

Pulmonary renal syndrome in the Arabian Gulf region: A case report

Abdelkarim Waness

ABSTRACT

Introduction: Pulmonary renal syndrome refers to any pathologic condition that presents with varying concomitant lung and kidney symptoms and manifestations due to a common pathophysiologic insult. They are rarely encountered by health care professionals, including in the Arabian Gulf region, but can have severe therapeutic consequences. **Case Report:** We present a case of microscopic polyangiitis that manifested itself with pulmonary hemorrhage and acute kidney injury. The patient survived the initial insult but developed end-stage renal disease requiring ongoing hemodialysis. This report will review etiologies of pulmonary renal syndrome, clinical signs, diagnostic modalities, and therapeutic options for patients afflicted with this syndrome. **Conclusion:** Diagnostic and therapeutic challenges remain with pulmonary renal syndrome in the Arabian Gulf region despite advanced therapeutic interventions such as renal transplantation.

Keywords: Microscopic polyangeiitis, Alveolar hemorrhage, Plasmapheresis, Hemodialysis

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INTRODUCTION

Pulmonary renal syndrome (PRS) are rare medical syndrome defined by the co-existence of pulmonary hemorrhage and renal insult. PRS are, in fact, the clinical end-result many pathophysiologic entities. They can have variable presentations from dramatic respiratory distress to occult manifestations. PRS can represent both a diagnostic and therapeutic challenge requiring a close multidisciplinary teamwork. Cases of PRS are, occasionally, diagnosed in the Arabian Gulf region; namely within the Gulf Cooperation Council Countries (Saudi Arabia, Kuwait, United Arab Emirates, Qatar, Bahrain, Oman), Iraq and Iran.

CASE REPORT

A 60-year-old female, with history of diabetes mellitus, essential hypertension and hypothyroidism presented to a tertiary care center with dyspnea, cough and moderate hemoptysis for four days. Her medications included insulin, an ace inhibitor, and thyroid hormone replacement. On examination, she was in mild respiratory distress. Her vital signs were as follows: temperature 37.2°C, pulse 102 bpm, respiratory rate 18/minute, blood pressure 169/56 mmHg, and oxygen saturation 98% on room air. She had audible rhonchi especially in the left upper chest area. The rest of her examination was unremarkable. Laboratory results were (normal range in brackets): serum sodium 135 mmol/L (135–145 mmol), serum potassium 7.4 mmol/L (3.5–5.0 mmol), serum chlorine

106 mmol/L (98–107 mmol), bicarbonate 16 mmol/L (22–29 mmol), BUN 32.6 mmol/L (< 8.3 mmol), serum creatinine 657 $\mu\text{mol/L}$ (it was 136 $\mu\text{mol/L}$ seven months prior to this admission) (62–106 dL), WBC $9.4 \times 10^3/\text{mm}^3$ ($4.5\text{--}11.0 \times 10^3/\text{mm}^3$), hemoglobin 8.2 g/ $\mu\text{mol/L}$ (12.6–17.4 g/L), platelets $193 \times 10^3/\mu\text{L}$ (140–400/ mm^3), INR 1.0 (0.8–1.2), PTT 26.8 (27.7–42.1). Her c-ANCA level was negative, the p-ANCA level was elevated at 79 U/mL (<5). Anti-nuclear antibodies (ANA), rheumatoid factor (RF), anti-DNA antibodies, anti-small muscle antibodies, cryoglobulin level, complements C3 and C4 levels were all normal. Chest X-ray showed diffuse patchy airspace opacities mostly in the left lung (Figure 1). Computed tomography (CT) scan of the chest confirmed extensive left lung ground glass opacities and interstitial thickening with patchy involvement of the right upper lobe (Figure 2). She underwent bronchoscopy with broncho-alveolar lavage (BAL) that

visualized blood in the bronchioles, worse on the left side. Cultures for acid-fast bacilli (AFB), fungal and viral causes were negative. Because of deteriorating renal function, hemodialysis was initiated. Left kidney biopsy showed diffuse diabetic glomerulosclerosis, acute pauci-immune glomerulonephritis with mesangial cellular expansion, crescentic formation and tubular epithelial cell changes (Figure 3). Her final diagnosis was microscopic polyangiitis. The patient was treated with corticosteroids and plasmapheresis. Her hemoptysis resolved slowly. However, she progressed to end-stage renal disease during her hospital stay. Six weeks post-discharge, the patient was clinically stable undergoing hemodialysis three times a week.

DISCUSSION

Causes of Pulmonary Renal Syndromes Goodpasture's syndrome

This was first described in 1919 by Ernest Goodpasture. This autoimmune condition can be interchangeably confused with PRS. The histopathological hallmark of this disease is the presence of anti-Glomerular basement membrane (anti-GBM) antibodies directed against type IV collagen in the GBM. Their immunological insult can affect both kidneys and lungs resulting usually in rapid progressive glomerulonephritis associated with alveolar hemorrhage. Occasionally, the insult is confined only to the kidneys or lungs separately. Goodpasture's syndrome, in association with primary systemic vasculitides, constitutes the most frequent etiologies of PRS. The prevalence of anti-GBM disease is low in the Arabian Gulf region (it is estimated between 1.5–4.4%) [1]. The diagnosis is suspected clinically and confirmed by renal biopsy. Prognosis is worse for patients who require immediate dialysis at presentation. Treatment armamentarium include immunosuppression, plasmapheresis, dialysis, and kidney transplantation.

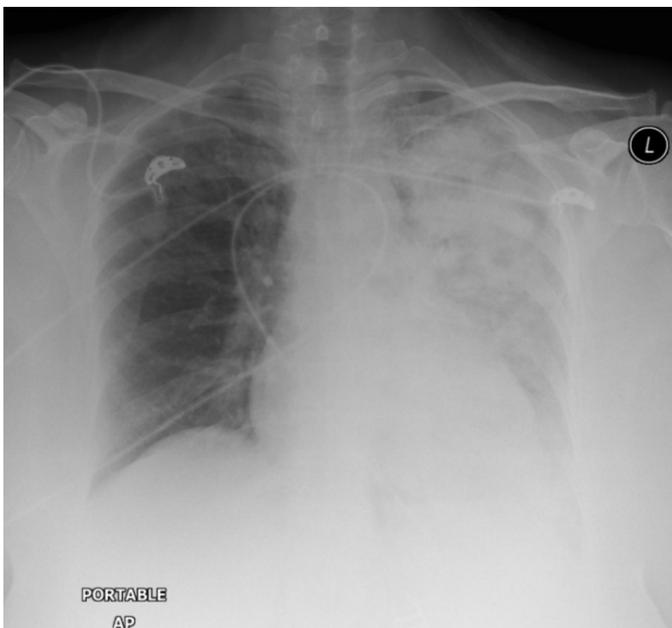


Figure 1: Chest X-ray with diffuse patchy airspace opacities more pronounced in the left lung.



Figure 2: Computed tomography scan of the chest showing left lung ground glass opacity and interstitial thickening.

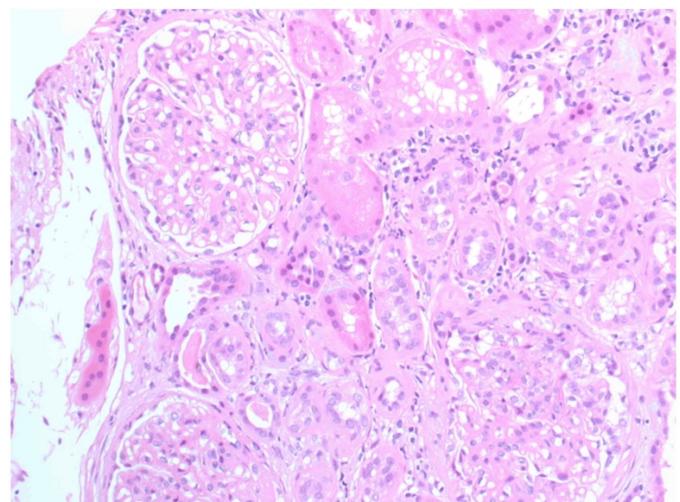


Figure 3: Kidney biopsy (Hematoxylin & Eosin stain) showing diffuse diabetic glomerulosclerosis, acute pauci-immune glomerulonephritis with mesangial cellular expansion, crescentic formation and tubular epithelial cell changes.

Systemic vasculitides

These include different varieties of necrotizing conditions affecting large, medium, or small size vessels. Antineutrophil cytoplasmic autoantibodies (ANCA) seems to play a major pathophysiological role in many vasculitides. Two principal serological subtypes of ANCA may be detected. Bosch et al. detected, in their study of 95 patients detected 26% and 74% cytoplasmic pattern (c-ANCA) and perinuclear pattern (p-ANCA), respectively. The majority of c-ANCA corresponded to anti-proteinase 3 (anti-PR3) antibodies (diagnostic for Wegener's granulomatosis); while the overwhelming p-ANCA corresponded to anti-myeloperoxidase (anti-MPO) antibodies principally detected in patients with rapidly progressive glomerulonephritis (RPGN) and hemorrhagic alveolar capillaritis [2]. Recent research have identified a new ANCA, directed against human lysosome membrane protein-2 (LAMP-2), that possibly has a concurrent action with PR3-ANCA or MPO-ANCA, for renal ANCA-associated vasculitides (AAV) [3]. The presence of ANCA and their subsequent histological immune complex deposits is not a prerequisite for the development of necrotizing arteritis. Primary systemic vasculitides are an important cause of PRS. Occasionally, cases of ANCA-positive Goodpasture's overlap syndrome are diagnosed.

Wegener's granulomatosis: Can share pathogenic, pathological, and clinical features with other vasculitides. This necrotizing arteritis has predilection for the upper respiratory system, but can cause hemoptysis and glomerulonephritis. Sporadic cases of Wegener's granulomatosis causing PRS are rarely discovered [4].

Churg-Strauss syndrome (CSS): First described in 1951 and also known as 'allergic granulomatous angiitis', CSS is another ANCA-associated arteritis. Asthma is a central feature of this condition. Although less frequent, alveolar hemorrhage and renal involvement can be observed. Adult and pediatric cases are occasionally diagnosed in the Gulf-countries [5].

Microscopic Polyangiitis (MPA): The most common ANCA-associated small vessel vasculitis. Most patients will exhibit MPO-ANCA positive serology; however PR3-ANCA serology can be present [6]. It can affect any body organ, pulmonary hemorrhage and nephritis are common. The latter usually progresses to end-stage renal disease requiring continuous hemodialysis.

Polyarteritis Nodosa (PAN): A systemic vasculitis affecting medium and small muscular arteries, preferentially at vessel bifurcations, resulting in microaneurysm formation, aneurysmal rupture with hemorrhage, thrombosis, and, consequently, organ ischemia or infarction ANCA is rarely positive in PAN; with positive MPO-ANCA however, PAN can have close clinical resemblance to MPA [7].

Behçet's syndrome (BD): A multisystem disease of unknown etiology with well-established presence in the Gulf countries BD has many symptoms including neuropsychiatric expressions, oral and genital ulcerations up to 5-10% of patients with this condition can have pulmonary manifestations such as hemoptysis

[8].

Henoch-Schonlein Purpura (HSP): Most common systemic vasculitis in children with documented cases in the Gulf countries [9]. It is usually a self-limiting disease. Pulmonary complications, such as pulmonary hemorrhage, can be observed in HSP [10].
Mixed Cryoglobulinemias: Vasculitides with close association to some connective tissue diseases such as systemic lupus erythematosus (SLE), and Sjogren syndrome. Viral infections, particularly hepatitis C infection, play a role in the development of this pathology. Hepatitis C infection is prevalent in the Gulf region especially among patients undergoing chronic hemodialysis, and cases of cryoglobulinemias are routinely encountered [11].

Renal disorders

Immunoglobulin A (IgA) nephropathy: First described by Berger and Hinglais in 1968. IgA nephropathy is characterized by predominant IgA deposition in the glomerular mesangium. Its prevalence in the Gulf countries has been increasing recently according to a study from Bahrain by Arrayed et al. [12]. Gross hematuria and renal insufficiency are the main features of IgA nephropathy, however it can rarely cause alveolar hemorrhage [13]. The mechanism of PRS in IgA nephropathy is probably linked to a pauci-immune vasculitis induced by IgA ANCA [14]. Diagnosis is confirmed by kidney biopsy. Prognosis of IgA nephropathy is generally favorable although some cases progress to end-stage renal disease

Idiopathic immune-complex glomerulonephritis (IICG): Can be a misnomer since it is not confined to the kidneys; indeed, cases of IICG with alveolar hemorrhage have been documented. Furthermore, it is suggested that both anti-MPO antibodies and serum MPO are closely related to the pathogenesis of idiopathic crescentic glomerulonephritis [15].

Connective tissue disorders

Systemic lupus erythematosus (SLE): Prevalent in the Gulf countries. It can affect both genders and different age groups [16]. Lupus nephritis is a very common complication occurring in 37–69% of patients affected with SLE in a study from the United Arab Emirates [17]. Furthermore, SLE can have a wide spectrum of other manifestations including intractable alveolar hemorrhage.

Rheumatoid Arthritis (RA): Routinely encountered in the Gulf region since decades ago a recent Saudi study reported a high mortality rate of 16% in local population having extra-articular manifestations of RA including renal and respiratory tracts involvement [18].

Progressive Systemic Sclerosis (PSS): The genetic makeup of the local population may play a role in the development of such condition [19]. Rare cases of PSS or mixed connective tissue disease (MCTD) associated with MPO-ANCA-positive arteritis can be diagnosed. They cause crescentic glomerulonephritis and hemoptysis [20].

Sjogren's syndrome (SS): Also known as sicca syndrome, is a chronic auto-immune inflammatory disease affecting primarily the lacrimal and salivary glands occasionally observed in the Gulf countries. Although rare, it can cause glomerulonephritis. On the other hand, pulmonary manifestations and particularly non-specific interstitial pneumonia bullae formation, and pulmonary nodular amyloidosis. SS causing diffuse pulmonary hemorrhage and subsequently PRS has been documented [21].

Polymyositis/Dermatomyositis: An idiopathic inflammatory myopathy known with its possible malignancy association. Among other symptoms, it can cause severe diffuse alveolar hemorrhage. Sporadic cases are documented in the region [22].

Other etiologies of PRS: Other potential etiologies that might be observed in the Gulf area include:

Anti-phospholipid syndrome (APS): An auto-immune disorder characterized by the wide-spread development of both arterial and venous thrombosis. APS was documented to cause PRS rarely [23].

Drugs: Such as hydralazine, allopurinol, sulfasalazine, or penicillamine can induce ANCA-positive vasculitis or anti-GBM-like disease and subsequently manifest itself in PRS [24].

Occupational exposure: A relationship between ANCA-associated (especially MPO ANCA)-glomerulonephritis and silica exposure has been postulated with documented cases of PRS [25].

Signs and symptoms: The two main clinical pillars for pulmonary renal syndromes include: pulmonary symptoms and renal symptoms. Pulmonary hemorrhage can have spectacular and dramatic presentation, and patients can present with cough, wheezing, dyspnea and possibly cyanosis. Renal symptoms can be subtle or manifest such as flank pain, hematuria, oliguria and renal insufficiency. Constitutional symptoms such as fever, chills, fatigue, arthralgia, myalgia, and weight loss are common. A variety of specific symptoms related to the underlying medical condition can be seen. Seizure, migratory mononeuritis multiplex, or even stroke can be the vasculitic manifestations within the nervous system. Oral ulcerations and even gross nasal septum or palatal destruction are prominent with WG and BD. Leukocytoklastic (palpable) purpura and even cutaneous ulceration can be a prominent feature with HSP and PAN. Connective tissue conditions can offer a wealth of clinical signs such as shiny tight skin, cutaneous telangiectasias or calcinosis, malar or heliotrope rashes, arthritic deformities; or signs and symptoms of pleural, pericardial, or peritoneal irritation. Clinicians must be on the look-out for such findings in order to diagnose and treat the underlying condition, and not only the PRS manifestations.

Diagnostic tools: Many laboratory findings in PRS are non-specific such as anemia, leukopenia, thrombocytopenia, elevated sedimentation rate, increased serum creatinine level, electrolyte disturbances, and presence of red blood cells (RBC) or RBC-casts in the urine. More specific laboratory tests are dictated by the clinical picture. These include

antinuclear antibodies, anti-double strand DNA antibodies, rheumatoid factor, anti-neutrophil cytoplasmic autoantibodies (ANCA), anti-phospholipid antibodies, anti-smooth muscle antibodies, cryoglobulin level. Radiologically, chest X-ray can be normal or show alveolar infiltrates, pulmonary nodules or cavitations. CT scan of the chest can confirm prior observations or discover occult benign or malignant findings. Renal sonography can be normal or possibly shows stigmata of ongoing prior kidney disease. Bronchoscopy with BAL and possibly tissue biopsy are very valuable. The diagnosis of PRS is clinched after doing a kidney biopsy in the majority of cases. Other tissue samples, such skin or nerve biopsies, might help clarify the diagnosis. If the co-existence of pulmonary hemorrhage and renal injury is purely coincidental and has no immunopathologic relationship, the condition then is termed false-positive PRS or non-specific PRS [26].

PRS treatment considerations: The therapeutic approach to PRS can be complex and is generally multidisciplinary. Some considerations in the management of PRS are:

(a) Educational: Consanguinity is prevalent in the Gulf countries. It would be of great benefit to educate the general population about the risks of such practice. Further, stressing patients' education about PRS and its possible complications is paramount.

(b) Supportive therapy: This must be provided in earnest within the confinement of qualified centers. Supportive care can be vital in the management of PRS. Indeed, it has been proven that measures such as temporary mechanical ventilation and hemodialysis can reduce patients' mortality [27]. Moreover, physical and psychological supports might be needed for some patients.

(c) Immunosuppression: Corticosteroids and immunosuppressors, such as cyclophosphamide aim at cutting down the production of auto-antibodies seen in many PRS [28]. Plasmapheresis assists with the removal of already circulating auto-antibodies. Immunosuppression comes, however, with a heavy price at times such as drug toxicity and decreased immunity resulting in severe infections.

(d) Dialysis: Patients with PRS usually develop rapid progressive form of glomerulonephritis requiring early dialysis intervention. Despite appropriate support, the majority of them will lose the remaining kidney function after the initial insult. Such patients will end up dialysis-dependant for a prolonged period of time [29].

(e) Renal transplantation: This is another option for patients afflicted with auto-immune conditions complicated by end-stage renal disease. In the Gulf countries, and in spite of recent improvement, there is still an increasing demand for kidney transplantation done both locally and abroad [30].

(f) Medical Research: Clinical research, such as by the National Institutes of Health in the United States of America, is being conducted to find possible genetic factors in the pathogenesis of some of the etiologies of PRS. Despite generous financial resources in the most Gulf countries, medical research remains restricted with limited funding.

CONCLUSION

Pulmonary renal syndrome occur routinely in the populations of the Arabian Gulf. All possible etiologies are encountered with similar aggressiveness as other regions of the world. Despite major leaps in healthcare improvement, ongoing challenges such with renal transplantation persist. A better medical research pathway for such pathologies certainly needs to be boosted in this region.

Author Contributions

Abdelkarim Waness – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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