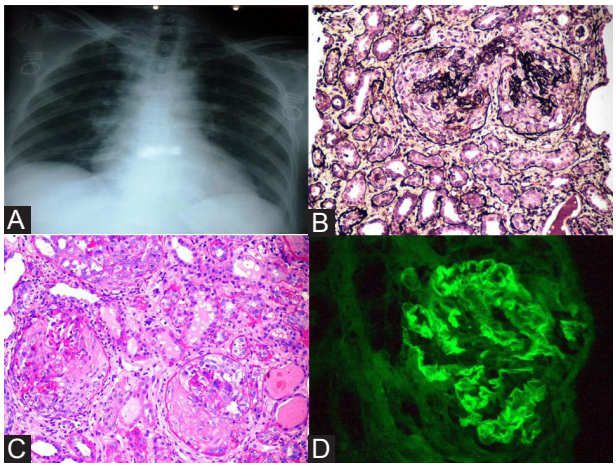

Figure 1. Chest X-ray at the time of admission and renal biopsy findings on light microscopy and immunofluorescence.

later. She, however, remained dialysis dependent and developed shortness of breath on the same day, for which she was electively ventilated and chest X-ray at this time is shown in Figure 2A. She developed poor oxygen saturation and expired two days later. A postmortem needle biopsy of the lungs was performed and shown in Figure 2B, C.

2. Questions

Describe the X-ray chest findings.
Describe the renal biopsy findings.
Describe the lung biopsy findings.
What is the significance of dual positivity of anti-GBM and ANCA in crescentic glomerulonephritis (CresGN)?
Describe the management of the condition.

3. Discussion

3.1. Describe the X-ray chest findings

The first X-ray chest (Figure 1 A) shows clear lung fields. No focal mass or opacification is noted. However, the second chest roentgenogram (Figure 2A) is grossly abnormal and shows diffuse alveolar shadowing of both lung fields. This appearance is seen in a limited number of conditions, including diffuse pulmonary edema, adult respiratory distress syndrome (ARDS) and diffuse alveolar hemorrhage. The findings in our case reflect diffuse alveolar hemorrhage, as the other causes were ruled out by history and lack of improvement on ultrafiltration.

Describe the renal biopsy findings

Renal biopsy was adequate with up to 38 glomeruli. All of these were grossly abnormal and showed crescent formation. Majority of the crescents (n = 23) were cellular (Figure 1B), 11 were fibrocellular (Figure 1C), and four were fibrous. There was no vasculopathy

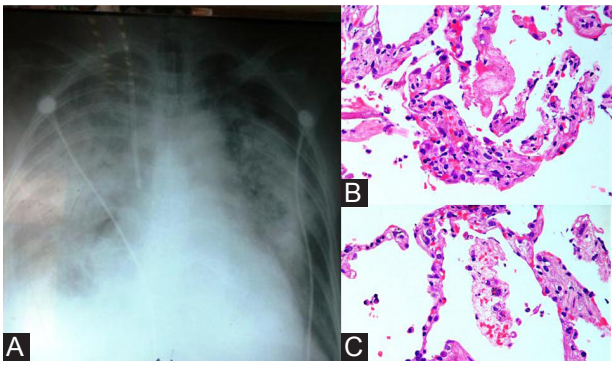

Figure 2. Chest X-ray at the time of respiratory distress and postmortem lung biopsies

or vasculitis of the vessels included in the biopsy. There was moderate degree of tubular atrophy and interstitial inflammation. A few tubules also showed necrotic debris and neutrophils in the lumena. IF for IgG showed diffuse strong (3+) linear positivity along GBM, while the crescentic proliferation was negative (1D). The renal biopsy findings, especially the polyphasic nature of crescents, suggest that the glomerular lesions are primarily caused by ANCA-associated pathology, with superimposed anti-GBM antibody nephritis.

3.2. Describe the lung biopsy findings

The needle biopsy of the lungs done postmortem showed intra-alveolar fibrin deposition and hemorrhage. In addition, alveolar walls also showed evidence of capillaritis and hemorrhage (Figure 2B). These findings are consistent with the lung involvement in Good pasture's syndrome. There was also hypertrophy of type II pneumocytes. No infective organism was found. No viral inclusions were seen.

3.3. What is the significance of dual positivity of anti-GBM and ANCA in CresGN?

The serologic evidence of double positivity for both ANCA and anti-GBM antibodies is fairly common in patients with either antibody and a clinical picture of rapidly progressive GN (RPGN) (1,2). Up to 20-25% of patients with anti-GBM antibody nephritis have associated ANCA positivity (3). On the other hand, 5% of ANCA-associated GN patients have anti-GBM antibodies in their sera (4). Interestingly, our patient had both types of ANCA antibodies, a phenomenon very rarely reported in literature. Some studies have shown that patients with dual positive antibodies have a poor prognosis when presenting with severe disease and behave more like anti-GBM disease than vasculitis (3). Other authors have suggested that these patients behave as vasculitis-variant of anti-GBM antibody

nephritis (4). Presumably, the predominant behavior depends on the predominance and primacy of either antibody. The recovery of renal functions is rare with dual positivity of the above markers.

3.4. Describe the management of the condition

There are three main tenets of treatment of anti-GBM antibody nephritis; removal of the antibody from the circulation by plasmapheresis; prevention of further antibody production by the immunosuppression; and eliminating or avoiding future exposure to potential triggering agents. However, the key to successful treatment is the early diagnosis and institution of therapy. Delay in these often leads to fatal outcome as in our case.

4. Final Diagnosis

Anti-GBM antibody associated nephritis complicating ANCA-associated disease.

Authors' contribution

Both authors contributed equally to the case quiz.

Conflicts of interest

The authors declared no competing interests

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