ABSTRACT

The pulmonary–renal syndrome (PRS) refers to the combination of diffuse alveolar haemorrhage and rapidly progressive glomerulonephritis (RPGN). Pulmonary-renal syndrome can originate from various systemic autoimmune diseases. ANCA-associated vasculitides account for approximately 60%, Goodpasture's Syndrome for approximately 20% of the cases. It is almost always autoimmune in nature, therefore steroids and other immunosuppressants have role in its treatment. The underlying renal pathology is a form of focal proliferative glomerulonephritis. The lung pathology is in form of diffuse alveolar hemorrhages.

Key Words: Pulmonary renal syndrome; Wegener's granulomatosis; microscopic polyangiitis; systemic lupus erythematosus.

INTRODUCTION

Pulmonary–renal syndrome (PRS) is defined as the combination of diffuse alveolar haemorrhage (DAH) and glomerulonephritis. PRS are caused by a wide variety of diseases, including various forms of primary systemic vasculitis (Wegener'sgranulomatosis and microscopic polyangiitis), Goodpasture's syndrome which is associated with autoantibodies to the alveolar and glomerular basement membrane and systemic lupus erythematosus. The diagnosis is mainly based on the identification of particular patterns of clinical, pathologic, radiologic and laboratory features. The majority of cases of pulmonary-renal syndrome are associated with ANCA, either c-ANCA or p-ANCA, due to autoantibodies against the target antigens proteinase-3 and myeloperoxidase respectively. The antigen target in Goodpasture's syndrome is type IV collagen. The pulmonary-renal syndrome (PRS) is a rare and life-threatening condition. The clinical picture of PRS includes hemoptysis (not always present) due to alveolar hemorrhages, acute-onset anemia and renal abnormalities ranging from isolated urinary abnormalities to rapidly progressive glomerulonephritis. A significant number of patients will present with rapid clinical deterioration and require admission to the intensive care unit (ICU). This is attributed either to exacerbation of the disease activity itself, or to infectious complications secondary to severe immunosuppressive treatment. Diffuse alveolar haemorrhage is characterized by the presence of a haemorrhagic bronchoalveolar lavage (BAL) in serial BAL samples. In the clinical setting of an acute nephritis syndrome, percutaneous renal biopsy is commonly performed for histopathology and immunofluorescence.
studies. Treatment of generalized ANCA-associated vasculitis consists of corticosteroids and immunosuppressive agents.\textsuperscript{[5-7]}

**Pathology**
The underlying pulmonary lesion in the majority of cases of pulmonary–renal syndrome is small-vessel vasculitis which is characterized by a destructive and inflammatory process that involves arterioles, venules and alveolar capillaries which.\textsuperscript{[8]} These vasculitis have a heterogeneous pathogenesis and there are three different pathophysiological mechanisms of injury.\textsuperscript{[9]}

1. mediated by anti-neutrophil-cytoplasmic antibodies (ANCA),
2. immune-complex mediated vasculitis of small vessels or
3. by antibodies against the glomerular basement membrane (Goodpasture syndrome).

In the kidney, a rapidly progressive glomerulonephritis (RPGN) is caused by damage of the capillaries and basal membranes with leakage of erythrocytes, which is followed by an influx of macrophages, fibrinogen and the formation of crescents. In the lungs, a diffuse alveolar hemorrhage is caused by a pulmonary capillaritis.\textsuperscript{[10]}

In the case of ANCA-associated systemic vasculitis the ANCA is detected in about 80% of patients. Besides the correlation of ANCA titers with disease activity there is evidence of a pathogenetic role of ANCA. The ANCA is formed against two proteins named myeloperoxidase (MPO) and proteinase 3 (Pr3) and these are detected in the cytoplasm of non-stimulated neutrophils. Finally cell necrosis and apoptosis contribute to vascular inflammation process. In Pauci-immune glomerulonephritis there is absence of immune-complex deposition, immunoglobulins or complement within the biopsy sample.\textsuperscript{[11]}

**Classification of PRS according to the pathogenetic mechanism involved (Etiopathological classification)\textsuperscript{[12]}**

A) **Pulmonary–renal syndrome associated with anti-GBM antibodies: Goodpasture’s syndrome (GPS)**

B) **Pulmonary–renal syndrome in ANCA-positive systemic vasculitis**
1. Wegener’s granulomatosis (WG)
2. Microscopic polyangiitis
3. Churg–Strauss syndrome (CSS)
4. Other vasculitis

C) **Pulmonary–renal syndrome in ANCA-negative systemic vasculitis**
1. Henoch–Schönlein purpura
2. Mixed cryoglobulinaemia
3. Behçet’s disease
4. IgA nephropathy

D) **ANCA-positive pulmonary–renal syndrome without systemic vasculitis: Idiopathic pulmonary–renal syndrome**
Pauci-immune necrotizing glomerulonephritis and pulmonary capillaritis

E) **Pulmonary–renal syndrome in drug-associated ANCA-positive vasculitis**
1. Propylthiouracil
2. D-Penicillamine
3. Hydralazine
4. Allopurinol
5. Sulfasalazine

F) **Pulmonary–renal syndrome in anti-GBM-positive and ANCA-positive patients**

G) **Pulmonary–renal syndrome in autoimmune rheumatic diseases (immune complexes and/or ANCA mediated)**
1. Systemic lupus erythematosus
2. Scleroderma (ANCA?)
3. Polymyositis
4. Rheumatoid arthritis
5. Mixed collagen vascular disease

H) **Pulmonary–renal syndrome in thrombotic microangiopathy**
1. Antiphospholipid syndrome
2. Thrombotic thrombocytopenic purpura
3. Infections
4. Neoplasms
l) Diffuse alveolar haemorrhage complicating idiopathic pauci-immune glomerulonephritis

Epidemiologic Aspects

Goodpasture’s syndrome is not common and has an incidence of approximately 0.5 to 1 case per million people per year. Gender distribution is equal in both sexes and there is no gender predisposition. Goodpasture’s syndrome has a bimodal age distribution, with a large number of patients presenting at ages 20 to 30 and at ages 50 to 68. Whites are more frequently affected than blacks. Antineutrophil cytoplasmic autoantibody–associated vasculitis (ANCA) is the most common primary systemic small vessel vasculitis to occur in adults. Although the etiology is sometimes unknown, the incidence of vasculitis is increasing, and the diagnosis and management of patients is challenging because it is relatively infrequent, and has variable clinical expression. In patients presenting with PRS secondary to systemic vasculitis, pulmonary hemorrhage appears in 40% of WG cases and 30% of microscopic polyangiitis (MPA) cases, and it rises when renal involvement is severe. Pulmonary hemorrhage in these disorders carries a mortality rate of 10%. Diffuse alveolar hemorrhage in systemic lupus erythematosus (SLE) remains a devastating pulmonary complication; mortality rates are around 45-50%, and it occurs in less than 2% of patients with SLE. Evidence for glomerular involvement is also present in large number of patients. Single-center experience suggests that 60% to 70% of cases with PRS are associated with ANCAs, and 20% are associated with anti-GBM antibodies. [17,18]

Pathophysiology of PRS with respect to each pathological type

(i) PRS associated with anti-GBM antibodies: Goodpasture’s syndrome [19-22]

The term ‘Goodpasture’s syndrome’(GPS) includes diffuse alveolar hemorrhage and rapidly progressive glomerulonephritis (RPGN) and it is associated with anti-GBM antibodies. It is rare, however this syndrome is responsible for about 20% of acute renal failure due to consequences of RPGN. The disease is hereditary in nature as it has been described in brothers and in identical twins. More than 80% of patients carry the HLA alleles DR15 or DR4 whereas the alleles DR7 and DR1 are rarely found. Environmental factors, such as smoking, infections and previous hydrocarbon exposure, have been implicated in triggering the disease. In GPS, the target antigen is the non-collagenous (NC1) domain of the α3 (IV) collagen chain, it is one of the six chains (alpha-1 to alpha-6 [α1 to α6]) which are entitled in making type IV collagen. This target antigen is primarily found on the inert aspect of the lamina densa, which is the middle layer of the glomerular and alveolar basement membranes. Anti-GBM antibodies bind the glomerular basement membrane, activating complement and proteases, resulting in the disruption of the filtration barrier and Bowman’s capsule and causing proteinuria and crescent formation.

(ii) Pulmonary–renal syndrome in ANCA-positive systemic vasculitis [23-27]

Circulating ANCA autoantibodies are detected in the majority of patients presenting with PRS. ANCA is not confirmatory for specific type but it leads to differential diagnosis to three major systemic vasculitides syndromes which are associated with ANCA, includes: Wegener’s granulomatosis, microscopic polyangiitis and Churg–Strauss syndrome. The suspicion of a pulmonary-renal syndrome in an ANCA-associated systemic vasculitis can often be taken from a careful history and thorough clinical examination with detection of other vasculitic signs like eye inflammation, intractable rhinitis / sinusitis, skin rashes, arthralgia, myalgia or polyneuropathy.

Wegener’s disease or Wegener’s granulomatosis (WG) is characterized by the triad of systemic necrotizing vasculitis, necrotizing granulomatous inflammation of the upper and lower respiratory tract, and
necrotizing glomerulonephritis. The disease usually involves Caucasians (80–97%) with a mean age at the time of diagnosis of 40–55 years, although persons of every age may be affected. The lungs are involved in 90% of cases. In a small percentage of patients, a limited form of the disease that spares the kidney. In active disease in about 90% of cases c-ANCA are directed against proteinase 3.

Microscopic polyangiitis (MPA) is a systemic small-vessel vasculitis manifested by pauci-immune necrotic glomerulonephritis (80–100% of patients), pulmonary capillaritis (10–30%), skin lesions and arthralgias. Microscopic polyangiitis is characterized by a necrotizing vasculitis of small vessels with minimal or missing immune deposits and an inflammation of the pulmonary capillaries. Typically, there is p-ANCA directed against myeloperoxidase.

The Churg-Strauss syndrome (CSS) is characterized by recurrent asthma attacks and allergic rhinitis, and a detectable eosinophilia (> 1500/mm3) and necrotizing granulomas and / or necrotizing arteritis with a Wegener’s granulomatosis-like presentation. c-ANCA or anti-PR3-Ab detected rarely while p-ANCA and anti-MPO-Ab can be detected in up to 62% of cases. The Churg-Strauss syndrome can be distinguished clinically from Wegener’s granulomatosis or Microscopic polyangiits by asthma attacks and eosinophilia. In Churg–Strauss syndrome, renal involvement is milder compared with Wegener’s disease, Goodpasture’s syndrome and microscopic polyangiitis.

(iii) Pulmonary–renal syndrome in drug-associated ANCA-positive vasculitis

Drugs are one of the reversible causes of ANCA-positive vasculitis. The drugs most frequently implicated in the pathogenesis of the syndrome are propylthiouracil and hydralazine. ANCA are detected in 22% of patients receiving propylthiouracil, but very patients develop clinical manifestations of systemic vasculitis including pulmonary–renal syndrome. Other drugs which are included in the etiology of PRS are D-Penicillamine, allopurinol and sulfasalazine. If the causative drug is discontinued, it causes regression of the disease; however, some patients continue to present positive ANCA or even recurrent disease and may require long-term immunosuppressive treatment. In general, drug-induced disease has a more benign course than ANCA positive pulmonary–renal syndrome of other aetiology.

(iv) Pulmonary–renal syndrome in autoimmune rheumatic diseases

These may be immune complexes mediated and/or ANCA mediated. These include systemic lupus erythematosus, scleroderma, polymyositis rheumatoid arthritis and mixed collagen vascular disease. Pulmonary–renal syndrome has been reported more commonly in systemic lupus erythematosus and systemic sclerosis, and rarely in rheumatoid arthritis and mixed connective tissue disease. Pulmonary hemorrhage is a rare complication of SLE (2%), and is associated with high mortality rates (60%). Acute alveolar hemorrhage in SLE usually occurs as a PRS. In most cases, the lung showed “bland” alveolar hemorrhage with little or no inflammation. Alveolar hemorrhage in SLE is characterized by bland alveolar wall changes and seems to be similar pathogenically to the lupus microangiopathy of the kidney. Pulmonary–renal syndrome is a rare but lethal complication of systemic sclerosis, and pulmonary fibrotic disease often coexists with it. ANCA, more commonly the perinuclear ANCA or MPO ANCA, have been detected in some systemic sclerosis patients. Systemic sclerosis-PRS has a poor prognostic indication; that is, all patients died within 12 months of admission.

(v) PRS in thrombotic microangiopathy

Pulmonary–renal syndrome may occur in conditions like antiphospholipid syndrome (APS), thrombotic thrombocytopenic purpura, malignancies and infections.
Patient evaluation and clinical features

These disorders exhibit considerable heterogeneity in clinical presentation both in severity and prognosis. Early recognition needs 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. Frequent presentation of PRS includes patient presenting with breathlessness and fever with pulmonary infiltrates seen on a chest radiograph. Many patients deteriorate rapidly and present with life threatening respiratory and/or renal failure. Similarities exist with presentation of pneumonia or severe cardiac failure with pulmonary oedema. Clinically apparent haemoptysis secondary to diffuse alveolar haemorrhage (DAH) occurs in about 55% of cases. In one-third of cases of DAH however, haemoptysis does not manifest clinically. Haemoptysis is usually of small volume (<200 ml/24 h) and may be accompanied by a low grade fever, breathlessness and cough.

Acute kidney injury may be apparent from blood levels of blood urea and serum creatinine which carries greater diagnostic significance in the presence of an active urinary sediment. In urine complete analysis, proteinuria is more common than haematuria but when both are present, this is indicative of glomerular membrane damage due to glomerulonephritis. Proteinuria is usually below the nephrotic range. Urine microscopy may show red cell casts or dysmorphic red cells.

Plain chest radiography or computed tomography of the chest may reveal a distribution of infiltrates from perihilar shadow extending towards the lower zones to frank consolidation mimicking an ARDS appearance. In 25% of cases, chest radiography may be normal. A rare but important cause of DAH which should be ruled out is idiopathic pulmonary haemosiderosis which may result in prolonged diffuse alveolar hemorrhages but renal impairment is not a feature of this disorder.

Blood test abnormalities may include a normochromic, normocytic anaemia with features of acute kidney injury in the form of raised blood urea and serum creatinine levels. Underlying thrombotic thrombocytopenic purpura (TTP) is suggested by evidence of haemolysis with fragmented red blood cells on peripheral blood film. Serum antibody detection of anti-GBM, ANA and/or ANCA is key to diagnostic work-up if a PRS is suspected. However the level of ANCA titre is not considered part of the diagnostic criteria in systemic vasculitis. Whilst the presence of a positive cytoplasmic ANCA (cANCA) (directed against PR3 antigen) correlates with underlying Wegener’s granulomatosis (present in 90% of cases), perinuclear ANCA (pANCA) (directed against MPO) may be helpful in clinicopathological classification (Table 1). Anti-GBM antibodies detected using different immunoassays including immunoperoxidase labelling have a sensitivity of 95 to100% with a specificity of 90e100% for Goodpasture’s disease. Only 35 to70% of patients with CSS has a positive cANCA with 10% being positive for PR3. In fact CSS is more often ANCA negative than positive, and where positive, usually it is associated with c-ANCA or p-ANCA.

Flexible bronchoscopy is generally used in the exclusion of infection and confirmation of diffuse alveolar hemorrhages. Classically serial bronchial
washings show blood stained lavage fluid and cytology of the washings may show haemosiderin-laden macrophages.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Proteinase-3-Antibody</th>
<th>Myeloperoxidase (MPO)-Antibody</th>
<th>ANCA negative</th>
<th>Anti-GBM-Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegener’s Granulomatosis</td>
<td>70 %</td>
<td>20 %</td>
<td>10 %</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Microscopic Polyangiitis</td>
<td>30 %</td>
<td>60 %</td>
<td>10 %</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Churg-Strauss-Syndrome</td>
<td>10 %</td>
<td>60 %</td>
<td>30 %</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Goodpasture Syndrome</td>
<td>&lt;10%</td>
<td>&lt;30%</td>
<td>70%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Table 1. Showing serology and sensitivity of different form of ANCA positive vasculitis and Goodpasture syndrome.

The diagnosis of RPGN is done by renal biopsy: in light microscopy there is a glomerulonephritis with crescent formation in the Bowman’s capsule (extracapillary proliferation) in more than 50% of the glomeruli. In immunohistology, the type of immunoglobulins and the deposition pattern differ viz. capillary, mesangial, glomerular or linear along the glomerular basement membrane. Only in Goodpasture syndrome, linear deposits are found along the glomerular basement membrane. In case of an ANCA triggered form, immune deposits are missing (pauci-immune RPGN). In contrast, in immune-complex vasculitis, there can be found a different picture, usually with granular deposition of IgG, IgM, IgA or complement.

Specific management of PRS

Patients with vasculitis frequently die of sepsis. The risk of hospital aquired infection in these patients is very high due to immune-suppression.

Respiratory and airway management

In Wegener’s granulomatous there may be subglottic stenosis therefore intubation may be difficult and require smaller endotracheal tube inexperienced hands. In acute lung injury due to diffuse alveolar haemorrhage large tidal volumes or pressure changes may exacerbate damage to pulmonary microvasculature. Lung protective ventilation, as used in the management of ARDS, with tidal volumes of 6 ml/kg and inspiratory plateau pressures below 30 cmH2O with permissive hypercapnia may reduce lung injury to these patients.

Drug Therapy

(A) ANCA associated PRS: [43-46]

(a) Induction of remission

The introduction of cyclophosphamide in conjunction with steroids in the management 5-year mortality was lowered from 50% with glucocorticoid treatment alone to 12% with combination therapy. Induction of remission is most commonly achieved with high dose intravenous methylprednisolone (0.5-1 g/day) for 3 to 5 days for which there is no substantial evidence base. This is coupled with pulsed intravenous cyclophosphamide administered every 2 to 3 weeks (15 mg/kg/pulse) on 6 to 9 occasions or as a daily oral regime (1 to 2 mg/kg/day). With this treatment, about 85% of patients achieve remission. Transition to maintenance therapy may occur 6–12 months after the initiation of induction therapy or after clinical remission.

(b) Maintenance of remission

The most effective method of maintenance of remission is also the subject of ongoing trials and there is considerable inter-practitioner variability over both choice of immunosuppression and duration of treatment. Glucocorticoids are continued at low dose for a minimum of 18 months along with a cytotoxic agent. Relapse will occur in 11–57% of patients in remission. Some relapses are severe, resulting in end-organ damage. Female or black patients and those patients with severe kidney disease, lung
disease or upper airway disease and anti-Pr3 serum antibodies are shown to be more resistant to initial treatment. In these cases, the use of alternative agents must be considered. Recent investigation suggested TNF-α inhibitors, B-cell depletion agents, mycophenolate mofetil (MMF), leflunomide and antithymocyte globulin for treatment. New agents are shown to be effective in certain cases but are followed by high relapse and complication rates.

(B) Goodpasture’s syndrome [47]
Immunosuppressive treatment should also be urgently initiated. Daily plasma exchange should be started. Plasmapheresis should be discontinued if tests for anti-GBM antibodies are found negative. A mean of 14 courses of treatment is usually needed until the anti-GBM antibody titre is normalized. Prompt and aggressive plasmapheresis for ANCA-positive anti-GBM-positive patients may be needed for renal recovery.

(C) Systemic lupus erythematosus [48-50]
Pulmonary haemorrhage in the case of lupus nephritis carries a poor prognosis. Urgent immunosuppression should be given with high dose methylprednisolone and cyclophosphamide. New therapies such as Rituximab and MMF are in trial stages which bring about successful remission in 80% of cases. Relapse rates are high however despite the improved toxicity profile. To avoid the severe side effects of the treatment of systemic lupus erythematosus, including bone marrow suppression, haemorrhagic cystitis, opportunistic infections, malignant diseases and premature gonadal failure, new agents such as mycophenolate mofetil and rituximab are under investigation.

(D) Acute catastrophic antiphospholipid syndrome [51]
In pulmonary–renal syndrome related to acute catastrophic antiphospholipid antibody syndrome (APS), the mainstay of therapy is anticoagulation.

(E) Thrombotic thrombocytopenic purpura [52]
In cases of pulmonary–renal syndrome and thrombotic thrombocytopenic purpura, mortality exceeded 90% before the application of plasmapheresis. But if plasmapheresis is initiated early the response to treatment is 80%. If plasmapheresis treatment is delayed plasma transfusion for von Willebrand factor cleavage protein are indicated.

Despite rigorous treatment, almost 66% of patients with small-vessel vasculitis and pulmonary–renal syndrome will need renal transplantation within less than 4 years of initial presentation.

CONCLUSION
Clinical suspicion is key to diagnosis as the symptom complex of PRS is often non-specific. The disorder has a wide range of severity of presentation from the general outpatient clinic to the ICU setting. Pulmonary renal syndrome in the ICU is a life-threatening entity with an acute onset and with a fulminant course if left untreated. Appropriate management of such patients includes early and accurate diagnosis, exclusion of infection, close monitoring and specialized immunosuppressive treatment along with plasma exchange in certain cases. Relapses are quite common in treated patients. Newer immunomodulatory agents could confer life-saving options for refractory disease in the future. Renal transplantation remains the only alternative for patients with pulmonary–renal syndrome who develop end-stage renal disease.

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