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A REVIEW ON PULMONARY-RENAL SYNDROMES

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ABSTRACT

Pulmonary-renal syndromes are a group of disorders characterized by necrotizing glomerulo nephritis and pulmonary hemorrhage. The coexistence of circulating anti-neutrophil cytoplasmic antibody (ANCA) and anti-glomerular basement membrane (GBM) disease in children affected by this syndrome is exponential; with unfavorable out come in five out of seven patients reported to date. We describe a child with PRS associated both circulating anti-myeloperoxidase (anti-MPO) ANCA and anti-GBM disease on renal biopsy who was successfully treated with immunosuppressive therapy. The present article is to provide the intensivist with an overview of pulmonary-renal syndrome, focusing on new concepts of its pathogenesis and treatment innovations. Pulmonary-renal syndromes are a group of disorders characterized by necrotizing glomerulo nephritis and pulmonary hemorrhage. The coexistence of circulating anti-neutrophil cytoplasmic antibody (ANCA) and anti-glomerular basement membrane (GBM) disease in children affected by this syndrome is exponential; with unfavorable out come in five out of seven patients reported to date. We describe a child with PRS associated both circulating anti-myeloperoxidase (anti-MPO) ANCA and anti-GBM disease on renal biopsy who was successfully treated with immunosuppressive therapy. The present article is to provide the intensivist with an overview of pulmonary-renal syndrome, focusing on new concepts of its pathogenesis and treatment innovations.

INTRODUCTION

Pulmonary-renal syndromes (PRS) are defined by the combination of diffuse alveolar hemorrhage and glomerulonephritis (Goodpasture, 1919; Staton and Tange, 1958). The three most common causes of PRS presenting to the respiratory physician are ANCA positive small vessel vasculitis, anti-glomerular basement membrane (anti-GBM) disease (Goodpasture's disease) and Systemic lupus Erythematosus (SLE). The diffuse alveolar hemorrhage is defined by the triad of hemoptysis, diffuse alveolar infiltrates and low hematocrit. However, the clinical presentation is variable (slight cough, progressive dyspnea, manifest hemoptysis) and these symptoms don't have to occur simultaneously (Hauber and Zabel, 2007).

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Slowly protracted courses through to fulminant organ failure are described. A rapid-progressive glomerulonephritis (RPGN) is manifested by a raid progressive renal function loss (a few days to few weeks) and the presence of a nephritic sediment with erythrocytes of a glomerular origin and possibly red cell casts.

Epidemiology

Granulomatosis with polyangiitis (GPA) is a small vessel necrotizing vasculitis with an incident of 10 cases/million with equal male/female preponderance. It occurs predominantly in Caucasian populations and presents between the age of 40 and 55 years in over 70% of cases. Its prognosis has recently been characterized into a bio modal distribution in mortality with an increased risk of death from infection, vasculitis and renal failure in the first year followed by a second peak 8 years from diagnosis which is so far unexplained (Luqmani *et al.,* 2011). Microscopic polyangiitis (MAP) also causes a necrotizing vasculitis and may be clinically difficult to distinguish from

GPA. It has a similar incidence and mean age of onset around 50 years. As with GPA, it is more common in Caucasian populations and in its severest from causes a pauci-immune glomerulonephritis with alveolar haemorrage (Schwarz *et al.,* 2000). In general pulmonary involvement occurs in 30-50% of cases whereas renal involvement extends to over 95% of cases. Churg-strauss (CSS) is a rare systemic and pulmonary vasculitis with an incidence of less than 3 cases/million. Through a higher incidence is quoted in asthmatic populations (64 cases/ million) this may be due to misdiagnosis (Harrold *et al.,* 2005). Males are affected twice as commonly as females and onset is in middle-age. Anti-GBM (Goodpasture's) disease is an even more rare cause of PRS with an annual incidence of 1 case/million. Males are four times more likely to be affected with disease presenting most commonly between 20 and 30 years of age. A second peak in females over appear to be at increased risk of isolated glomerulonephritis (Salama *et al.,* 2001). SLE presenting as alveolar hemorrhage in the context of lupus nephritis is extremely rare and a grave prognosis with mortality figures between 30% and 50% though interestingly these figures do not seem to be affected by the presence or absence of renal failure at presentation.

Pathophysiology

The underlying cause of a pulmonary-renal syndrome is usually a systemic vasculitis of small pulmonary and renal vessels. These vasculitides have heterogeneous pathogenesis-there are three different path physiological mechanisms of injury (Niles *et al.,* 1996).

- Mediated by anti-neutrophil-cytoplasmic anti bodies (ANCA)
- Immune-complex mediated vasculitis of small vessels.
- Antibodies against the glomerular basement membrane (Goodpasture's syndrome).

Table 1. ANCA Causes of pulmonary-renal syndrome (McCabe *et al.,* 2011)

ANCA-positive vasculitis
• Granulomatosis with polyangiitis(wegener's)
• Microscopic polyangiitis
• Charge strauss syndrome
Anti-glomerular basement membrane antibodies (anti-GBM) e Goodpasture's syndrome
Autoimmune connective tissue disease
• Systemic lupus erythematosus
• Polymyositis
• Scleroderma
ANCA-negative vasculitis
• Henoch Schonlein purpura
• Mixed cryoglobulinaemia
• igA nephropathy
• Behcet's disease
Drug-induced vasculitis e hydralazine
• Propylthiouracil
• D-penicillamine
Idiopathic pulmonary-renal syndrome

ANCA-positive vasculitis

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Drug-induced vasculitis e hydralazine

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Idiopathic pulmonary-renal syndrome

Diagnosis

Basic steps

As with many systemic vasculitis the diagnosis of pulmonary-renal syndrome is made in three steps:

- Adequate evaluation and networking of existing and past patient's symptoms.
- Stablishing the diagnosis by laboratory, technical and biopsy examinations.
- Differential diagnosis of vasculitis

Imaging

The value of imaging refers to the extent of pulmonary capillaries resulting in diffuse alveolar Hemorrhage: in a conventional X-ray or in a computer tomography of the chest confluent or mixed interstitial-alveolar infiltrates are found.

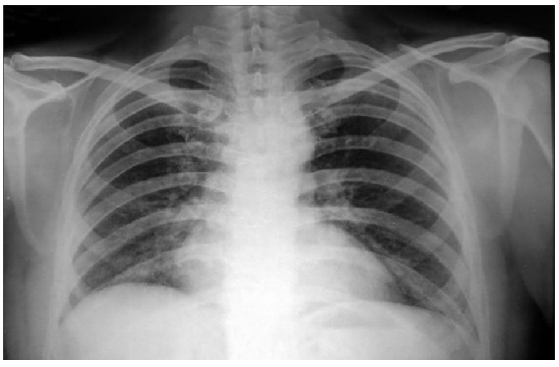

Fig. 1. Diffuse alveolar hemorrhage in chest X-ray in Wegener's granulomatosis (McCabe *et al.,* 2011)

Serology

Antibodies against the glomerular basement membrane (GMB) can be found typically in the rare God pasture's syndrome. The above briefly described heterogeneous pathogenesis of

small vessels vasculitis results in the immunological classification considering serological/immunological parameters such as anti-neutrophil-cytoplasmic antibodies (ANCA) by immunofluorescence-optical findings (perinuclear or cytoplasmic fluorescence) or ELISA against the target antigen proteinase 3 or myeloperoxidase (Bosch *et al.,* 2006). In addition, the eosinophils, IgE and the extended autoimmune serology: anti-nuclear factor (ANA), anti-ds-DNA, C3, C4 and cryoglobulins can be determined. The rapid availability of these antibodies has improved the time to establish an early diagnosis, which is prognostically relevant (Bosch *et al.,* 2006).

Table 2. ANCA-sensitivity (Bosch *et al.,* 2006)

Diagnosis	Proteinease-3- antibody	Myeloperoxidase (MPO)	ANCA negative	Anti-GBM-Ab
Wegner's granulomatosis	70%	20%	10%	<10%
Microscopic polyangiitis	30%	60%	10%	<10%
Churg-strauss-syndrome	30%	60%	30%	<10%
Goodpasture syndrome	<10%	<30%	70%	95%

Renal biopsy

The diagnosis of RPGN is done by renal biopsy: in light microscopy there is a glomerulonephritis with crescent information in the Bowman's capsule compartment (extra capillary proliferation) in more than 50% of the glomeruli. The further work is carried out by immune his to chemistry and electron microscopy. In immune histology, the type of immunoglobulins and the deposition pattern (capillary, mesangial, granular, linear along the glomerular basement membrane) differ. Only in Good pasture 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.

Bronchoscopy

The diagnosis of diffuse alveolar hemorrhage includes the clinical picture and a bronchoscopy with a Broncho alveolar lavage and the microscopic detection of siderophages. Especially in the case of diffuse infiltrates in imaging without hemoptysis a bronchoscopy can be helpful and a definite diagnosis can be established (Hauber *et al.,* 2007).

Differential diagnosis of the pulmonary renal-syndrome

As already stated the pulmonary-renal syndrome is usually caused by a systemic small vessels vasculitis, these can be categorized (Niles *et al.,* 1996; Salant, 1987; De Groot, 2005; Jennette *et al.,* 1994; Falk *et al.,* 1997).

- Morphological criteria (size of the infecting vessels, presence or absence of granulomas),
- Etiological criteria (idiopathic or secondary forms) and
- Immunological criteria (ANCA-associated vasculitis, immune-complex vasculitis or caused by anti-basement antibodies).

ANCA-associated small vessel vasculitis

The Chapel Hill Consensus Conference classification defines.

- Wegner's granulomatosis
- Microscopic polyangiitis and
- Churg-Strauss syndrome.

Renal Involvement is present in many systemic diseases, especially in the small vessel vasculitis-pointed out by Gallo in the New England Journal of Medicine: "The kidney is often a window on systemic disease" (Gallo, 1991). 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 vasculitis signs (eye inflammation, intractable rhinitis/ sinusitis, skin rashes, arthralgia, myalgia or polyneuropathy).

Wegener's granulomatosis: Wegener's granulomatosis is a necrotizing vasculitis of the small and medium-sized vessels, associated with granulomas inflammation of the upper and lower respiratory track and the frequent finding of glomerulonephritis. In active disease in about 90% of cases c-ANCA are directed against proteinase (Hoffmann *et al.,* 1992).

Microscopic polyangiitis

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 are p-ANCA directed against myeloperoxidase (Jennette *et al.,* 1994; Falk *et al.,* 1997). Wegener's granulomatosis and microscopic polyangiitis shows comparable organ involvement, but the symptoms of the upper respiratory tract are usually milder in microscopic polyangiitis, because there is no granulomatous inflammation. Compared to Wegener's granulomatosis disease recurrence is rare in patients with microscopic polyangiitis.

Churg-Strauss Syndrome

Churg-Strauss syndrome is characterized by recurrent asthma attacks and allergic rhinitis, an intermittently or permanently detectable eosinophilia (>1500/mm^3) and necrotizing granulomas and /or necrotizing arteritis with a Wegener's granulomatosis-like presentation. The serological diagnosis is less clear: c-ANCA or anti-PR3-Ab detected only rarely, p-ANCA and anti-MTO-Ab can be detected in up to 60% of cases (Hoffmann *et al.,* 1992). The Churg-Strauss syndrome can be distinguish clinically (asthma attacks, eosinophilia) from Wegner's granulomatosis are microscopic polyangiitis. Renal involvement is seen in approximately 25% of patients.

Goodpasture's syndrome

Goodpasture's syndrome is a rare disease with an incidence of 0.1-1per million per year and affects mainly Caucasian males. It is characterized by hemoptysis and / or radiological evidence of pulmonary infiltrates and a RPGN, which usually

develops after hemoptysis. There is very reliable detection of anti- GBM antibody; the identified antigen is the C-terminal end of the alpha-3-chain of the type IV collagen. The immunohistological work up of the renal biopsy shows linear IgG deposits in the glomerular basement membranes (Goodpasture, 1919; Salama *et al.,* 2001; Hudson *et al.,* 2003). Compared to the ANCA-associated small vessel vasculitides (Wegener's Granulomatosis, Microscopic polyangiitis and Churg-Strauss syndrome) there are no other, general vasculitic symptoms in patients with Goodpasture syndrome.

Immune-complex vasculitis of small vessels

Immune-complex vasculitides like

- Systemic lupus erythematosus
- Cryoglobulinaemia vasculitis and
- Purpura schoenlein-Hennoch (Markus *et al.,* 1989).

Are important differential diagnostic considerations of the pulmonary-renal syndrome. They can be distinguishing by the previously described extended–serological diagnostic workup.

PRS in intensive care

A significant number of patients with PRS deteriorate rapidly and present with life threating respiratory and renal failure requiring admission to ICU. Their management represents a major challenge as mortality is of the order of 25-59%. If left untreated, PRS can follow a fulminant course and is often fatal (Griffiths and Brett, 2003).

Intensive care unit specific management

In the ICU the management of pulmonary-renal syndromes centers on immunosuppression therapy (outlined later) and supportive care. Some important aspects of supportive care are listed below:

Minimizing the risk of sepsis

Patients with vasculitis frequently die of sepsis (Semple *et al.,* 2005) in a series of 26 patients with necrotizing vasculitis admitted to ICU, 75% died of sepsis (Cruz *et al.,* 2003). The risk of nosocomial infection in these patients is very high due to immune-suppression. Severe infection due to cyclophosphamide occurs in about 10% of cases and has a high mortality.

Respiratory and airway management

Respiratory and airway management in GPA there may be subglottic stenosis which can result in difficult intubation. Smaller endo-tracheal tubes or tracheostomy may be needed (Griffiths and Brett, 2003) in acute lung injury due to diffuse alveolar hemorrhage 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 6ml/kg and inspiratory plateau pressures below 30cm H_2O with permissive hypercapnia may reduce lung injury.

Treatment

ANCA associated PRS: remission induction treatment outcomes for systemic vasculitis prior to the introduction of glucocorticoids were dismal with survival at 1year from diagnosis in the region of 20-30% (Westman *et al.,* 1998). The introduction of cyclophosphamide in conjunction with steroids in the 1970s heralded a new age in vasculitis management in that 5years mortality was lowered from 50% with glucocorticoid treatment alone to 12% with combination therapy (Fauci *et al.,* 1983). Induction of remission is most commonly achieved with high dose intravenous methylprednisolone (0.5 gel g/day) for 3-5days for which there is no substantial evidence base. This is coupled with pulsed intravenous cyclophosphamide administrated every 2-3 weeks (15 mg/kg/pulse) on 6-9 occasions or as a daily oral regimen (1-2mg/kg/day). In the presence of severe renal disease defined as a serum creatinine >500mmol/L, there is additional short term benefit from plasmapheresis in terms of renal recovery in the 18 months. A recent trial of rituximab for induction of remission in ANCA associated disease was not superior to standard intravenous cyclophosphamide. Sustained- remission rates were high in both groups however.

Maintenance of remission

The most effective method `of maintenances 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. Currently, glucocorticoids are continued at low dose for a minimum of 18 months alongside a steroid sparing agent. This is usually extended to 2 years total in those with PR3 positive ANCA in view of their higher rate of relapse (Hogan *et al.,* 2005). The most widespread European practice is switching from cyclophosphamide to azathioprine at the 3-6 months interval from diagnosis. Biological therapies studied include the TNF-a inhibitor infliximab and the TNF0-a receptor protein Etanercept. These along with rituximab, which is an anti-CD20 antibody that depletes B cells, initially looked promising candidates for remission induction. Both anti-TNF-a agents tested however recently been demonstrated to be as cyclophosphamide in two randomized controlled trials (Jones *et al.,* 2010; Stone *et al.,* 2010).

Anti-glomerular basement membrane disease - good pasture's

Urgent plasma exchange is initiated when this diagnosis is suspected to deplete plasma of circulating anti-GBM antibody. There is evidence to suggest earlier commencement has beneficial effect on long-term renal recovery (Levy *et al.,* 2001). On average a 14 day course of plasma exchange is completed which is usually adequate to return anti-GBM antibody to normal titers. Immunosuppression is started alongside this therapy usually consisting of oral prednisolone (1mg/kg) and oral cyclophosphamide (2-3mg/kg/day). Available evidence suggests completely an uric patients respond poorly to this regimen going on to require long term renal replacement therapy with consequent poor survival in the region of 50% at 2 years (Levy *et al.,* 2001). Systemic lupus erythematosus pulmonary hemorrhage in the context of lupus nephritis caries 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 (Appel *et al.,* 2009; Smith *et al.,* 2006). Relapse rates or high however despite the improved toxicity profile (Merrill *et al.,* 2009). Recent studies looking at rituximab as add on therapy in SLE have failed to show significant benefit but this is most likely due to poor trial design (Merrill *et al.,* 2009; Furie *et al.,* 2009).

Conclusion

The pulmonary renal syndrome is very rare disease but represents a serious medical emergency with significant cant morbidity and mortality. Appropriate management of such patients include early and specialized immunosuppressive treatment. Renal transplantation remains the only alternative for patients with pulmonary renal syndrome.

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