ORIGINAL ARTICLE

Pulmonary Renal Syndrome: Experience from Tertiary Centre in Mumbai

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Abstract

Introduction: Pulmonary Renal Syndrome (PRS), is characterized by diffuse alveolar haemorrhage (DAH) and glomerulonephritis (GN), occurring simultaneously. It has high mortality and dialysis dependence at one year, if not timely diagnosed and aggressively treated.

Objectives: To study etiology and short term outcome of PRS in India

Materials and Methods: This study included patients of PRS seen in a tertiary care center in Mumbai, by one consultant from 1997- 2013, analyzed retrospectively and from January 2014 to December 2015 collected prospectively from six medical units, intensive care unit, nephrology and respiratory units. Patients with DAH (haemoptysis, breathlessness and x-ray chest with bilateral alveolar shadows with sparing of apices) and glomerulonephritis (Proteinuria, heamaturia, hypertension with or without raised serum Creatinine) were included in the study after carefully excluding other causes of haemoptysis and breathless like tuberculosis, pulmonary oedema, pneumonia, ARDS. During prospective enrollment of patients, in all admitted patients with haemoptysis, urine examination was carried out to specifically look for proteinuria and red blood cells in urine, same was also followed in those admitted for breathlessness with chest x-ray suggestive of alveolar haemorrhage. Patients were extensively investigated for etiology and were treated with steroids and pulse cyclophosphamide (after ruling out infectious etiology). Supportive care with ventilator or dialysis was given as per usual indications. Palsmapheresis was initiated in those with serum Creatinine ≥ 5.7mg/dl. Rituximab was used in refractory cases, as per treating physicians' choice. Final outcome was death or discharge.

Results: There were 25 patients of PRS (13 retrospective, 12 prospective), with following etiology : Granulomatosis with polyangiitis (GPA) 7, Microscopic polyangiitis (MPO) 4, Churg Strauss Syndrome (EGPA) 1, Goodpasture's syndrome 1, lupus 5, leptospirosis 5, dengue 2. All were given steroids, 18 (72%) were given pulse Cyclophosphamide (barring those with leptospirosis and dengue), ventilator support in 14 (56%) patients (8 invasive, 6 non-invasive), haemodialysis 3, plasmapheresis 1, Rituximab 2. Seventeen (68%) patients survived, mortality was high in those requiring invasive ventilator.

Conclusions: Most common etiology of PRS is ANCA positive vasculitis in India. With high degree of suspicion for DAH in patients presenting with haemoptysis, breathlessness and alveolar opacities in chest x-ray and carefully investigating by simple urine examination for evidence of GN, timely diagnosis of PRS can be made. With timely appropriate treatment survival is 68%. Patients with PRS due to leptospirosis or dengue have features suggestive of underlying disease (like icterus with raised bilirubin but < 200U SGOT/SGPT, subconjunctival haemorrhage, typical rash of dengue with thrombocytopenia).

Introduction

PRS, is a combination of diffuse alveolar haemorrhage (DAH)and glomerulonephritis (GN), occurring simultaneously. Historically such 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. DAH is characterized by haemoptysis, breathlessness, fall in haemoglobin, hypoxia in severe cases, bilateral alveolar shadows with sparing of apices on chest x-ray. Whereas glomerulonephritis is generally rapidly progressive (hypertension, proteinuria-haematuria and rapidly rising serum Creatinine). All investigators have reported a prodrome,[2-4] followed by 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, but up to 8-12 months of prodrome has been reported. A remarkable feature of PRS is a rapid progression from a cough with haemoptysis to hypoxic respiratory failure over a few hours

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Table 1: Baseline characteristics of PRS patients N=25

Age	34.12±13.5yr (14-60 Yr)
Sex	11 M : 14 F
Duration of symptoms before diagnosis	38 days (3-395 d)
Presenting Features (respi/renal/both:12/2/11)	
Haemoptysis	17 (68%)
Breathlessness	22 (88%)
Cough	17 (68%)
Hypertension	14 (56%)
Oliguria	4 (16%)
Oedema	4 (16%)
Raised Creatinine	23 (92%)
Urine with proteinuria, Haematuria	25 (100%)
Fever	18 (72%)
Joint pain	3 (12%)
Rash	6 (24%)
Serum Creatinine mg/dl	2.78±1.7 (0.7-6.7)
Haemoglobin gm/dl	9.3±1.46 (6.8-12)
ESR mm at 1 hr	73.12±34.52 (18-132)
X-ray chest (N=28), Abnormal : Normal	24 : 4

or days. Haemoptysis is common but not invariable, and its absence may delay the diagnosis. Those cases of PRS 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 is not a single disease, it has a differential diagnosis of its own, most common cause being ANCA positive vasculitis, others being connective tissue diseases, Goodpasture syndrome, infections, drugs, neoplasms. The diagnosis rests on the identification of particular patterns of clinical, radiologic, pathologic and laboratory features. Timely diagnosis of PRS is important, considering high mortality (25-50%)[5,7], need for ventilatory support (35-50%)[6,7] and dialysis dependence at 1 year in over 70%[6]. Most of cases of pulmonary renal syndrome are undiagnosed because of lack of awareness, rarity, lack of facility to confirm diagnosis. PRS may be confused with other common disorders like pulmonary tuberculosis, bronchopneumonia, ARDS, pulmonary oedema, thus delaying instituting steroids, immunosuppressants and plasma exchange.

Material and Methods

Study design: This is an observational study, with serial recruitment of patients, retrospective from 1997- 2013 (single consultant's data) and prospective from January 2014- December 2015, from 6 medicine units, medical ICU, nephrology and respiratory units (ie from 9 areas), in a tertiary care centre from Mumbai.

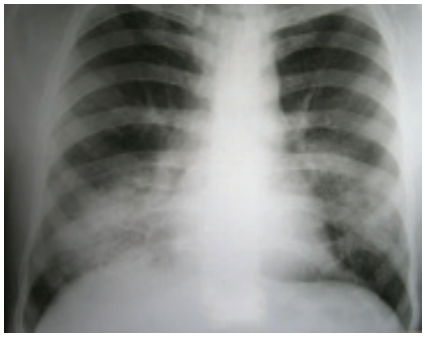

Fig. 1: Bilateral alveolar shadows with apical sparing in DAH

Inclusion criteria: All patients of either sex and any age having [A] features suggestive of diffuse alveolar hemorrhage (DAH) in lung Hemoptysis/ breathlessness not obviously attributable to tuberculosis, pneumonia, carcinoma and bronchiectasis. X-ray chest showing alveolar opacities with sparing of apices s/o DAH and [B] Glomerulonephritis / [RPGN] Hematuria (clinical or microscopic) RBC or RBC Casts in urine analysis, Hypertension, with or without raised serum Creatinine.

Exclusion criteria: Other causes of haemoptysis/ breathlessness, like tuberculosis, bronchopneumonia, pulmonary oedema, ARDS or of renal failure like septicaemia with ARF

Detail medical history, examination, urine routine, biochemistry, chest x-ray (wherever necessary HRCT chest), Anti Neutrophilic Cytoplasmic Antibody (ANCA) by immunofluoroscence which if positive anti-MPO or anti-PR3 antibody by ELISA, ANA (by IF), Anti-GBM antibody, Cryoglobulins, HBsAg, anti-HCV were performed. Kidney biopsy was performed in some cases, with patient's consent. Daily chest x-ray were performed to observe response to Inj. Methyl Prednisolone (disappearance of alveolar opacities) for initial 3-5 days.

Investigations and management protocol for prospectively enrolled patients: For prospective enrollment of patients, during 24 months, all patients who were admitted to hospital for haemoptysis or for breathlessness with chest x-ray suggestive of DAH, immediate urine routine examination was performed on a non-catheterized urine sample to look for haematuria. Similarly for patients admitted with nephritis, history of haemoptysis in previous few months was specifically asked and chest film at admission and from recent past (if available) were specifically seen for any alveolar opacities.

All patients of PRS were treated with Inj. Methyl Prednisolone (followed by oral Prednisolone 1mg/kg), Inj. Cyclophosphamide 750-1000 mg pulse (barring those with PRS due to obvious infections like leptospirosis or dengue). Supportive care with ventilator, dialysis was given when indicated. For those with Creatinine ≥ 5.7mg/kg plasma exchange was given. Rituximab was used in refractory cases.

Outcome was survival or death.

Results

There were total 25 patients of PRS (13 retrospective, 12 prospective), M:F :: 11:14, average age 34.12 ± 13.5 years (14-60 yr), average disease duration before diagnosis of PRS 38 days (range 3- 395 days). Table 1 depicts baseline characteristics of these patients. Out of 25 patients, 12 had only respiratory complaints, 2 renal and 11 patients both respiratory and renal abnormality at presentation. In patients presenting with pure respiratory complaints, renal involvement was detected because of specifically looking for red blood cells in urine in all admissions with haemoptysis, or with alveolar shadows on chest x-ray (Figure 1). Haemoptysis, breathlessness and cough were present in 68%, 88%, and 68% patients respectively, whereas hypertension, oliguria, oedema in 56%, 16% and 16%. History of fever, joint pain and rash was given by 72%, 12% and 24% respectively. Five patients were known SLE patients, 3 of them with poor compliance and one with regular follow up but refractory disease for 9 years and one misdiagnosed outside as tuberculosis. In 5 patients clinical suspicion of leptospirosis (jaundice, fever, myalgia) and in 2 that of dengue (fever, rash, thrombocytopenia) with laboratory test confirmation was already done and during their hospital stay they developed DAH

Table 2: Chest Imaging in PRS

Chest x-ray N=28	
Bilateral infiltrates	16
Unilateral infiltrates	4
Unilateral consolidation	2
Normal	4
Waxing and waning infiltrates	2
HRCT Chest N=11	
GGO	8
Consolidation	3
Fibrosis	1
Nodule	2

GGO- Ground glass opacities

as a complication, with raised serum Creatinine and hematuria.

Serum creatinine was more than 1mg/dl in 92% patients, with average Creatinine at presentation being 2.78±1.7mg/dl (range 0.7- 6.7), haemoglobin at presentation ranged from 6.7-10.9 gm/dl (mean 9.3±1.46), erythrocyte sedimentation rate ranged from 18-132mm at 1 hr (mean 73± 34 mm). Thrombocytopenia (platelets < 1 lac/cumm)was present in patients of leptospirosis, dengue and SLE; whereas remaining patients had normal or high (>4.5 lac/cumm) platelet count. There were 28 chest x-rays in these 25 patients, (Table 2) 16 revealed bilateral alveolar infiltrates with sparing of apices, 4 unilateral infiltrates, 2 unilateral consolidation, 2 waxing and waning shadows, 4 x-rays were normal. High resolution CT scan of chest was performed in 11 patients and revealed, ground glass opacities in 8, other reported findings being consolidation 3, fibrosis 1, and nodules 2.

Table 3 depicts etiology of PRS, in 11 (44%) it was ANCA positive vasculitis (7 GPA, 4 MPA), 5 SLE, 1 Goodpasture syndrome (anti-GBM positive), 1 Churg Strauss syndrome, 5 leptospirosis and 2 dengue. No patient had both ANCA and anti-GBM antibodies. Kidney biopsy was performed in 6 patients and revealed crescentic GN in 4, membranous nephropathy in one and Consistent with Wegener's granulomatosis in ESRD in one.

Tables 4 and 5 depict treatment given and outcome. All were given Inj. Methyl Prednisolone 1gm for 3 days, followed by oral Prednisolone. Inj Cyclophosphamide was given in 18 (72%) patients in whom PRS was not a complication of leptospirosis or dengue. Fourteen patients required ventilatory support, 8 invasive and 6 non-invasive ventilator. Haemodialysis

Table 3: Etiology of PRS N=25

Etiology	No. of cases	Percentage
ANCA positive	11	44%
GPA c-ANCA and anti-PR3 +ve	7	28%
MPA p-ANCA and anti-MPO +ve	4	16%
ANCA Negative	14	
Goodpasture syndrome Anti-GBM +ve	1	4%
SLE	5	20%
Churg Strauss syndrome / EGPA	1	4%
Infective	7	28%
Leptospirosis	5	20%
Dengue	2	8%

GPA- Granulomatosis with polyangiitis, MPA- Microscopic polyangiitis

was used in 3, plasma exchange in 1, and Rituximab in 2 (both SLE). Overall survival was 68% (17 out of 25), 32% (8 out of 25) died. Out of 19 patents with predominantly respiratory involvement 8 patients who required invasive ventilator; all died, whereas 6 on NIV survived. All six with predominantly renal involvement survived.

Discussion

This study included 25 patients of PRS, both prospective and retrospective, managed over 19 years in a single tertiary care centre in Mumbai. Out 25 patients of PRS, 13 are retrospective cases studied by single physician from 1997- 2013 in one medicine unit (ie 13 cases in 204 months by one consultant) and remaining 12 cases are collected prospectively from 2014- 2015, in the same institute from 6 medicine units, MICU, Nephrology and respiratory unit (ie 12 cases from 9 areas ie nine consultants, over 24 months). Thus with high index of suspicion, in a busy tertiary care centre, one case of PRS in 16-18 months was diagnosed by a consultant. Duration of symptoms before diagnosis of PRS was made was 38 days (3-395 days). Five patients were misdiagnosed before admission to our institution, 3 presenting with fever and haemoptysis were misdiagnosed as tuberculosis (later confirmed as PRS due to SLE 1, EGPA 1-with eosinophilia and waxing and waning infiltrates on chest x-ray and MPA 1), 2 with GPA with PRS, presenting with breathlessness were misdiagnosed as allergic rhinitis with ILD (on HRCT) 1 and bronchial asthma 1. Both these patients had normal chest x-ray at some point of time during their illness.

Table 4: Treatment of PRS N=25

Treatment	No. of patients (%)
Steroids	30 (100)
Cyclophosphamide	18 (72)
Ventilatory support	14 (56)
Haemodialysis	3 (12)
Plasmapheresis	1 (4)
Rituximab	2 (8)

Our patients were a decade younger than reported in literature.[8] Diagnosis of DAH is challenging. Triad of haemoptysis, radiographic abnormality (typically diffuse alveolar opacities/ interstitial opacities/ fibrosis), unexplained drop in haematocrit should make one suspect DAH, These features are individually present in 60-70%, 80-100%, 60-70% patients of PRS respectively, whereas the whole triad is reported in up to 38% in a meta-analysis of 112 cases.[9] In our study the triad was present in 68% patients. Haemoptysis may be absent in about one third cases, alveolar shadows may be unilateral (10-20%) or chest x-ray may be normal in 10-20% patients and drop in haemoglobin may not be possible to document, if previous Hb is not available. Also, if haemoglobin < 12 gm/dl is used as a cut off for anaemia as in western literature, most Indian patients are anaemic (100% in our study and with 10gm/dl as cut off 80% had low hemoglobin). Most consistent feature in the triad is alveolar opacities (reported in 93% in meta-analysis)[9] was present in 96% in our study. So, in a patient with respiratory symptoms like haemoptysis, breathlessness, cough; if alveolar opacities are present on chest x-ray one should consider diagnosis of DAH and should specifically look for evidence of glomerulonephritis (Hypertension, proteinuria, haematuria with or without raised serum Creatinine). Though bronchoalveolar lavage is very useful in the diagnosis of DAH and also gives material for culture to rule out infection, and for biopsy, it is not always practical in non- respiratory units on an urgent basis, and often not performed by chest physicians in a patient with haemoptysis unless sputum AFB is negative. Carbon monoxide diffusion capacity (DLCO), is raised in 30% patients in first 48 hours after alveolar haemorrhage, the test may not be available at odd hours and at bedside in a critically ill patient. On high resolution CT chest, alveolar haemorrhage is seen as GGOs in acute stage and later as fibrosis, both these

Table 5: Outcome in PRS N=25

Number of patients		Survived	Died	P value
		N (%)	N (%)	
25		17 (68)	8 (32)	
Ventilator	N=14	6	8	
Invasive	N=8	0	8	0.003 *
Non-invasive	N=6	6	0	0.003 *
No ventilator	N=11	11	0	
Serum creatinine	mg/dl			
<1.5	N=6	2 (66.7)	2 (33.3)	
1.5-5.7	N=17	12 (70.4)	5 (9.4)	
> 5.6	N=2	1	1	>0.05
Predominantly respiratory	N=19	11	8	
Predominantly renal	N=6	6	0	
GPA	N=7	3 (42.9)	4 (57.1)	
MPA	N=4	3 (75)	3 (25)	
SLE	N=5	2 (40)	3 (60)	
Goodpasture	N=1	1	0	
CSS	N=1	0	1	
Leptospirosis	N=5	5	0	
Dengue	N=2	2	0	

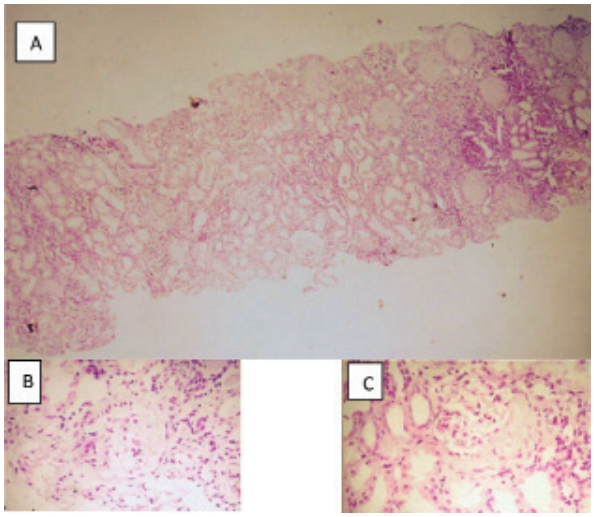

Fig. 2: Kidney biopsy (H and E) A. Most glomeruli sclerosed, fibrinoid necrosis (B) and crescent (C) in relatively preserved glomeruli

features have a long list of differential diagnosis. Thus diagnosis of PRS (clinical+ radiological+ serological+ histological) is by suspecting DAH when x-ray chest reveals alveolar opacities in a patient with respiratory symptoms and documenting GN by urine examination, hypertension with /without raised serum creatinine, and sending serological test for ANCA (which is the most common cause for PRS), ruling out mimics by all possible means, and documenting quick response (disappearance) of alveolar opacities within 24-48 hours of administering Inj. Methyl Prednisolone, and then performing kidney biopsy to document GN. When bacterial infection is in doubt this can be done under cover of antibiotics (infiltrates of infectious etiology don't disappear as fast as alveolar haemorrhage). PRS is generally not a presenting feature of SLE and develops in a known case of lupus. Infections like Leptospirosis, malaria, dengue would have their clinical features and laboratory tests for diagnosis. Low platelets occur in SLE and infections, whereas platelet count is normal or high in vasculitis and other CTD which can cause PRS.

In our patients breathlessness was most common presenting complaint (88%) followed by haemoptysis (68%), meaning thereby in 32% patients with DAH, haemoptysis was absent. Haemoptysis is reportedly absent in 30-40% patients of PRS[10]. Alveolar opacities were present at some point of time in (96%) 24 out of 25 cases, in one patient with normal chest x-ray, HRCT chest revealed GGOs and areas of fibrosis in lower and middle lobes, she was c-ANCA and anti-PR3 positive, Urine 100-120 RBCs /hpf, serum Creatinine 1mg/dl, kidney biopsy (Figure 2) was reported as most glomeruli sclerosed, 14 glomeruli relatively preserved and show mononuclear infiltrates, fibrinoid necrosis and crescents, biopsy consistent with Wegener's granulomatosis in end stage renal disease. But her GFR was 30ml/min (persisted for 5 years and improved to 50ml/min after 5 years). She was symptomatic for 8 months prior to diagnosis.

Table 2 depicts features of chest imaging in our patients. Most common imaging finding was bilateral alveolar opacities with sparing of apices (Figure 1), 6 unilateral opacities (sparing apices, which are commonly involved in Tuberculosis) and 4 out of 28 chest x-rays were normal at some point of time, but 3 patients' x-rays at other times revealed infiltrates. Other investigators have reported 7-20% normal chest x-rays in DAH. There are few studies reporting HRCT chest findings in DAH. In acute stage of AH, HRCT shows lobar or lobular ground glass opacities[16,17] (GGOs), later over 2-3 days may show interlobular septal thickening superimposed on areas of ground-glass opacity giving crazy pavement pattern, between chronic recurrent bleeding events ill-defined centrilobular nodules reflecting intra-alveolar accumulation of pulmonary macrophages usually uniform in size (1-3 mm) diffusely distributed may be seen, sev**ere** repeated haemorrhage may progress with features of interstitial fibrosis. CT chest is required in cases of suspected DAH with normal CXR findings. Table 3 depicts etiology, ANCA positive vasculitis being the most common cause of PRS in 11 out of 25 (7 GPA and 4 MPA), second being SLE (this may be due to referral bias as our unit is in-charge of rheumatology services, 1 was our regular follow up for 9 years, and on MMF for LN, 1 misdiagnosed outside as pulmonary tuberculosis, and three SLE patients were diagnosed cases but non-compliant with treatment), one patient was Goodpasture syndrome, 1 EGPA, 5 leptospirosis and 2 dengue.

Table 4 depicts treatment given to these 25 patients. All were treated with immunosuppressants (Inj. MPS in all 25, Inj. Cyclophosphamide in 18 patients, barring those with infectious etiology for PRS. Total 14 patients required ventilator support. Six patients on non-invasive ventilator survived but eight on invasive ventilator died. Haemodialysis was given to 3 patients. There were 2 patients with serum Creatinine >5.7mg/dl, but only one could afford plasma exchange, he was a case of MPO, the other non-affording patient was of Goodpasture syndrome. He received haemodialysis, survived but became dialysis dependent. Both controlled and uncontrolled studies have suggested that routine addition of plasmapheresis is unnecessary. However, when renal

function is impaired to the point that dialysis is required, the addition of plasma exchange increases the chance of renal recovery.[12,13,14,15] In the MEPEX trial the addition of PLEX to immunosuppressive therapy was found to improve 12-months renal outcomes in AAV patients presenting with severe renal dysfunction (serum creatinine > 5.8 mg/dl)[14] Two out of 5 SLE patients were given Rituximab.

Seventeen (68%) patients survived. Cruz and Hugh have reported 61% and 64% survival respectively. In an Indian study, by Rajgopal et al 31% survival is reported. Mortality occurred predominantly in patients with severe respiratory distress requiring invasive ventilator (Table 5). There was no relation of serum Creatinine to mortality.

Conclusion

DAH should be suspected in a patient presenting with breathlessness, haemoptysis, alveolar opacities (on chest x-ray) and anemia. Look for RBCs in the urine of such patients to detect associated renal involvement. And vice a versa in patients of nephritis/ RPGN ask for history of haemoptysis and look for alveolar infiltrate, thus timely diagnosing PRS. ANCA positive vasculitis is the most common cause of PRS. With steroids, pulse Cyclophosphamide and supportive care, 68% survival can be achieved. In our cohort, outcome was better in infection associated PRS than vasculitis or CTD associated PRS.

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