Research Article

Pulmonary-renal syndromes: Experience from an Indian Intensive Care Unit

Srinivas Rajagopala, Baburao Kanthamani Pramod Sagar, Molly Mary Thabah, B.H. Srinivas[1], Ramanathan Venkateswaran, Sreejith Parameswaran[2]

Abstract

Background: The etiology of patients presenting with pulmonary-renal syndrome (PRS) to Intensive Care Units (ICUs) in India is not previously reported. **Aims:** The aim was to describe the prevalence, etiology, clinical manifestations, and outcomes of PRS in an Indian ICU and identify variables that differentiate immunologic causes of PRS from tropical syndromes presenting with PRS. **Materials and Methods:** We conducted a prospective observational study of all patients presenting with PRS over 1-year. Clinical characteristics of patients with "definite PRS" were compared with those with "PRS mimics." **Results:** We saw 27 patients with "provisional PRS" over the said duration; this included 13 patients with "definite PRS" and 14 with "PRS mimics." The clinical symptoms were similar, but patients with PRS were younger and presented with longer symptom duration. Ninety-two percent of the PRS cohort required mechanical ventilation, 77% required vasopressors and 61.5% required dialysis within 48 h of ICU admission. The etiologic diagnosis of PRS was made after ICU admission in 61.5%. Systemic lupus erythrematosus (54%) was the most common diagnosis. A combination of biopsy and serology was needed in the majority (69%, 9/13). Pulse methylprednisolone (92%) and cyclophosphamide (61.5%) was the most common protocol employed. Patients with PRS had more alveolar hemorrhage, hypoxemia and higher mortality (69%) when compared to "PRS mimics." **Conclusion:** The spectrum of PRS is different in the tropics and tropical syndromes presenting with PRS are not uncommon. Multicentric studies are needed to further characterize the burden, etiology, treatment protocols, and outcomes of PRS in India.

Keywords: Crescentic glomerulonephritis, diffuse alveolar hemorrhage, pulmonary-renal, rapidly progressive renal failure, systemic lupus erythrematosus

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.158261

Quick Response Code:

Introduction

"Pulmonary-renal syndrome" (PRS) refers to the co-occurrence of rapidly progressive glomerulonephritis and alveolar hemorrhage.[1] Although any clinical condition with co-occurrence of renal failure and acute respiratory failure can be termed as PRS, this term is reserved for pulmonary infiltrates due to capillaritis and crescentic glomerulonephritis.[2] The most common causes of PRS include anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), anti-glomerular basement membrane (anti-GBM) disease, and systemic lupus erythematosus (SLE). These three diseases groups contribute to more than 80% of patients with PRS in the west.[3,4] The syndromic presentation

From:
Departments of Medicine, [1]Pathology and [2]Nephrology, Jawaharlal Institute of Postgraduate Medical Education and Research, Dhanvantri Nagar, Puducherry, India

Correspondence:
Dr. Srinivas Rajagopala, Department of Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Dhanvantri Nagar, Puducherry - 605 006, India.
E-mail: visitsrinivasan@gmail.com

How to cite this article: Rajagopala S, Sagar BP, Thabah MM, Srinivas BH, Venkateswaran R, Parameswaran S. Pulmonary-renal syndromes: Experience from an Indian Intensive Care Unit. Indian J Crit Care Med 2015;19:316-25.

may be similar in all these etiologies; however, there are differences in pathogenesis, diagnostic tests required, histopathological features, treatment protocols, and prognosis.[5] In the tropics, several fulminant infections presenting with alveolar hemorrhage and renal failure may mimic PRS[6] and may be more prevalent than vasculitis presenting with PRS. A high index of suspicion is required to identify PRS early and distinguish it from "PRS mimics" because of treatment implications.[7] We conducted the present study to describe the prevalence, etiology, spectrum, and outcomes of PRS in an Indian Intensive Care Unit (ICU) and identify clinical characteristics at presentation that may help distinguish patients subsequently diagnosed with "definite PRS" from "PRS mimics."

Materials and Methods

The study was a prospective observational study between January 2014 and December 2014 in a large tertiary care hospital in South India. All patients aged >18 years with a medical illness requiring intensive care were admitted to the medical ICU/High Dependency Unit (HDU) of our hospital. At ICU/HDU admission, clinical status examination, blood chemistry, blood gases, urine routine examination and chest radiography were performed in all patients. The measure of the severity of illness at ICU admission was performed by the Acute Physiological and Chronic Health Evaluation II (APACHE II) scoring system within 6 h of ICU admission. Choice of antibiotics, enteral nutrition protocol, blood sugar monitoring and glycemic protocol, decision on dialysis and administration of blood products, choice of fluid and vasopressors were determined by written ICU protocols.

Study subjects

Case series

Patients were diagnosed with "PRS" provisionally at ICU admission if they fulfilled all the below; acute illness (≤4 weeks) with evidence of renal and lung involvement at ICU admission, "active urinary sediment" on urine examination and pulmonary involvement consistent with diffuse alveolar hemorrhage (DAH) or vasculitis. "Active urinary sediments" was defined by the presence of at least one of the below; albuminuria (≥3+ on dipstick testing, >300 mg on 24-h collection or a urine protein/creatinine ratio >45 mg/mol), red blood cells (RBCs) or casts (RBCs or leukocyte casts) in urine microscopy examination with or without azotemia.[8] DAH was defined by the presence of at least two of the following; chest infiltrates consistent with DAH, hemoglobin ≤11 g/dL, and hemoptysis. In the absence of hemoptysis or a definite drop in hemoglobin, bronchoalveolar lavage fluid (BALF) showing grossly bloody returns or increasing bloody aliquots or hemosiderin-laden macrophages ≥20% was used as criteria for DAH.[9] All patients with "provisional PRS" who did not have a clear diagnosis at presentation underwent an echocardiogram, ultrasound of the kidneys, and appropriate bacterial cultures; the need for peripheral smears and antigen (histidine-rich protein 2) testing for malaria, IgM enzyme-linked immunosorbent assay (ELISA) for leptospirosis, nested PCR for scrub typhus or other appropriate tests was decided by the treating intensivist. Patients initially labeled as "provisional PRS," but with no definite evidence of DAH or had a nonimmune etiology for PRS on subsequent evaluation were labeled as "PRS mimics" [Figure 1]. In patients with "definite PRS," evaluation for the underlying etiology of PRS was initially performed with a panel of anti-nuclear antibody by indirect immunofluorescence (IIF), antinuclear cytoplasmic antibodies (ANCA) by IIF, anti-GBM antibodies by ELISA and complement levels (C3, C4). Appropriate guided-biopsies were performed from involved target organs (kidneys and/or lungs) to further characterize the individual diagnosis of PRS.[10,11] Treatment was initiated when the syndromic diagnosis of "definite PRS" was made with pulse methylprednisolone 1 g daily for 3 days, followed by 1 mg/kg/day enteral prednisolone and IV cyclophosphamide 750 mg/m^2 in the absence of infection or recent major gastrointestinal bleeding. Pantoprazole was administered to all patients during steroid therapy. The dose of cyclophosphamide was modified for an estimated eGFR <10 mL/min to 75% of the estimated dose. Six hundred mg mesna IV in three divided doses was administered in all patients along with cyclophosphamide. Rituximab was not used because of unavailability. Plasmapheresis (hemonitics PCS® 2 centrifugal pump) was initiated with 1.5 plasma volume exchanges (60 mL/kg) in the presence of definite DAH or serum creatinine >5.6 mg/dL and "definite PRS;" fresh frozen plasma (FFP) was used as

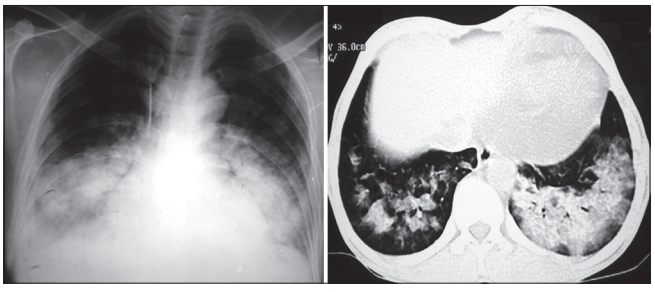

Figure 1: Composite image of the chest radiograph (left) and computed tomography (CT) of the chest (right) of patient 1 with showing bilateral lower lobe consolidation with corresponding asymmetric ground glass opacities and crazy-paving on CT. A clinical diagnosis of alveolar hemorrhage (DAH) was made

replacement. Four percent albumin was also used when available. The ICU treating team in concurrence with the nephrology team initiated hemodialysis. Hemodialysis was performed by intermittent hemodialysis over 4 h or sustained low-efficiency dialysis over 9–12 h, when hemodynamically unstable. The decision on the number of sessions of plasmapheresis and hemodialysis and subsequent immunosuppression was decided in consensus with the rheumatology and nephrology teams. Bleeding was managed with random donor platelets or single donor platelets, FFPs, cryoprecipitate and packed red cell transfusions (RBCs) as guided by the results of platelet count, hemoglobin, prothrombin time, activated partial thromboplastin time, and fibrinogen levels. Prothrombin concentrates or activated factor VIIa were not used due to unavailability. Asymptomatic platelet counts ≤20,000/ml were treated prophylactically to a count greater than this level. Packed RBCs were transfused if ongoing major bleeding or if hemoglobin was ≤7 g/dL to a level greater than this.

Outcome measures

Data were abstracted prospectively in a predefined data collection form [Appendix 1] and a descriptive analysis was performed. The age, gender, symptoms and their duration, APACHE II scores at ICU admission, time to diagnosis after ICU admission, treatment administered and outcomes were compared between patients with "definite PRS" and "PRS mimics."

Ethics

The study was approved by the scientific society (JSASC) and Research Ethics Committee of our Hospital. All data abstracted was anonymized, thus ensuring confidentiality and patient privacy.

Statistics

Statistical analyses were performed using SPSS version 14 (IBM Corporation, United States). Continuous variables were described in a descriptive fashion (mean ± standard deviation, median, interquartile range), and discrete variables were described as frequency proportions. Comparisons for continuous variables were performed using the Mann–Whitney test and proportions using the Chi-square test or Fisher's exact test where appropriate. Statistical significance was assessed at the 2-sided $P \leq 0.05$ level.

Results

We saw 27 patients with "provisional PRS" over the said duration; this included 13 patients with a subsequent diagnosis of "definite PRS" and 14 patients with "PRS mimics" [Table 1 and Figure 2]. The "definite PRS" cohort accounted for 5% (13/254) of ICU/HDU admissions with a diagnosis of renal failure requiring dialysis and 0.9% (13/1325) of the total ICU/HDU admissions during this period.

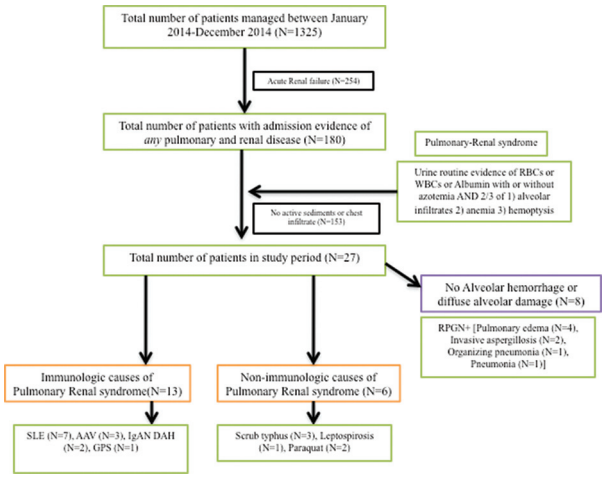

Figure 2: Study flow-chart

The clinical characteristics of the individual patients are described in Table 1. Two of these patients (case 9 and 12, both with IgA vasculitis) have been previously described. Patients presenting with PRS were 20–30 years and SLE was the most common etiology of PRS (Table 2, 54% of all patients). Breathlessness and leg swelling were the most common complaints; hemoptysis at presentation was seen in 46% (6/13) only. Patients were symptomatic for a median of 2 (8) weeks before seeking healthcare at any center and were admitted to our ICU after a median of another 4 (5.5) weeks evaluation at several other centers. Patients were admitted with advanced organ dysfunction to the ICU, with a mean APACHE II score of 19.8 ± 7.6 at admission. Mechanical ventilation was required in 92% (12/13) for hypoxemic respiratory failure due to DAH, 77% (10/13) required vasopressors, and 61.5% (8/13) required dialysis within 48 h of ICU admission. The etiologic diagnosis of the PRS was made after ICU admission in 8/13 (61.5%) of patients, with a median delay of 4 (5.5) days. In those with a diagnosis prior to ICU admission, a diagnosis of SLE (4/5, 100%) and IgA nephropathy (1/5) had been made at a median of 9 (12) months prior to the current symptoms. Fifteen percent (2/13) had evidence of nephrotic syndrome at presentation. Recognition of alveolar hemorrhage was mostly clinical, with 77% (10/13) having a drop in hemoglobin and 9/13 (69%) having infiltrates consistent with alveolar hemorrhage [Figures 1 and 3]. Only 3/13 (23%) of our cohort needed broncho-alveolar lavage for the diagnosis of alveolar hemorrhage and BALF

Table 1: Summary of clinical findings of patients with immunologic etiology of PRS in our ICU (*n*=13)

Age/ gender	Symptoms at presentation					Symptom duration (weeks)	Renal findings			Pulmonary findings						APACHE II	Diagnosis	Treatment	Outcome
	Dyspnea	Hemoptysis	Cough	Oliguria	Edema		Urine	S. Cr	Bx	Imaging	Hh drop	Hb	PaO_2/FiO_2	BAL	MV	Others			
15/male	Y	Y	N	Y	Y	2	RBCs alb+	4	CGN, IIF-linear IgG+	Cons	Y	5	150	N	Y	IgG anti-GBM	28	GPS	Pulse MP, CYC, PEx	D-d7[!]
16/female	Y	N	Y	N	Nephrotic	2	Alb+	1.4	DGN, IIF-IgG, IgM, C3+	Cons, PE	N	8.6	132	Y	Y	ANA, PM LBx	26	SLE	Pulse MP	D-d2
17/female	Y	Y	Y	Y	Y	1	RBCs alb+	22.4	CGN, IIF-neg	Nodular	Y	4.1	150	N	Y	P-ANCA	29	MPA	Pulse MP, CYC, HD, PEx	A, CKD
22/female	Y	Y	Y	N	N	1	RBCs alb+	0.9	FPGN, IIF-IgG, IgM, C3+	Cons	Y	9.6	94	N	Y	ANA, anti-ds DNA	13	SLE	None	D-d2
35/female	Y	N	N	Y	Y	12	RBCs alb+	6	FPGN, IIF-IgG, IgM, C3+	Cons	Y	5.8	136	N	Y	ANA, anti-ds DNA	20	SLE	Pulse MP, HD, CYC	D-d7[#]
21/ female ^	N	N	N	Y	Y	0.5	RBCs alb+	4.3	MsGN, IIF-IgG, IgM, C3+	Cons, PE	Y	8.6	160	N	Y	ANA	20	SLE	Pulse MP, HD, PEx	D-D2
22/female	Y	N	N	N	Y	1	RBCs alb+	1.8	DGN, IIF-IgG, IgM, C3+	Nodular	Y	7.8	106	N	Y	ANA	10	SLE	Pulse MP, CYC, PEx	A
18/female	N	Y	Y	N	Y	24	RBCs alb+	7	CGN, IIF-neg	Cons	Y	6.1	310	N	N	P-ANCA	12	MPA	Pulse MP, CYC, PEx	A, CKD
45/female	Y	Y	Y	Y	Y	2	RBCs alb+	8.8	CGN, IIF-IgA+	Cons	Y	6.2	80	N	Y	LBx: IIF IgA+	26	IgAN	Pulse MP, CYC, PEx, ECMO	D-d8[**]
29/female	Y	N	N	N	N	12	RBCs	1.2	Not done	Cavity	N	8.8	320	Y	Y	ANCA-, SLBx	11	GPA, HLH	HLH 2004	D-D23[%]
25/female	Y	N	N	Y	Nephrotic	24	Alb+	5.6	DGN, IIF-IgG, C3+	Cons, PE	Y	5.5	106	N	Y	ANA	26	SLE	Pulse MP, CYC	A, CKD
22/female	Y	Y	Y	Y	N	12	Alb+	6	CGN, IIF-IgA+	Cons	Y	6.8	280	N	Y	PM Bx: IIF IgA+	12	IgAN	Pulse MP	D, D23[@]
45/female	Y	N	Y	N	N	2	RBCs	1.1	Not done	Cons	N	10.1	280	Y	Y	ANA, IgM aCL	26	SLE, APLA	Pulse MP	D, D4

[!]Died due to pseudomonas-related ventilator acquired pneumonia; [#]Enterobacter bacteremia; [**]Acinetobacter-related bloodstream infection; ^ Had pain abdomen and melena with evidence of mesenteric vasculitis at presentation; [%]Admitted with HLH and initial etiologic work-up negative. Developed cavity, alveolar hemorrhage and nephritis on ventilator and BAL Hemosiderin-laden macrophages, ANCA negative and SLBx consistent with GPA; [@]Died D23 due to ventricular fibrillation during dialysis. S. Cr: Serum creatinine (mg/dL); Bx-Biopsy; Hb: Hemoglobin; Pao_2: Partial pressure of Oxygen mmHg; FiO_2: Fraction of inspired concentration of oxygen; BAL: Bronchoalveolar lavage; MN: Mechanical ventilation; APACHE II: Acute physiology and chronic health evaluation score II (at admission); Y: Yes; N: No; +: Present; RBC: Red blood cells; Alb: Albumin; CGN: Crescentic glomerulonephritis; FPGN: Focal proliferative glomerulonephritis; MPGN: Membranoproliferative glomerulonephritis; MsGN: Mesangio-proliferative glomerulonephritis; IgAN: IgA Nephropathy, IgG anti-GBM: Glomerular basement membrane antibody; ANA: Anti-nuclear antibody; ANCA: Anti-neutrophil cytoplasmic antibody; anti-dsDNA: anti-double stranded deoxyribonucleic acid antibody; SLBx-surgical lung biopsy; IIF: Indirect immunofluorescence; IgM aCL: Anticardiolipin antibody; GPS: Goodpasture's syndrome; SLE: Systemic lupus erythrematosus; MPA: Microscopic polyangiitis; GPA: Granulomatosis with polyangiitis; HLH: Hemophagocytic histiocytosis; APLA: Antiphospholipid antibody syndrome; MP: Methylprednisolone; CYC: Cyclophosphamide; HD: Hemodialysis; PEx: Plasma exchange; HLH 2004: HLH protocol; A: Alive; D: Died; d2: Day 2; ICU: Intensive care unit; PRS: Pulmonary-renal syndromes

Table 2: Summary of clinical findings of patients with immunologic cause of PRS in our ICU (*n*=13)

Clinical characteristic	Value
Age (mean±SD)	25.5±10.2 years
Gender (male:female)	3:10
Etiology of PRS	Systemic lupus erythrematosus (7/13, 54%), AAV (3/13, 23%), IgAN (2/13), GPS (1/13)
Symptoms at presentation	Breathlessness (12/13, 92%), hemoptysis (6/13, 46%), cough (7/13, 54%), oliguria (7/13, 54%), edema (9/13, 69%), fever (6/13, 46%)
Duration of symptoms, median (IQR)	2 (8) weeks
Duration to presentation after initial evaluation, median (IQR)	4 (5.5) weeks
Initial tests	
Urine microscopy	RBCs (10/13, 77%), RBC casts (5/13, 38%), WBCs (5/13, 38%), Albuminuria (11/13, 85%)
Initial serum creatinine, median (IQR)	4 (5.5) mg/dL
Renal biopsy (*n*=11)	CGN (5/11, 45%), DGN (3/11, 27%), FPGN (2/11, 27%)
Chest radiology (*n*=13)	Consolidation (8/13, 61.5%), Reticulo-nodular (4/13, 30.75%), pleural effusions (6/13, 46%), cavity (1/13, 8%)
CT (*n*=6)	Consolidation (3/6, 50%), GGO (5/6, 83%), pleural effusions (4/6, 67%), cavity (1/6, 17%)
Hemoglobin (mean±SD)	7.15±1.9 g/dL
Drop in hemoglobin in hospital (≥2 g/dL)	10/13 (77%)
Broncho-alveolar lavage fluid ≥20% HALMs (*n*=3)	3/3 (100%)
Skin manifestations	15% (2/13) purpuric rash
Neurologic manifestations	None
Platelet counts, median (IQR)	87000 (154000) μg/dL
PaO_2/FiO_2 (mean±S.D)	170.4±81.6 mmHg
APACHE II score at ICU admission (mean±SD)	19.8±7.6
Time to diagnosis from ICU admission, median (IQR)	4 (5.5) days
Diagnosis achieved by	Serology alone (2/13, 15.5%), biopsy alone (2/13, 15.5%), both (9/13, 69%)
Course in hospital	
Mechanical ventilation	12/13 (92%)
Mechanical ventilation duration, median (IQR)	96 (202) h
Dialysis	8/13 (61.5%), median 4 (9) sessions per patient
Vasopressors	10/13 (77%), median (IQR) 4 (4.5) days
Highest serum creatinine, median (IQR)	5.8 (5.9) mg/dL
Highest serum bilirubin, median (IQR)	0.8 (1.7) mg/dL
Lowest PaO_2/FiO_2	79±21.3 mmHg
Treatment	
Pulse methylprednisolone, followed by steroids	12/13 (92%)
Pulse cyclophosphamide	8/13 (61.5%)
Plasmapheresis	6/13 (46%), median (IQR) 4 (4.5) sessions
Outcomes	
Alive/dead	4/9 (31% survival)
Complications of treatment	Infection 7/13 (54%) drug toxicity 2/13 (15%)
Chronic kidney disease among survivors	3/4, (75%)
Length of ICU stay, median (IQR)	7 (6) days
Length of hospital stay, median (IQR)	11 (12.5) days

CGN: Crescentic glomerulonephritis; FPGN: Focal proliferative glomerulonephritis; DGN: Diffuse glomerulonephritis (class IV lupus nephritis); GPS: Goodpasture's syndrome; SLE: Systemic lupus erythrematosus; AAV: ANCA associated vasculitis; IgAN: IgA nephropathy; RBCs: Red blood cells, WBCs: White blood cells; GGO: Ground glass opacities; SD: Standard deviation; IQR: Interquartile range; ICU Intensive care unit; APACHE II: Acute physiology and chronic health evaluation score II (at admission); CT: Computed tomography; PRS: Pulmonary-renal syndromes

showed increasing hemorrhagic returns [Figure 3] in all. The etiologic diagnosis of PRS was made using a combination of biopsy (mostly renal, Figures 4-6) and serology in most of the patients (69%, 9/13). Percutaneous or surgical lung biopsy was performed in 15% (2/13) of the "definite PRS" cohort only [Figure 5, right]. Pulse methylprednisolone followed by enteral steroids (12/13, 92%) and pulse cyclophosphamide (8/13, 61.5%) was the most common protocol employed. In those who did not receive cyclophosphamide, a fulminant fatal course (4/5, 80%) or an active infection (1/5, 20%) prevented initiation of this protocol. Plasmapheresis was administered in 46% (6/13), for a median of 4 (4.5) sessions per patient. PRS was associated with very high mortality (9/13, 69%). Mortality was biphasic with an early peak at 48 h due to fulminant DAH and later (median day 8) due to infection aggravated by immunosuppression. Morbidity in survivors was also high; chronic kidney disease in survivors was seen in 75% (3/4) and brain abscess in another patient (1/4). Two of the survivors are dialysis-dependent at 3 months after discharge (50%, 2/4).

Patients subsequently diagnosed to "PRS mimics" were older, had a high-grade fever and shorter duration

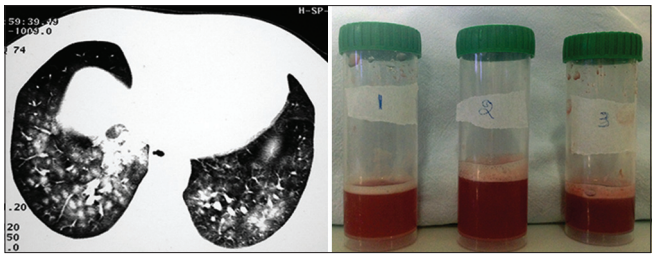

Figure 3: Composite image of the chest-computed tomography (left) of patient 10 with granulomatosis with polyangiitis showing bilateral lower lobe air-space nodules with ground glass opacities. A thick-walled cavity in the right upper lobe was also present (not shown). Broncho-alveolar lavage showed increasingly hemorrhagic returns diagnostic of alveolar hemorrhage. Surgical biopsy confirmed granulomatosis and polyangiitis

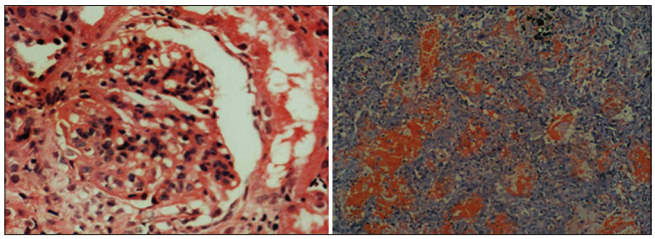

Figure 5: Composite image of percutaneous renal biopsy specimen (left, H and E×400) of patient 2 with systemic lupus erythematosus showing endocapillary proliferation and cellular crescent and postmortem lung biopsy specimen showing alveolar septa expanded by inflammatory infiltrate and diffuse alveolar hemorrhage (right, H and E, ×400). Immunofluorescence of the kidney specimen showed full-house pattern (not shown)

of symptoms when compared to patients with PRS. Clinical symptoms and severity of illness at presentation, however, were similar in both groups [Table 3]. A drop in hemoglobin (odds ratio [OR] 20, $P = 0.01$) and worse hypoxemia was seen more often in the PRS group and this was associated with a greater need for transfusions and vasopressors (OR 6, $P = 0.03$). The diagnosis of PRS was associated with higher mortality (OR 5.6, $P = 0.04$) when compared to syndromes mimicking PRS.

Discussion

Small vessel vasculitis is the most common cause of PRS worldwide and this syndrome represents its polar fulminant presentation.[3,12] AAV and Goodpasture's syndrome are rare disorders; an incidence of 10 cases/million and 1 case/million, respectively, has been reported in Caucasians.[13] While small series of systemic vasculitic syndromes have been reported from India,[14,15] prevalence in the Indian population remains unclear. SLE is a commonly recognized autoimmune disease in our population.[16] SLE presenting with alveolar hemorrhage is rare, is reported in 1–5.4% of patients[17] and often occurs in association with lupus nephritis.[18,19] There is no systematic data on patients presenting with PRS from India; a search in PubMed using the terms "vasculitis" or "PRS" and "India" supplemented by an

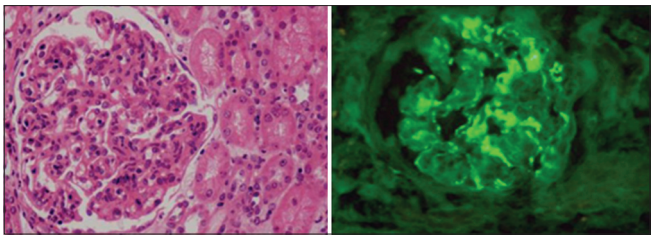

Figure 4: Composite image of percutaneous renal biopsy specimen (left, H and E ×400) of patient 4 with systemic lupus erythrematosus showing endocapillary proliferation with basement membrane thickening and duplication. Immunofluorescence (right, FITC stain, monoclonal antibody for IgG, DAKO, USA, ×20) showed full-house pattern (also positive for IgM, C3, C1q, κ and λ [not shown])

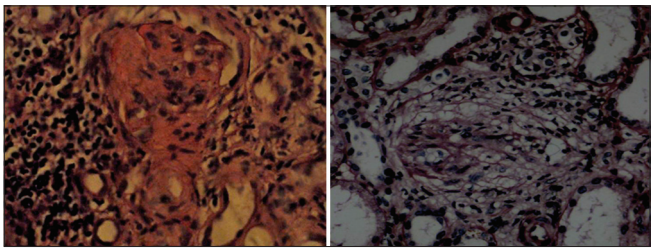

Figure 6: Composite image of percutaneous renal biopsy specimen (left, H and E ×400) of patient 3 with microscopic polyangiitis (MPA) showing a cellular crescent and fibrinoid necrosis within the glomerulus and afferent arteriole. The photomicrograph on the right (H and E ×400, patient 8 with MPA) shows perivascular inflammatory infiltrate with few palisading macrophages and a small focus of fibrinoid necrosis. Immunofluorescence of the kidney specimens showed no staining with IgG, IgM, C3, C1q, κ and λ (pauci-immune, not shown)

IndMed search using the term "vasculitis" turned up 1334 references with representative cases of every reported vasculitis syndrome and several tropical infections mimicking vasculitis. Large tertiary hospitals in India report a diagnosis of about 10–15 patients of systemic vasculitis each year.[15]

The exact etiology or trigger for small-vessel vasculitis remains unknown. The pathogenesis involves *in-situ* microangiopathy due to a Type II hypersensitivity, immune-complex mediated damage, and autoantibody driven cell-mediated damage; PRS can be classified as Type I (GPS), Type II (SLE), and Type III (AAV) based on this pathogenetic model. The nomenclature and our understanding of the individual vasculitis syndromes are evolving.[10,15]

A wide variety of diseases can present with PRS [Table 4a].[2] Our cohort was different from prior published series of PRS in several aspects; a large proportion were patients in whom the diagnosis was first made in the ICU, presentation was late with severe hypoxemia and need for multi-organ support and a large proportion of patients were diagnosed with SLE. The diagnosis is usually made prior to ICU admission

Table 3: Comparison of clinical findings between patients with PRS and PRS "mimics"

Clinical characteristic	PRS (*n*=13)	PRS mimics (*n*=14)	Statistics
Age (mean±SD)	25.5±10.2 years	38.4±12.87 years	0.009
Gender (male/female)	3/10	7/7	OR 0.3, *P*=0.23
Duration of symptoms prior to presentation, median (IQR)	2 (8) weeks	0.87 (0.8) weeks	0.002
Duration to presentation after initial evaluation, median (IQR)	4 (5.5) weeks	2.5 (6.18) weeks	1.00
Initial symptoms			
Breathlessness, *n*/*N* (%)	12/13 (92%)	14/14 (100%)	*P*=0.48
Hemoptysis, *n*/*N* (%)	6/13 (46%)	6/14 (43%)	OR 1.14, *P*=0.86
Oliguria, *n*/*N* (%)	7/13 (54%)	8/14 (57%)	OR 0.88, *P*=0.86
Fever, *n*/*N* (%)	6/13 (46%)	6/14 (43%)	OR 1.14, *P*=0.86
Temperature ≥102°F	0/13	6/14	OR 20.7, *P*=0.04
Initial tests			
Initial Serum creatinine (mg/dL)	4 (5.5)	2.5 (6.18)	1.00
Hemoglobin (g/dL), mean±SD	7.15±1.9	8.5±2.08	0.08
Drop in hemoglobin in hospital (≥2 g/dL), *n*/*N* (%)	10/13	2/14	OR 20, *P*=0.01
Platelet counts (μg/dL), mean±SD	87000 (154000)	199000 (172250)	0.2
PaO_2/FiO_2 at ICU admission, mean±SD	170.4±81.6	199±64.5	0.32
APACHE II score at ICU admission, mean±SD	19.8±7.6	16.5±5.8	0.23
Time to diagnosis from ICU admission, median (IQR)	4 (5.5) days	4 (4.5) days	0.65
Course in hospital			
Mechanical ventilation, *n*/*N* (%)	12/13 (92%)	12/14 (86%)	OR 2.0, *P*=1.0
Mechanical ventilation duration, median (IQR)	96 (202) h	96 (129.5)	0.54
Dialysis, *n*/*N* (%)	8/13 (61.5%)	8/14 (57%)	OR 1.2, *P*=0.81
Dialysis sessions, *n*/*N* (%)	4 (9)	1 (6.25)	0.46
Vasopressors, *n*/*N* (%)	10/13 (77%)	5/14 (36%)	OR 6, *P*=0.03
Highest serum creatinine, median (IQR)	5.8 (5.9) mg/dL	6.35 (4.25) mg/dL	0.58
Highest serum bilirubin, median (IQR)	0.8 (1.7) mg/dL	1.25 (1.42) mg/dL	0.35
Lowest PaO_2/FiO_2, mean±SD	79±21.3 mmHg	119.6±53.2 mmHg	0.01
Outcomes			
Alive/total, *n*/*N* (%)	4/13 (31%)	10/14 (72%)	OR mortality, 5.6, *P*=0.04
Length of ICU Stay, median (IQR)	7 (6) days	6 (3.5) days	0.79
Length of hospital stay, median (IQR)	11 (12.5) days	12 (9) days	0.9

Pao_2: Partial pressure of oxygen mmHg; FiO_2: Fraction of inspired concentration of oxygen; ICU: Intensive care unit; APACHE II: Acute physiology and chronic health evaluation score ii (at admission); SD: Standard deviation, IQR: Interquartile range, OR: Odds ratio; PRS: Pulmonary-renal syndromes

Table 4a: Causes of PRS

Anti-GBM antibodies related
Anti-GBM disease (GPS, including "double-positive patients ^ ")
AAV
GPA, previously Wegener's granulomatosis
MPA
EGPA, previously Churg-Strauss syndrome
Collagen vascular disease related
SLE
Primary APLA
Polymyositis
Systemic sclerosis
Rarer causes of PRS
IgA Vasculitis (Henoch-Schonlein purpura and IgA nephropathy)
Mixed cryoglobulinaemia
Behcet's disease
Drug-induced vasculitis
Hydralazine, propylthiouracil, D-penicillamine, phenytoin, mitomycin, allopurinol, sulfasalazine
Toxins: Acute silicoproteinosis, trimetallic anhydride (epoxy resin) toxicity
Idiopathic PRS
PRS mimics
Infections
Tropical infectious syndromes: Leptospirosis, malaria, hantavirus syndrome, scrub typhus
Infective endocarditis
Pneumonia with renal failure
Metastatic hematogenous bacterial infections: *Staphylococcus aureus*, others
Sepsis with disseminated intravascular coagulation
Thrombotic microangiopathies: TTP, DIC, HUS

Contd...

in the majority of patients[20], though upto 50% may be undiagnosed.[21] The larger contribution of SLE in our series might reflect a referral bias or a relative larger burden of SLE compared to primary vasculitic syndromes in South India.

Management of severe vasculitis in tropical ICUs poses several peculiar challenges; patients may present late without a prior diagnosis due to poor recognition of vasculitic syndromes in primary care, unavailability or longer turnaround time of specialized investigations like ANCA, difficulty or unavailability of expertise in performing guided biopsies in critically ill patients for diagnosis and lack of skilled personnel to perform specialized therapies like plasmapheresis. These add to the usual clinical dilemmas caused by the protean manifestations [Table 4b] that the vasculitis syndromes [Table 5] can present with.[21,22] Finally, diagnosis may be delayed due to the similarity of the clinical syndrome to several tropical infections presenting with pulmonary and renal involvement [Table 4b]. Though the clinical findings were very similar, a diagnostic dilemma necessitating invasive surgical/percutaneous lung biopsies and delay in empiric treatment occurred in only 18.5% (5/27,

Table 4a: Contd...

Pulmonary malignancy associated glomerulopathy
Tuberculosis
Lung abscess
Others
Congestive cardiac failure with acute renal failure
Acute renal failure with fluid overload/pulmonary edema
Pulmonary thromboembolism with renal vein thrombosis (secondary to nephrotic syndrome)
Cholesterol or Fat emboli syndrome

^"Double-positive" refers to dual Anti-GBM and ANCA positivity and is seen in 20-30% of anti-GBM disease patients. TTP: Thrombotic thrombocytopenic purpura; HUS: Hemolytic uremic syndrome; DIC: Disseminated intravascular coagulation; GBM: Glomerular basement membrane; AAV: ANCA-associated vasculitis; EGPA: Eosinophilic granulomatosis with polyangiitis; SLE: Systemic lupus erythematosus; APLA: Anti-phospholipid antibody syndrome; PRS: Pulmonary-renal syndromes; GPS: Goodpasture's syndrome; MPA: Microscopic polyangiitis

Table 4b: Characteristic clinical findings in PRS

Findings of nephritis
Hypertension, edema, signs of fluid overload
Active urinary sediment on microscopy (albuminuria, RBC casts, dysmorphic RBCs, sterile pyuria) with or without azotemia
Signs of diffuse alveolar hemorrhage
Anemia or drop in hemoglobin, bilateral chest infiltrate, hemoptysis
Other chest radiological appearances
Cavitation, nodules, interstitial infiltrates
Multi-system involvement (seen in smaller proportion of patients)
Neurological: Cerebral infarcts, Mononeuritis multiplex
Cardiovascular: Myocarditis, pericarditis
Upper airway: Sinusitis, ear involvement, stenosis, deformity
Musculoskeletal: Arthritis, myositis, arthralgia
Skin: Rash, Raynaud's phenomenon
Constitutional symptoms: Low-grade fever, anorexia and weight loss (if protracted onset)

RBCs: Red blood cells; PRS: Pulmonary-renal syndromes

Figure 7) of our cohort of "provisional PRS" patients. The diagnoses made in the "PRS mimics" cohort included pulmonary complications of immunosuppression for crescentic glomerulonephritis as well as leptospirosis, scrub typhus, and paraquat poisoning; these are all well-recognized causes of PRS in the tropics.

We observed a high mortality in patients with PRS admitted to the ICU in our series. The large proportion of patients with DAH related to SLE, high APACHE II scores and the need for vasopressors and dialysis at the presentation could explain the observed poor outcome. The need for catecholamine support and renal replacement therapy is independently associated with mortality.[23] Apart from the early mortality due to fulminant DAH, infections aggravated by immunosuppression also worsened outcomes. Though mortality for PRSs is improving,[24,25] survival rates as low as 20–50% remain common.[23-26]

The strengths of the study are the prospective and uniform nature of data collection and real-world experience with PRS in the tropics. The limitations include the single-center experience, limited numbers, inability to perform lung biopsy in a large majority, and lack of information on disease-specific activity scores. Lung biopsy is seldom performed in sick patients with alveolar hemorrhage undergoing mechanical ventilation and adds no information when the diagnosis of DAH

Table 5: Features that help distinguish the individual PRS

Characteristic	GPA	MPA	EGPA	GPS/anti-GBM disease	SLE
Mechanism	Type II, IV			Type II reaction by	Type III, immune
Immunology	ANCA mediated damage to vessel wall, fibrinoid necrosis			antibodies to COL 3A4	complexes, complement activation
Pathology	Granulomatous vasculitis, fibrinoid necrosis	Fibrinoid necrosis, GN, capillaritis	Eosinophilic vasculitis	GN, fibrinoid necrosis alveolar wall	Secondary vasculitis
Eosinophils	−	−	++++	−	−
Clinical features					
Ear, nose, throat	Necrotizing destructive	Not usual	allergic	Not involved	Not involved
Lung	Nodule, cavity, infiltrate	Infiltrates, GGO	Asthma, infiltrate, nodule	GGO	Effusions, NSIP, GGO, COP, PAH, UIP
Renal	++++	++++	+−+	++++	+++
Nerve	++	+++	++++	−	+
Heart	+	+	++ (Mortality)	−	−
ACR criteria for classification ^	Nasal or oral inflammation, abnormal CxR with nodules, cavities or fixed infiltrates, abnormal urinary sediment, granulomatous inflammation on biopsy of an artery or perivascular area			Small vessel vasculitis Disease defined by RPGN±DAH and anti-GBM antibodies	Secondary vasculitis. Classification criteria for SLE (4/11) needed for a diagnosis
Updated Chapel Hill Consensus* (small-medium vessel vasculitis)	Small vessel vasculitis, pauci-immune Granulomas+, NV+	No granulomas, NV+	Eosinophil-rich, necrotizing inflammation		
ANCA	80-95% PR3, 5-20% MPO, 0-20% ANCA negative	40-80% MPO 35% PR3, 0-20% ANCA negative	40% MPO, 35% PR3, upto 60% ANCA negative	Unusual; anti-GBM IgG. MPO-ANCA overlap 20-30%-severe disease	Not seen; ANAs+. IF for ANCA is difficult

Contd...

Table 5: Contd....

Characteristic	GPA	MPA	EGPA	GPS/anti-GBM disease	SLE
Complement levels	Normal				Depressed
Prognosis	Remission rates of 88-90% at 12 months with induction therapy. Relapse rates are 15% by 18 months. Mortality is 18-30% for stage 4 AAV		Rare, not well defined	Good; renal involvement dominates outcomes	Very rare; aggressive course and poor outcomes

^ACR criteria do not distinguish GPA from MPA; ≥2 required and have 88% sensitivity and 92% specificity for AAV. ANCA is not a criterion for classification, *2012; ANCA is noted as potential value but not included as a criterion for diagnosis. ANCA: Anti-neutrophil cytoplasmic antibody; COL: Collagen; GN: Glomerulonephritis; +: Present; −: Absent; AAV: ANCA associated vasculitis; ANA: Anti-neutrophil antibody; PR3: Proteinase 3, MPO: Myeloperoxidase; Ig: Immunoglobulin; DAH: Diffuse alveolar haemorrhage; CxR: Chest radiograph; GBM: Glomerular basement membrane; NSIP: Nonspecific interstitial pneumonia; GGO: Ground glass opacity; COP: Cryptogenic organizing pneumonia; PAH: Pulmonary artery hypertension; UIP: Usual interstitial pneumonia; RPGN: Rapidly progressive GN; IF: Immunofluorescence; EGPA: EGPA: Eosinophilic granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; GPS: Goodpasture's syndrome; SLE: Systemic lupus erythematosus

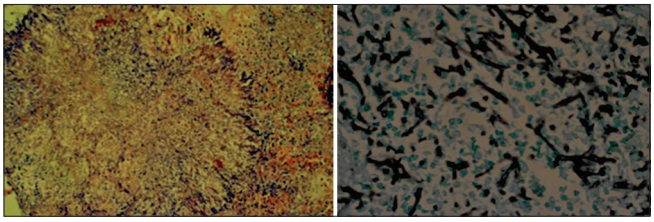

Figure 7: Composite image of percutaneous lung biopsy specimen (left, H and E ×200) from a patient with crescentic glomerulonephritis and cavitating nodules showing alveoli filled with neutrophils and collection of hyphal forms. High-power view (right, Gomori-Methanamine Stain ×400) confirms thin septate fungal hyphae with acute angle branching, strongly suggestive of aspergillus species

is clear and disease activity is evident. Activity scores correlate only with long-term outcomes and ICU-specific severity scores have been associated with short-term outcomes,[24] and this was our practice at the time of the study.

Conclusions

The spectrum of PRS is different in the tropics and tropical syndromes presenting with PRS are at least as common as small-vessel vasculitis. SLE was the most common etiology of PRS in our cohort. Patients with PRS were younger, had a longer duration of symptoms, and had a greater drop of hemoglobin and hypoxemia with higher mortality when compared to patients with "PRS mimics." Multicentric studies are needed to further characterize the burden, etiology, treatment protocols, and outcomes of PRS in India.

Financial support and sponsorship

Nil.

Conflict of Interest

There are no conflict of interest.

References

1. Goodpasture E. The significance of certain pulmonary lesions in relation to the etiology of influenza. Am J Med Sci 1919;158:863-70.
2. Nath A, Rajagopala S. Pulmonary renal syndromes: A pulmonologist's view. Clin Queries Nephrol 2015;4:1-10 doi:10.1016/j.cqn.2015.02.001. Last accessed on 2015 May 15.
3. West SC, Arulkumaran N, Ind PW, Pusey CD. Pulmonary-renal syndrome: A life threatening but treatable condition. Postgrad Med J 2013;89:274-83.
4. Gallagher H, Kwan JT, Jayne DR. Pulmonary renal syndrome: A 4-year, single-center experience. Am J Kidney Dis 2002;39:42-7.
5. Rodriguez W, Hanania N, Guy E, Guntupalli J. Pulmonary-renal syndromes in the intensive care unit. Crit Care Clin 2002;18:881-95.
6. Kothari VM, Karnad DR, Bichile LS. Tropical infections in the ICU. J Assoc Physician India 2006;54:291-8.
7. Maroun E, Kushawaha A, El-Charabaty E, Mobarakai N, El-Sayegh S. Fulminant leptospirosis (Weil's disease) in an urban setting as an overlooked cause of multiorgan failure: A case report. J Med Case Rep 2011;5:7.
8. Little MA, Pusey CD. Rapidly progressive glomerulonephritis: Current and evolving treatment strategies. J Nephrol 2004;17:S10-9.
9. Collard HR, Schwarz MI. Diffuse alveolar hemorrhage. Clin Chest Med 2004;25:583-92.
10. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, *et al.* 2012 revised International chapel hill consensus conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1-11.
11. Hochberg MC. Updating the American college of rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
12. Al Bshabshe AA, Al-Khalidy H, Omer HA, Al-Amri DH, Hamad A, Abdulwahed SR, *et al.* Pulmonary renal syndrome associated with Wegener's granulomatosis: A case report and review of literature. Clin Exp Nephrol 2010;14:80-4.
13. Watts RA, Al-Taiar A, Scott DG, Macgregor AJ. Prevalence and incidence of Wegener's granulomatosis in the UK general practice research database. Arthritis Rheum 2009;61:1412-6.
14. Bambery P, Sakhuja V, Bhusnurmath SR, Jindal SK, Deodhar SD, Chugh KS. Wegener's granulomatosis: Clinical experience with eighteen patients. J Assoc Physicians India 1992;40:597-600.
15. Sharma A, Mittal T, Rajan R, Rathi M, Nada R, Minz RW, *et al.* Validation of the consensus methodology algorithm for the classification of systemic necrotizing vasculitis in Indian patients. Int J Rheum Dis 2014;17:408-11.
16. Kumar A. Indian guidelines on the management of SLE. J Indian Rheumatol Assoc 2002;10:80-96.
17. Santos-Ocampo AS, Mandell BF, Fessler BJ. Alveolar hemorrhage in systemic lupus erythematosus: Presentation and management. Chest 2000;118:1083-90.
18. Shen M, Zeng X, Tian X, Zhang F, Zeng X, Zhang X, *et al.* Diffuse alveolar hemorrhage in systemic lupus erythematosus: A retrospective study in China. Lupus 2010;19:1326-30.
19. Martínez-Martínez MU, Abud-Mendoza C. Diffuse alveolar hemorrhage in patients with systemic lupus erythematosus. Clinical manifestations, treatment, and prognosis. Reumatol Clin 2014;10:248-53.
20. McCabe C, Jones Q, Nikolopoulou A, Wathen C, Luqmani R. Pulmonary-renal syndromes: An update for respiratory physicians. Respir Med 2011;105:1413-21.

21. Semple D, Keogh J, Forni L, Venn R. Clinical review: Vasculitis on the intensive care unit – Part 1: Diagnosis. Crit Care 2005;9:92-7.
22. Papiris SA, Manali ED, Kalomenidis I, Kapotsis GE, Karakatsani A, Roussos C. Bench-to-bedside review: Pulmonary-renal syndromes – An update for the intensivist. Crit Care 2007;11:213.
23. Befort P, Corne P, Filleron T, Jung B, Bengler C, Jonquet O, *et al.* Prognosis and ICU outcome of systemic vasculitis. BMC Anesthesiol 2013;13:27.
24. Cruz BA, Ramanoelina J, Mahr A, Cohen P, Mouthon L, Cohen Y, *et al.* Prognosis and outcome of 26 patients with systemic necrotizing vasculitis admitted to the intensive care unit. Rheumatology (Oxford) 2003;42:1183-8.
25. Khan SA, Subla MR, Behl D, Specks U, Afessa B. Outcome of patients with small-vessel vasculitis admitted to a medical ICU. Chest 2007;131:972-6.
26. Semple D, Keogh J, Forni L, Venn R. Clinical review: Vasculitis on the intensive care unit – Part 2: Treatment and prognosis. Crit Care 2005;9:193-7.