CHAPTER

41

Pulmonary Renal Syndrome

Yojana Gokhale, Raosaheb Rathod

INTRODUCTION

1. Pulmonary Renal Syndrome (PRS), is a combination of diffuse alveolar haemorrhage (DAH) and glomerulonephritis (GN), occurring simultaneously.
2. DAH should be suspected in a patients with breathlessness, haemoptysis, alveolar opacities (on chest x-ray), anemia, hypoxemia. Look for RBCs in the urine of a patient of haemoptysis to detect associated renal involvement. And vice a versa ask for history of haemoptysis in patients of nephritis/ RPGN. This will lead to detection of PRS.
3. PRS is not a single disease, it has a differential diagnosis (Table 1) of its own, most common cause being ANCA positive vasculitis.
4. Timely diagnosis of PRS is important, considering high mortality (25-50%), need for ventilator support (35-50%) and dialysis dependence at 1 year in over 70%.
5. PRS may be confused with pneumonia, ARDS, pulmonary oedema, pulmonary tuberculosis, thus delaying instituting steroids and immunosuppressants.

HISTORIC BACKGROUND

Combination of pulmonary haemorrhage and glomerulonephritis (GN) was first described by Goodpasture in 1919. The term Goodpasture syndrome was adopted in 1958 to define these patients and pathogenic role of anti-glomerular basement membrane (anti-GBM) antibodies in some cases of pulmonary haemorrhage and GN was proven 10 years later. In an interesting study from Massachusetts General Hospital[1], out of 88 patients' sera, sent for anti-GBM antibodies in the setting of PRS, 48 tested positive for ANCAs, 6 for anti-GBM and 7 for both, whereas in 27 patients unrelated renal and pulmonary diseases were found.

CLINICAL FEATURES OF PRS

The classic clinical presentation of DAH is (a triad) haemoptysis, abrupt fall in haemoglobin and new pulmonary infiltrates (bilateral alveolar infiltrates with apical sparing) and dyspnoea. Some patients present with severe respiratory distress and some with pulmonary infiltrates which resolve and recur. However each of these features is variable and may be absent. Haemoptysis may be absent in 1/3rd patients. Chest radiograph may be normal in 20%, or show unilateral infiltrates in some. DAH may precede GN by weeks to months. But when they occur simultaneously patient has features of nephritis (oedema, hypertension, haematuria, with or without rising creatinine). PRS has a wide clinical spectrum (Figure 1) and a wide range of severity of presentation from the general outpatient clinic to the ICU setting. Two

Table 1: Differential Diagnosis of PRS

Clinical entities classified according to the pathogenetic mechanism (2/3rd cases of PRS are ANCA positive)
ANCA-positive systemic vasculitis
Wegener's granulomatosis Microscopic polyangitia Churg-Strauss syndrome
Associated with anti-GBM antibodies: Goodpasture's syndrome
ANCA-negative systemic vasculitis
Henoch–Schönlein purpura, mixed cryoglobuninaemia, Behcet's disease, IgA nephropathy
ANCA-positive PRS without systemic vasculitis: idiopathic PRS
Pauci-immune necrotic glomerulonephritis and pulmonary capillaritis
In drug-associated ANCA-positive vasculitis
Propylthiouracil, D- Penicillamine, Hydralazine, Allopurinol, Sulfasalazine
Anti-GBM-postive and ANCA-positive patients
Autoimmune rheumatic diseases (immune complexes and/or ANCA mediated)
Systemic lupus erythematosus
Scleroderma (ANCA?)
Polymyositis
Rheumatoid arthritis
Mixed collagen vascular disease
PRS in thrombotic microangiopathy
Antiphospholipid syndrome
Thrombotic thrombocytopenic purpura
Infections
Neoplasms
Diffuse alveolar haemorrhage complicating idiopathic pauci-immune glomerulonephritis

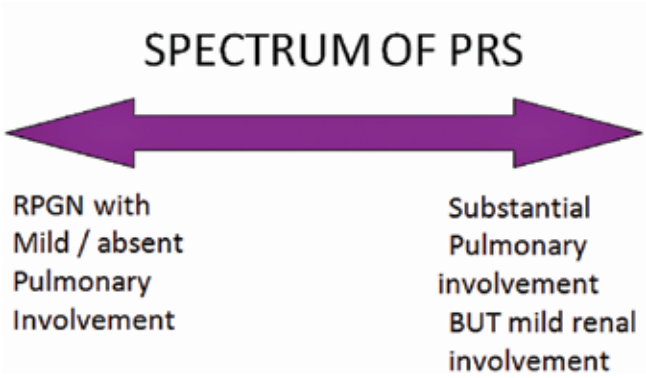

Fig. 1: Clinical spectrum of PRS

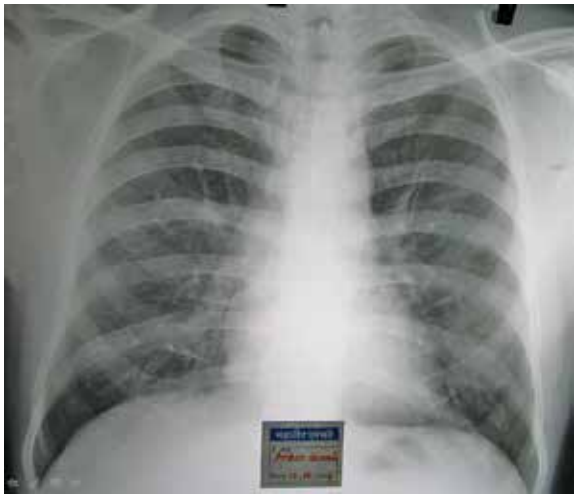

Fig. 2: Chest x-ray of case 1, depicting clear lung fields, when he had haemoptysis

illustrative cases are given below for better understanding of the spectrum of PRS.

CASE 1

M/43, presented to his family doctor in December 2004 with malaise, anorexia, haemoptysis. After baseline x-ray (Figure 2), he was started on anti tuberculosis treatment (ATT). Patient kept getting recurrent haemoptysis for which repeated x-ray chest were performed (Figure 3). In January 2006 he got admitted to our hospital with haempotysis and breathlessness. On examination, pulse-96/min, blood pressure- 180/100, respiratory rate-20/ min, he was pale, had no oedema, raised jugular venous pressure or cyanosis. There were bilateral fine crepitations on auscultation of chest. As per his old records his serum creatinine in August 2005 was 2mg/dl. His investigations at our hospital were as follows: Hemoglobin- 4.5gm/dl, WBC- 12000/cumm, ESR- 115mm at 1 hour, Urine Proteins2+, 15-20RBCs/hpf, x-ray chest revealed bilateral alveolar shadows with sparing of apices (Figure 4), ultrasound kidneys was reported as small contracted kidneys. Patient was clinically diagnosed as 'Pulmonary renal syndrome' and treated with Inj. Methyl Prednosolone 1gm daily for 3 days followed by oral Prednisolone 1mg/kg, Dialysis, pulse Cyclophosphmide. Plasma exchange, could not be performed in him due to lack of funds. He tested positive for p-ANCA (by immunoflurosecnce) and antibodies to myeloperoxidase

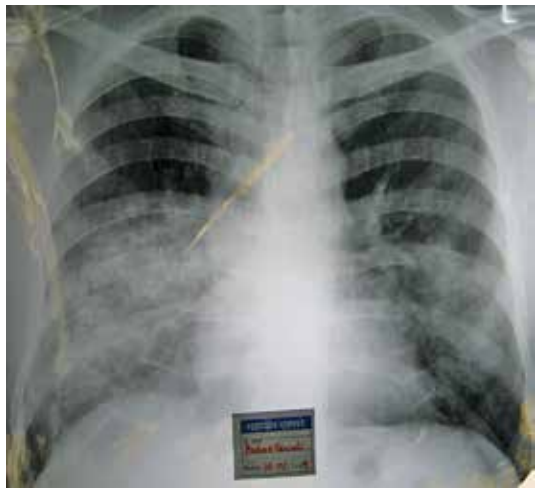

Fig. 3: Chest x-ray of case 1, bilateral alveolar shadows with apical sparing, S/O DAH

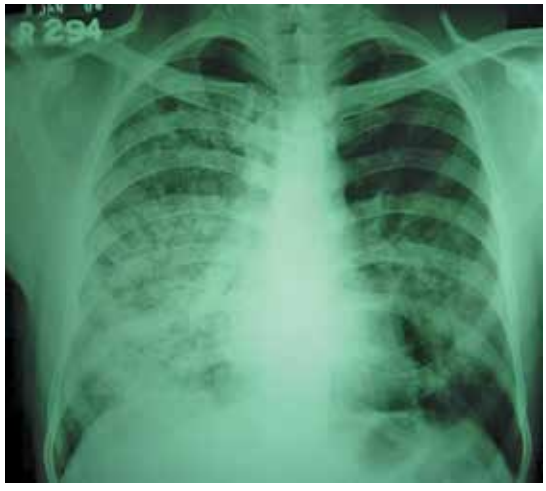

Fig. 4: Chest x-ray of case 1, DAH on admission

(MPO by ELISA). Anti- GBM and anti nuclear anti body, cryoglobulins, HBsAg, and anti-HCV, were negative. Thus he was ANCA positive small vessel vasculitis-microscopic poly angitis presenting as PRS. His kidney biopsy revealed crescentic GN (>50% crescents). He was discharged on oral Cyclophospamide (dose adjusted for creatinine clearance), with serum creatinine 2mg/dl, Hb- 7.5gm. At 6 months creatinine 2.3 mg/dl, Hb-10gm without dialysis. At 9 months creatinine 3.8 mg/dl. Patient was then lost to follow up.

Regarding PRS clinical presentation all investigators have reported a prodrome and an acute presentation. The prodrome consists of non-specific constitutional symptoms like malaise, fatigue, Fever, weight loss, Arthralgias, myalgias, Episcleritis, purpuric rash that precede acute presentation by an average of 3 months. Up to 8-12 months of prodrome has been reported.

Can we diagnose these patients before acute presentation? Say during the so called prodrome!

The occurrence of prodromal illness of significant duration in most cases indicates a need and opportunity for earlier diagnosis.

CASE 2

F/45, had respiratory symptoms for 8 months, initially upper respiratory (sneezing, nasal discharge and stuffiness of nose) which were diagnosed as allergic rhinitis by her doctor, later for her episodic cough and shortness of breath she was investigated and diagnosed as 'probable Interstitial Lung Disease' and treated with a short course of steroids on the basis of lung function tests, chest x ray (which was normal) and High resolution CT scan of chest (Figure 5)

After 8 months of treatment in private when she was admitted with us in November 1997, she had severe fatigue, with great difficulty doing her daily chores like cooking. But other than a tired look on her face and blood pressure 150/90, rest of the general and systemic examination was normal. Respiratory physician who was treating her, had told her husband that she had a lot of functional element… BUT as per her records her ESR was 135mm and urine examination revealed 120 RBCs /hpf!!! We suspected PRS and sent her blood for ANCA, ANA, ANTI-GBM antibodies. She was c-ANCA positive. Haemoglobin 8.5, WBC- 11,500/ cumm, Serum creatinine 1mg/dl, Ca- 9mg/dl, P- 3.5mg/dl. Her kidney biopsy (Figure 6) revealed 'multiple glomeruli, most were sclerosed, only 14 relatively preserved and showed fibrinoid necrosis and crescents. Biopsy consistent with the diagnosis of Wegener's Granulomatosis in end stage renal disease.' As her creatinine was 1mg/dl, we monitored her GFR. It was 30ml/min. She was treated with Steroids (Oral Prednisolone 1mg/kg for a month then tapered) and Cyclophosphamide (100 mg daily) for two years. Her GFR remained between 30-35 ml/min for next 5 years. In 2003 ie after 5 years GFR was 50ml and now 19 years later also it is maintained at 50 ml/min while she is taking Prednisolone 2.5mg/day and Methotreaxate 10mg per week. This patients is an excellent example of severity of renal damage (as per kidney biopsy and GFR) within just 8 months from onset of symptoms, and importance of timely adequate immunosuppression to salvage renal function.

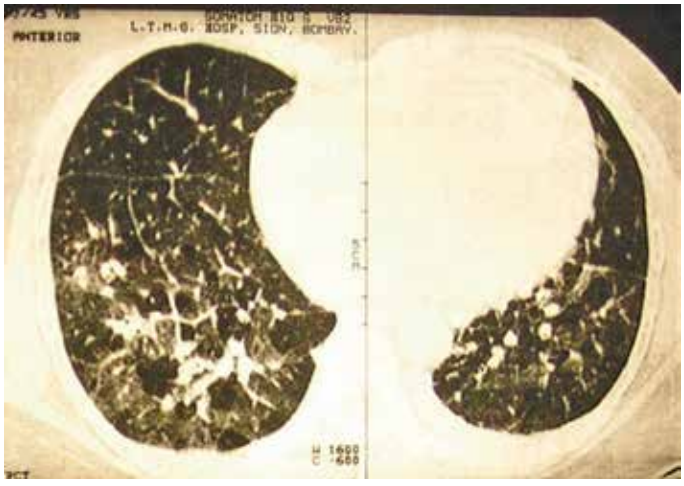

Fig. 5: HRCT chest of case 2, Ground glass opacities and fibrosis

Those cases of pulmonary-renal syndrome not related to Goodpasture's, syndrome usually have clinical features suggesting such diagnoses as vasculitis, acute synovitis, multiplex mononeuritis or previous history of SLE. PRS can be a presenting feature of ANCA positive vasculitis , but it's rare for SLE to presents as PRS. PRS is reported in 2% patients of SLE. It's known, patients of SLE who develops the complication. In PRS due to infectious causes (eg Leptospirosis) features of underlying disease (like jaundice) are present.

INVESTIGATIONS AND DIAGNOSIS IN PRS

What are the problems with timely diagnosis? (Clinical, Chest x-ray, serology(ANCA-ANA-anti-GBM antibody-Cryoglobulins), HRCT chest, DLCO, Bronchoscopy – BAL, biopsy)

Problems are mainly in the diagnosis of DAH.

1. On chest x-ray DAH may be misdiagnosed as infections like bronchopneumonia or tuberculosis or ARDS due sepsis, even raised creatinine may be attributed to MSOF, or it may also be misdiagnosed as pulmonary oedema due to renal failure.
2. Patient may be asymptomatic for DAH, haemoptysis may be absent in 1/3rd patients. In such cases x-ray chest may not be asked for.
3. Normal chest x-ray is reported in 20% patients with DAH.

Chest-CT is indicated in patients with hemoptysis with normal chest x-ray or with focal abnormality, atypical for

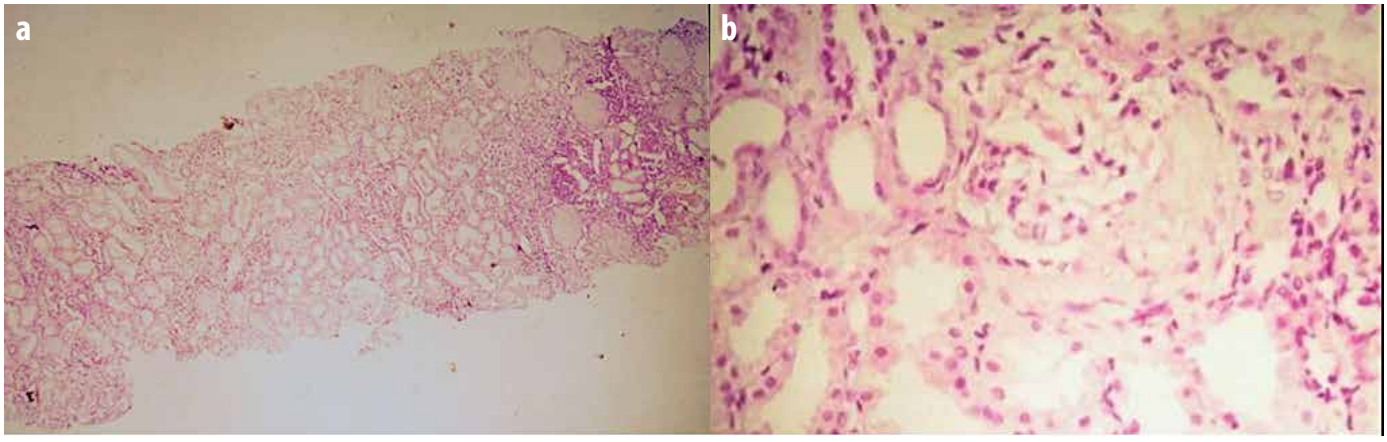

Fig. 6 (a, b): Kidney biopsy case 2, H&E, sclerosed glomeruli, fibrinoid necrosis & crescent (b)

TB. But HRCT chest plays a limited role in the assessment of patients with DAH . On HRCT, early DAH produces ground glass opacity and later fibrosis, a pattern that is seen in many conditions. In fact it generally gets reported as ILD and then one may not consider DAH as a diagnostic possibility.

Diagnostic criteria used for DAH are not uniform in all reports. Hemoptysis, alveolar opacities, anemia, hypoxemia, and/or elevated carbon monoxide transfer factor (DLCO) have been used to define DAH in many series. Carbon monoxide diffusion capacity (DLCO) is used as an adjunctive test to diagnose DAH. DLCO increases in DAH due to presence of haemoglobin in alveoli. If performed in the 1st 48 hours of DAH, an increase in DLCO of 30% over baseline or a value of ≥ 130% predicted is reported to be suggestive of DAH and is observed in 25% patients of DAH. Obtaining DLCO measurement is not practical at night and in critically ill patient.

BAL is more sensitive than any other criteria for the diagnosis of DAH. Fiberoptic bronchoscopy will show haemorrhages from many bronchopulmonary segments. It may show grossly pink/ red BAL in acute cases or haemosiderine laden macrophages (>30%).

A firm diagnosis of PRS is obtained by clinical presentation, serologic results and histological results although obtaining material for the latter may present practical difficulty in a critically ill patient. Tissue diagnosis should be obtained when cause of DAH is not confirmed by clinical/serological and bronchoscopic evaluation. Open lung biopsy is preferred over trans bronchoscopic lung biopsy. Lung biopsy shows RBCs/ hemosiderin laden macrophages in alveolar spaces. Evidence of capillaritis in the form of alveolar wall distruction and neutrophillic infiltration is rare. Diagnosis of GN is not a problem in presence of active urinary sediment and rising creatinine. Gold standard for diagnosis of PRS are lung/ kidney biopsy.

Author's personal suggestion is, treating physician should suspect DAH in a given clinical setting and chest x-ray abnormalities. In absence of fever, start Inj. Methyl prednisolone and daily repeat chest x-ray. The alveolar infiltrates of DAH disappear within 24-48 hours. When in doubt may give steroids under cover of higher antibiotics. But remember radiological improvement is not as fast in infection as in DAH, so, fast radiological improvement favours the diagnosis of DAH. Remember, majority cases of PRS are due to ANCA positive vasculitis, in which patients get leucocytosis, which may be mistaken to be due to infection. If there is confusion about DAH Vs pulmonary oedema (due to raised creatinine &/or hypertension) give injection Frusemide and look for clinical and radiologic improvement after few hours. If expected improvement does not occur, do consider DAH. It is also important to perform urine examination at the time of admission, before putting urinary catheter. Presence of proteinuria and haematuria rather than leucocytes or nitrites in urine should suggest GN over urosepsis, especially in presence of new onset hypertension. Urine routine is poor man's kidney biopsy! Also the later may not be possible in critically ill and those with serum creatinine more than 3mg/dl. Recommended treatment in acute nephritis/RPGN is immunosupression with Inj. MPS and Cyclophosphamide, with which improvement in Urine picture occurs rapidly, though fall in creatinine takes a little longer.

TREATEMENT OF PRS

1. Steroids and cyclophosphamide for all.
2. Add plasma exchange (7-14 days) in severe cases, Creatinine ≥ 5.7mg/dl to improve long term renal outcome, severe DAH, Good Pasture syndrome, Cryoglobulinaemia.
3. Ventilatory support, if in respiratory distress, hypoxia.
4. Add novel therapies (activated Factor VII, ECMO for DAH, Rituximab, IVIG) for refractory cases.

Immunosuppression is the cornerstone of treatment in ANCA associated PRS. Standard induction remission regimens include pulse intravenous methylprednisolone (500–1,000 mg) for 3–5 days. As the life threatening features subside, the dose can be reduced to 1 mg/kg prednisone daily for the first month, tapered over the next 3–4 months. Glucocorticoid therapy is combined with cytotoxic agents. Cyclophosphamide is the treatment of choice, at a dose of 0.5–1 gm/m^2 administered intravenously as a pulse per month or orally (1–2 mg/kg/day). Transition to maintenance therapy is done 6–12 months after the initiation of induction therapy or after clinical remission. The maintenance therapy includes low-dose corticosteroids coupled with cytotoxic agents. Despite rigorous treatment, many of patients with small-vessel vasculitis and PRS need renal transplantation within less than 4 years of initial presentation.

For CAPS related PRS anticoagulation is the main stay of treatment.

PERSONAL EXPERIENCE AND INDIAN DATA (PARTLY PRESENTED IN IRACON 2008)

I personally managed 13 PRS in my unit over 15 years. Gave MD thesis topic to PG student, who collected 12 PRS from 6 medical units, MICU, IRCU and AKD, in 30 months (Jul 2013-Dec 2015). Out of 25 PRS patients, there were 7 WG, 4 MPO, 1 CSS, 1 Good Pasture, 5 SLE, 7 infection related (Leptospirosis, dengue). All patients, other than those with infectious etiology were treated with steroids and Cyclophspamide, 1 Rituximab, 1 PE, 3 were dialysed, 14 required ventilator support (3 invasive, 11 NIV to start with but 5 had to be shifted to invasive ventilator), Overall survival was 68%, mortality 32%. In those who were on ventilator, mortality was 57% (all on NIV survived, all who eventually needed invasive ventilator, 8/14 died). In 2008, 1st author had collected Indian data on PRS by sending questionnaire to 61 rheumatologists, 12 had responded. Results were as follows : Total cases :113, (Rheumatic

diseases 97, Lepto-13, Dengue-3) WG : 45, MPA : 15, SLE : 30, APLA : 1, Goodpasture : 1, Other : 5 (PSS,CSS,TTP). Steroids + Cyc : all but infections, PE : 21, Ventilator : 37, Dialysis : 33, Other : Ritux. 5, IVIg 2, Death : 34 (38.4%), Dialysis dependence : 14. On an average rheumatologists with institutional attachment had seen 0-2 cases per year, and 0-25 cases over practice as 20 years of practice (average 8 PRS cases by individual rheumatologist over 20 years). In 30 months of PRS data collection by my PG student, all admitted patients with haemoptysis with breathlessness and alveolar shadows on chest film were subjected to urine routine examination, to detect simultaneous GN (In 12/25 patients presenting with respiratory complaints renal involvement was detected on investigations). And all admissions for GN and RPGN were specifically asked for history of haemoptysis in previous few months. This strategy, we believe, helped in detecting more PRS patients, who would otherwise probably be missed.

CONCLUSION

Considering the heterogeneity of severity of presentation, early recognition of PRS depends on a high index of clinical suspicion combined with a full assessment of the clinical picture, available serology, radiology and histology, and exclusion of alternative diagnoses. Timely institution of immunosuppressants and prevention of secondary infection is important in successful management of PRS, in ICU setting.

REFERENCES

1. Syndrome of lung haemorrhage and Nephritis is usually an ANCA-associated condition, *Arch Int Med* 1996; 156:440-445
2. Bench-to-bedside review: Pulmonary–renal syndromes – an update for the intensivist, *Critical Care* 2007; 11:213
3. Frankel SK, Cosgrove GP, Fischer A, Meehan RT, Brown KK. Update in the Diagnosis and Management of Pulmonary Vasculitis. *Chest* 2006; 129:452-465
4. Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosupresion, *Ann Intern med* 2001; 134:1033-1042, *Med* 2001; 134:1033-1042.
5. Pulmonary-renal syndrome: A 4-year, single-center Experience, *Am J Kidney Dis* 2002; 39:42-47.
6. Pulmonary-renal syndromes: An update for respiratory physicians, *Respiratory Medicine* 2011; 105:1413-1421
7. Pulmonary-renal syndromes: Experience from an Indian Intensive Care Unit, *Indian J Critical care medicine* 2015;316-25