

Pulmonary-Renal Syndrome with Negative ANCA and Anti-GBM Antibody

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Abstract

Pulmonary renal syndrome (PRS) portrays the event of renal failure in association with respiratory failure. PRS, portrayed by a mix of diffuse alveolar discharge (DAH) and rapidly progressive glomerulonephritis (RPGN), is brought on by changed etiologies, including Goodpasture's disorder, hanti-neutrophil cytoplasmic antibody (ANCA)- related little vessel vasculitis (ASVV), cryoglobulinemia, systemic lupus erythematosus, natural components and certain medications.

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Introduction

Pulmonary renal syndrome (PRS) describes the occurrence of renal failure in association with respiratory failure, characterised by autoimmune-mediated rapidly progressive glomerulonephritis (RPGN) and diffuse alveolar haemorrhage (DAH), respectively [1].

PRS, characterized by a combination of diffuse alveolar hemorrhage (DAH) and rapidly progressive glomerulonephritis (RPGN), is caused by varied etiologies, including Goodpasture's syndrome, anti-neutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitis (ASVV), cryoglobulinemia, systemic lupus erythematosus, environmental factors, and certain drugs [2].

Antiproteinase-3 (anti-PR3, c-ANCA) and antimyeloperoxidase (anti-MPO, p-ANCA) antibodies, which have been reported to play a major role in the pathogenesis of ASSV, are detectable in 70-90% of cases and facilitate diagnosis. It is very important to make the correct diagnosis and institute early adequate therapy in the acute phase of these diseases in order to preserve organ function.

Our present patient could not be classified into known subgroups because all commercially available serologic studies were negative. Therefore, a renal biopsy was performed for diagnostic clues at a later date. As a result, PRS was diagnosed on the basis of clinical manifestations and pathological findings.

Case Presentation

A 27 year old Egyptian man, heavy cigarette smoker who was in relatively good health until 2 month prior to admission to our unit when he developed lower limb edema and hypertension. He had not been recently treated with any medication apart from a history of drug abuse (tramadol abuse). He did not have past

history of medical disease. There was no significant history of hereditary disease in his family.

At that time, he sought medical advice as he developed bilateral lower limb swelling and felt dyspnoic. On examination a middle age guy with extensive lower limb odema, ascites, mild bilateral pleural effusion otherwise he was free. Results of his investigations were as follow; Urinalysis revealed proteinuria (+++) and hematuria (over 100) with no dysmorphic RBCs 24 h urinary protein was 14.5 g/day. Complete Blood Count: white blood cell count 8,900/ μ l; hemoglobin 14.5 g/dl; platelet count 291,000/ μ l; Serum creatinine 1.5 mg/dl; aspartate transaminase 25 IU/L; alanine aminotransferase 23 IU/L and total bilirubin 0.9 mg/dl serum albumin 1.9 g/dl, total cholesterol 416 mg/dl, TG 252 mg/dl, HDL 61 mg/dl, LDL 304 mg/dl. Virology markers for HBV and HCV were negative. ANA, Anti dsDNA and ANCA (Both P and C) were also negative.

Renal ultrasound showed normal size both kidneys, bilateral grade I to II nephropathy. Renal biopsy **Figure 1** was done and stained with Hematoxylin and Eosin (no immunofluorescence stain was done) and revealed focal proliferative glomerulonephritis, acute tubular injury and chronic interstitial nephritis. Patient started prednisone 60 mg/day, atorvastatin 20 mg/day and low dose of angiotensin Converting Enzyme Inhibitor (12.5 mg/day) to control his proteinuria, furosemide Proteinuria dropped to 4 g/day and serum creatinine remained static.

Two months later the patient presented with dyspnea, dry cough and rising serum creatinine. He was admitted to our hospital. At

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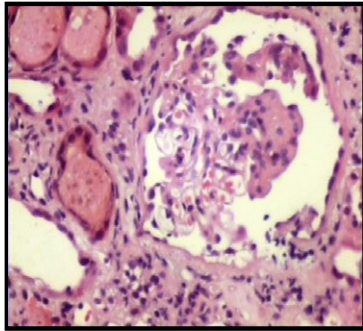


Figure 1a Results of the first renal biopsy (H&E stain).

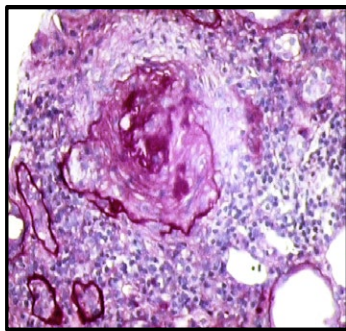


Figure 1b H&E: First biopsy showing focal proliferative glomerulonephritis (Mesangial hypercellularity).

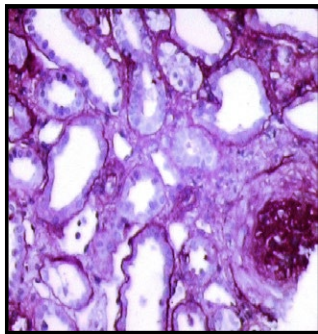


Figure 1c Fibrous crescents and with focal defects in Bowman's capsule.

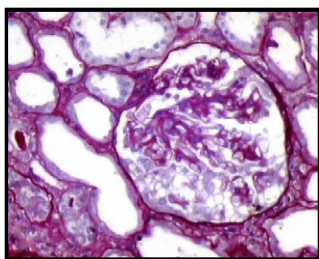


Figure 1d Segmental cellular crescent.

the time of admission, physical examination revealed feverish patient (a temperature of 37.9°C), blood pressure of 140/90 mm Hg, pulse rate of 90 beats/min and shallow rapid respiration (RR at a rate of 25 breaths/min). He had bilateral basal crackles, normal

heart sounds and no skin rash or joint swelling. The remaining physical examinations were unremarkable.

The laboratory findings on admission were as follows: white blood cell count 11,000/ μ l; hemoglobin 11.1 g/dl; platelet count 209,000/ μ l; creatinine 4 mg/dl; repeated 24 h urinary protein was 4 g/day. A chest X-ray showed bilateral basal homogenous opacities. A preliminary diagnosis of Pneumonia was suspected on admission and a combination of antibiotics were started (levofloxacin 500 mg/48 h, metronidazole 500 mg/8 h and ceftazidime 1 g/24 h). Serial daily laboratory work up was done for the patient revealing rising serum creatinine 4 mg/dl - 6.2 mg/dl - 6.9 mg/dl - 7.2 mg/dl - 8 mg/dl and decreasing hemoglobin 10 g/dl - 8.1 g/dl - 7.8 g/dl - 5.7 g/dl - 4.9 g/dl with no apparent evidence of external bleeding or hemolysis (repeatedly normal serum bilirubin and negative comb test). Non contrast CT chest was done showing bilateral lung infiltrates highly suspicious of diffuse alveolar hemorrhage (**Figure 2**).

Again ANA, Anti dsDNA, ANCA (P and C) were repeated and were negative. Anti GBM test (ELISA) was done and also was negative. The falling hemoglobin and the CT picture suggesting DAH raised the clinical suspicion of Pulmonary Renal Syndrome with Negative ANCA and Anti GBM antibodies, so a decision to increase the immunosuppression was taken. The patient received pulse steroid (solumedrol 1 g/day for three days followed by 80 mg oral prednisolone) followed by IV cyclophosphamide (1 g) to meet the aggressive clinical presentation while preparing for re-biopsy.

Renal biopsy was revised again by the same pathologist after the new insult and the diagnosis was: Focal proliferative glomerulonephritis with crescents, acute tubular injury and chronic interstitial nephritis.

Patient started regular sessions of hemodialysis for the deterioration of his renal function (his creatinine was 10.7 mg/dl). Re-biopsy was done and showed diffuse fibro-cellular crescents with diffuse interstitial fibrosis and tubular atrophy. Immunoperoxidase study revealed linear IgG pattern (**Figure 3**).

The patient had been improved regarding his general condition, pulmonary symptoms with reported radiological improvements. Unfortunately, the serum creatinine remained high and the renal condition was not responsive to the immunosuppressive therapy (steroid and cyclophosphamide).

After few weeks, the patient was discharged on regular hemodialysis with otherwise no other system complications and

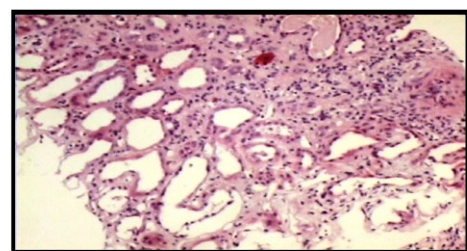


Figure 1e Acute tubular injury.



Figure 2 Non-contrast CT chest showing bilateral lung infiltrates highly suspicious of diffuse alveolar hemorrhage.

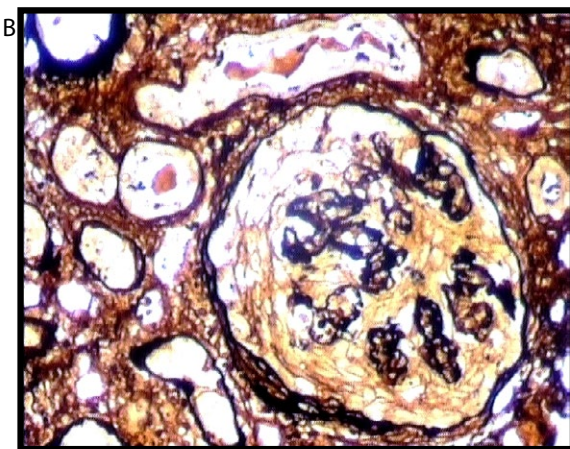
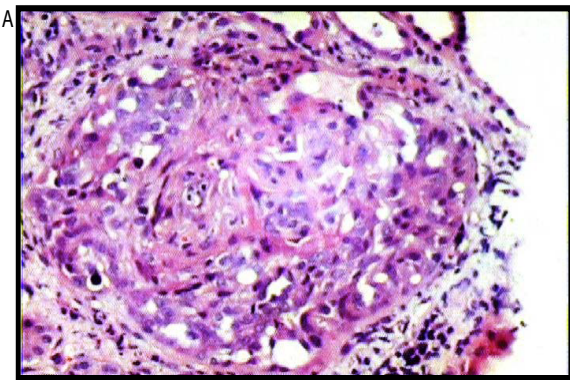


Figure 3 Results of the second renal biopsy (H&E stain). (a) Cellular crescents. (b) Voluminous crescents encroaching on the tufts.

after clinical and radiological improvements of his pulmonary condition.

Unfortunately, few weeks later, his family reported an attack of sudden respiratory embacement which was severe enough, the patient died at home before any rescue.

Discussion

The term pulmonary renal-syndrome (PRS), as first described by Goodpasture in 1919, is used to describe a combination of diffuse pulmonary hemorrhage and glomerulonephritis occurring as the presenting manifestation of multisystem autoimmune disease [3]. It represent a medical emergency associated with a high risk of fatal outcome, caused by various etiologies,

including Goodpasture's syndrome, antineutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitis (ASVV), cryoglobulinemia, systemic lupus erythematosus, environmental factors, and certain drugs [2-4].

ASVV, caused by microscopic polyangiitis (MPA), Wegener's granulomatosis and Churg-Strauss syndrome, represent approximately 70% of the cases of PRS. Antiproteinase-3 (anti-PR3, c-ANCA) and antimyeloperoxidase (anti-MPO, p-ANCA) antibodies are detectable in 70-90% of ASVV cases.

In addition circulating anti-GBM antibodies using ELISAs are found in up to 92% of the cases of anti-GBM disease. That is, approximately 90% of the patients with PRS have one or more autoantibodies. Few cases are reported as seronegative PRS; almost all of them were Asian [5].

With regard to treatment of seronegative PRS, no specific therapeutic options have been offered, attributed to limited numbers of cases. Plasma exchange was studied as a therapeutic option in two reported cases with favourable outcome [2].

PRS represent a life-threatening condition, and its overall mortality has been reported to be 12-50% [6]. Our present patient could not be classified into known categories of PRS because all commercially available serologic tests were repeatedly negative.

The clinical presentation of rapidly progressive glomerulonephritis with evidence of crescents formation together with pulmonary haemorrhage and linear IgG deposition along the capillary basement membrane is virtually diagnostic of Goodpasture's syndrome but failure to detect circulating anti-GBM antibodies did not support the diagnosis.

Diffuse alveolar haemorrhage (DAH) represents a broad clinical spectrum. It may develop acutely over a few days, or more insidiously, and may present as a mild illness or as fulminant respiratory failure.

A plain chest X-ray (CXR) is a sensitive but non-specific diagnostic aid in DAH, with up to 13% of patients with DAH demonstrating no features of alveolar shadowing on CXR at presentation and this happened in our case [7, 8].

High-resolution CT is superior to CXR in detecting DAH and is particularly valuable in cases of suspected DAH with normal CXR findings [9].

Glucocorticoid is the main therapy for the DAH syndrome associated with systemic vasculitis, connective tissue disease, and Goodpasture's syndrome [5]. Our patient showed marvelous improvement of his pulmonary affection after combined steroid and cyclophosphamide injections, other immunosuppressive as cyclophosphamide and plasma exchange therapy may also be considered. With plasma exchange, most cases would have recovered pulmonary haemorrhage (reabsorption of blood) and no permanent lung damage occurs, but damage to the kidneys is long lasting and that what actually happened in our case. It was reported that the differential diagnosis of the underlying immunologic disease for PRS with negative ANCA is occasionally time consuming and delays the initiation of plasmapheresis [4].

In ANCA-positive patients, the effect of plasmapheresis is partially related to the removal of circulating ANCAs, which are absent in ANCA-negative patients.

Our patient was not treated by plasma exchange for three reasons first, as we did not detect target autoantibodies to remove through plasmapheresis second plasmapheresis is a costly and expensive therapy in a developing country-like ours which is difficult to apply without strong evidence. Third, rapid improvement of the lung condition with immunosuppression and the presence of diffuse interstitial fibrosis and tubular atrophy in kidney biopsy were not encouraging parameters for its use. Although plasma exchange has shown to be beneficial in two reported cases of sero-negative PRS [4].

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Therefore, the precise effect of plasmapheresis in ANCA-negative ASVV warrants further investigation.

This reported case has important clinical implications because uncategorizable pulmonary-renal syndrome (PRS) with negative ANCAs and anti-GBM antibody is extremely rare and has high rates of fatal outcome. No treatment recommendations have been established for such cases.

Conclusion

In conclusion, PRS is a life-threatening condition that warrants prompt and appropriate treatment. Further investigations are needed to study the value of routine early plasmapheresis in PRS and the role of plasmapheresis in PRS caused by ANCA-negative ASVV to develop an optimal therapeutic strategy as well as to ensure better outcomes.