Original Article

Pulmonary renal syndromes: A pulmonologist's view

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ABSTRACT

Background: Pulmonary Renal Syndromes are heterogeneous group of disorders characterized by co-occurrence of rapidly progressive glomerulonephritis (RPGN) and alveolar hemorrhage due to an autoimmune etiology. This condition many a times presents as an emergency and can be rapidly fatal. A high index of suspicion is required to identify PRS early because appropriate diagnosis and timely institution of treatment is necessary for favorable results. 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) which are responsible for almost 80% of the cases. All these condition share similar clinical presentation however there are some salient features which differentiate them in terms of prognosis and management.
Methods: This is a narrative review using the search terms; "pulmonary renal syndrome, granulomatosis with polyangiitis; eosinophilic granulomatosis with polyangiitis; microscopic polyangiitis; anti-GBM disease and systemic lupus erythematosus.
Results: 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) which are responsible for almost 80% of the cases. All these condition share similar clinical presentation however there are some salient features which differentiate them in terms of prognosis and management. The response to immunosuppressive therapy and long term prognosis also differs because of distinguishing features in pathogenesis of these disorders. There is no consensus about the management protocols of pulmonary renal syndromes however, various immunological societies have laid down treatment protocols with variable success rates.
Conclusion: The syndrome of PRS has a high short-term mortality (20–40%). The rates of remission are >90% with current protocols and effective second line therapies exist for those who don't attain remission. Relapse rates are about 15% at 18 months and are higher with patients having PR3-ANCA and a diagnosis of GPA. A high index of suspicion is required to identify PRS early because treatment delays may be rapidly fatal.

1. Introduction

The term "Pulmonary Renal Syndrome (PRS)" was coined by *Goodpasture* in 1919 who described it as co-occurrence of rapidly progressive glomerulonephritis (RPGN) and alveolar hemorrhage due to an autoimmune etiology.[1] Although any clinical condition that involves RPGN and acute respiratory failure in combination can be termed as pulmonary renal syndrome, this term is reserved for alveolar hemorrhage and glomerulonephritis of immune etiology (Table 1). 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).[2] Anti-GBM disease involving both lungs and kidneys is also termed as *Goodpasture's syndrome (GPS)* and is the prototype of PRS. AAV is an umbrella designation for three major vasculitic syndromes; granulomatosis with polyangiitis (GPA; previously termed Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg Strauss Syndrome or CSS). All three are associated with ANCA and have similar features on renal histology (focal necrotizing, often crescentic pauci-immune glomerulonephritis). These three diseases groups

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Table 1
Causes of pulmonary renal syndromes.

Anti-Glomerular basement membrane antibodies related
Anti-GBM disease or Goodpasture's syndrome
ANCA-associated vasculitis (AAV)
Granulomatosis with polyangiitis (GPA)
Microscopic polyangiitis (MPA)
Eosinophilic granulomatosis with polyangitis (EGPA)
Collagen vascular disease related
Systemic lupus erythematosus (SLE)
Primary antiphosphopholipid antibody syndrome (APS)
Polymyositis
Scleroderma
Behcet's syndrome
ANCA-negative vasculitis
Henoch Schonlein Purpura (HSP)
Mixed cryoglobulinaemia
IgA nephropathy
Behcet's disease
Drug-induced vasculitis
Hydralazine
Propylthiouracil
ᴅ-penicillamine
Phenytoin
Mitomycin
Allopurinol
Sulfasalazine
Idiopathic pulmonary-renal syndrome

Table 2
Differential diagnosis of pulmonary renal syndromes.

Infections
Leptospirosis
Staphylococcus aureus
Legionella pneumophila
Hantavirus
Malaria
Sepsis with disseminated intravascular coagulation
Neoplastic
Atrial myxoma
Primary or metastatic lung disease
Drugs and toxins
Paraquat poisoning
Solvents
Cannabis
Cocaine
Miscellaneous
Congestive cardiac failure with acute renal failure
Acute renal failure with fluid overload
Infective endocarditis
Pulmonary thromboembolism with renal vein thrombosis
Cholesterol or fat emboli syndrome

contribute to more than 80% of patients with PRS. Other various possible causes of PRS and its mimics have been listed in Table 1. The syndromic presentation is similar in all these etiologies (Table 2); however there are differences in pathogenesis, diagnostic tests required, histopathological features, treatment protocols and prognosis (Table 3). A high index of suspicion is required to identify PRS early because treatment delays may be rapidly fatal.

2. Epidemiology

Epidemiological data for PRS as a syndrome are limited; data exists in the form of case series.[3] Incidence and prevalence data are however, available for specific etiologies of PRS from the West. The incidence rates of GPA, MPA, and EGPA respectively range between 2.1 and 15, 2.1–17.5, and 0.5–3.1 per million.[2] The exact incidence of anti-GBM disease is unknown but is thought to be one per million or lower.[4] Other authors have reported incidence rates of 0.7 per million to 21 per million and a prevalence ranging from 23.7 to 160 per million. MPA is relatively more common in Asians as compared to GPA but overall prevalence of MPA is higher in

Table 3
Clinical features of common causes of PRS.

Etiology	Upper respiratory tract involvement	Arthritis/ arthralgia	Rash	Renal involvement	Anemia	Cardiac involvement	CNS involvement
GPA	**Very common** Nasal discharge Mucosal ulceration Septal perforation Nasal deformity	**Common**	**Uncommon**	**Very Common**	+	**Rare** Pericarditis Coronary vasculitis Cardiomyopathy	**Uncommon** Cranial neuritis Mononeuritis multiplex CNS vasculitis
MPA	**Rare**	**Common**	**Common** Palpable purpura Livido reticularis Skin nodules Skin ulcers	**Very common**	+	–	**Common** Mononeuritis multiplex Cerebral infarctions Pachymeningitis
GPS	–	**Common**	**Rare**	**Very common**	+	–	–
EGPA	**Very common** Recurrent sinusitis Allergic rhinitis	**Common**	**Common**	**Uncommon**	+	**Common**	**Common** Mononeuritis multiplex Seizures
SLE	–	**Very common**	**Very common** Malar rash Discoid rash	**Common**	+	**Common** Pericarditis Endocarditis Myocarditis Conduction defects	**Common** Seizures
APS	–	Common	Common	Common	+		
HSP	–	Common	Common Palpable purpura Lower extremities Hips	Common	+	Uncommon Myocarditis	–
Behcet's disease	–	Common	Uncommon Folliculitis Erythema nodosum Acne like exanthem	Rare	+	Common Vascular aneurysms Pulmonary emboli	Uncommon Brainstem involvement Dural sinus thrombi

Abbreviations: APS – Primary antiphosphopholipid antibody syndrome, **EGPA** – Eosinophilic granulomatosis with polyangits, **GPA** – Granulomatosis with polyangiitis, **GPS** – Goodpasture's syndrome, **HSP** – Henoch Schonlein Purpura, **MPA** - Microscopic polyangiitis, **SLE** – Systemic lupus erythematosus.