We present two patients who presented to us with respiratory symptoms (case 1 haemoptysis and shortness of breath, case 2 cough and shortness of breath) with microscopic haematuria detected in routine urine examination. Both suffered from a similar disease. Timely intervention saved their lives and permanent organ damage in one.

Case 1

Forty three years old male from Dhule district of Maharashtra presented to his family doctor in December 2004 with malaise, anorexia, haemoptysis. After baseline x-ray (Figure 1) and blood tests he was started on anti tuberculosis treatment (ATT). Patient kept getting recurrent haemoptysis for which repeated x-ray chest were performed (Figure 2). In January 2006 he got admitted to our hospital with haemoptysis 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, no gallop or any organomegaly was present. 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, Erythrocyte Sedimentation Rate- 115mm at 1 hour, Urine Proteins2+, 15-20RBCs/hpf, x-ray chest revealed bilateral alveolar shadows with sparing of apices (Figure 3), ultrasound kidneys was reported as small contracted kidneys, sputum was negative for acid fast bacilli (5 samples) Patient was clinically diagnosed as ‘Pulmonary renal syndrome’ and treatment with Inj. Methyl Prednosolone 1gm daily for 3 days followed by oral Prednisolone 1mg/kg was started and first pulse of Cyclophosphmide 500mg was given, awaiting serology. (Antineutrophilic Cytoplasmic Antibody- ANCA, Anti-GBM antibody, ANA). His serum tested positive for p-ANCA (by immunofluoresecence)and antibodies to myloperoxidase (MPO by ELISA). His serum tested negative for Anti- GBM and anti nuclear anti body, cryoglobulins, HBsAg, and anti-HCV. So final diagnosis was ANCA positive small vessel vasculitis- microscopic poly angitis presenting as PRS. He was dialysed thrice ie till creatinine reduced to 3mg/dl and kidney biopsy was performed.
It revealed crescentic GN (>50% crescents). Oral Cyclophosphamide was given with dose adjusted for creatinine clearance. He was discharged on creatinine 2mg/dl, Hb-7.5gm. At 6 months creatinine 2.3 mg/dl, Hb-10gm with out dialysis. At 9 months creatinine 3.8 mg/dl. Patient was then lost to follow up. Plasma exchange, kidney biopsy specimen examination for immunofluorescence and electron microscopy could not be performed in him for lack of funds.

**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 4).

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

We performed her kidney biopsy (Figure 5). The report was ‘bit of kidney tissue showing multiple glomeruli, most are sclerosed, only 14 relatively preserved and show 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 (100mg daily) for two years. Her GFR remained between 30-35 ml/min for next 5 years. In 2003, ie after 5 years GFR was 50 ml/min and now 15 years later also it is maintained at 50 ml/min while she is taking Prednisolone 2.5mg/day and Methotreaxate 10mg per week.

**Discussion**

If we enumerate list of problems in our two patients:

1. **Clinical Problems** are Malaise, Anorexia, Weight loss, fatigue, cough, shortness of breath, Recurrent Haemoptysis (in case 1) and 2. **Laboratory Problems** are Anemia, Leukocytosis, Elevated ESR, Active Urine Sediment, Renal Failure, X-ray chest-DAH (in case 1), HRCT Chest: Bilateral Ground glass opacities (case 1) or bilateral reticular shadows (case 2) with GGOs in right bases. Thus both have a systemic illness with GN and pulmonary involvement ie PRS.

Pulmonary Renal Syndrome (PRS), is a combination of diffuse alveolar haemorrhage (DAH) and glomerulonephritis (GN), in most cases RPGN. It was first described by Good Pasture in 1919. The term Goodpasture syndrome was adopted in 1958 and the pathogenic role of anti-glomerular basement membrane antibodies (anti-GBM) in some cases of DAH and GN was proven 10 years later. An interesting study was conducted in Massachusetts general hospital on 88 patients’ sera (sent for anti-GBM test for DAH and GN from 1981-1993), after availability of ANCA test in the institute. It was found that 48 had ANCA, six had anti-GBM and seven had both. It has become clear now that several pathogenic mechanisms underlie this clinical syndrome of DAH and GN and the term PRS is now used to describe the condition.

PRS is not a single disease, it has a differential diagnosis of its own (Table 1). Timely diagnosis of PRS is important for associated high mortality (25-50%) need for Ventilatory support in 32-50% and dialysis dependence at 1 yr in up to 73% patients if not timely adequately treated.

But there are problems with timely diagnosis in ICU setting as common conditions like pneumonia, sepsis and cardiac failure are close differentials and premorbid signs symptoms of PRS are often nonspecific. Also as regards DAH, Patient may be asymptomatic for DAH, haemoptysis may be absent in 1/3rd patients. 2. On chest x-ray DAH may be misdiagnosed as infections like bronchopneumonia or tuberculosis or ARDS due sepsis, even raise creatinine may be attributed to MSOF, or it may also be misdiagnosed as pulmonary oedema due to renal failure. Chest x-ray is normal in 20% patients with

**Table 1 : Etiology of PRS**

- **Systemic Vasculitis** (2/3rd ANCA +ve)
  - Wegener’s Granulomatosis
  - Microscopic Polyangiitis
  - Churg-Strauss syndrome
  - Cryoglobulinemia
  - Henoch-Schonlein Purpura
- **Goodpasture’s Disease** (<5%)
- **Connective Tissue Disease**
  - Polymyositis/Dermatomyositis
  - Progressive Systemic Sclerosis
  - SLE, APLA
  - Primary Glomerular Disease
  - IgA nephropathy
  - Post-Infectious GN
  - Membranoproliferative GN
- **Drug, Infections, Neoplasm**
  - Haematopoetic stem cell transplant
- **Idiopathic Pulmonary Haemosiderosis**

![Kidney biopsy (H & E) A. Most glomeruli sclerosed, fibrinoid necrosis (B) and crescent (C) in relatively preserved glomeruli](image)
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 3-6 months. Up to 8-12 months of prodrome has been reported. And acute presentation is with cough, haemoptysis, hypoxic respiratory failure and RPGN. If patient is diagnosed in prodrome (as in case 2) we can salvage kidneys (note number of sclerosed glomeruli in Figure 5 with in 8 months of onset of symptoms). Those cases of PRS not related to Goodpasture’s, syndrome usually have clinical features suggesting such diagnosis as vasculitis, acute synovitis, multiplex mononeuritis or previous history of SLE. In PRS related to infections like leptospirosis, presence of other features of disease like jaundice aid in diagnosis and treatment is directed towards primary disease.

Table 2 gives list of investigations in PRS. Presence of autoantibodies is a predominant feature of PRS, it aids in diagnosis and in determining course of illness in PRS. Outcome is better in patients with PRS associated with ANCA than those with anti-GBM antibodies.

Treatment of PRS consists of Steroids and Cyclophosphamide for all, plasma exchange for severe cases (serum creatinine > 5.7mg/dl, life threatening...
DAH), supportive care (ventilator/dialysis) when necessary and novel therapies (Rituximab, IVIG, ATG, Factor VII, ECMO) for refractory cases. There is a place for antibiotics in PRS in SLE patients as infection is often a precipitating cause. Plasma exchange in patients presenting with serum creatinine >5.7 mg/dl has shown to improve renal survival at one year 43% Vs 19%.

**Conclusion**

Recognition of PRS is established by clinical features, serology and histology and may present practical difficulties in a critical care setting. The occurrence of prodromal illness of significant duration in most cases indicates a need for earlier diagnosis with the use of serological tests.

**References**