Pulmonary-Renal Vasculitic Disorders: Differential Diagnosis and Management

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Pulmonary-renal syndrome (PRS) is a combination of diffuse pulmonary hemorrhage and glomerulonephritis. Pulmonary-renal syndrome is not a single entity and is caused by a variety of conditions, including Goodpasture´s syndrome associated with autoantibodies to the glomerular and alveolar basement membranes, various forms of primary systemic vasculitis associated with serum positivity for antineutrophil cytoplasmic antibodies (ANCA), cryoglobulinemia, systemic lupus erythematosus, systemic sclerosis, antiphospholipid syndrome, environmental factors, and drugs. The majority of cases of PRS are associated with ANCAs. The antigen target in Goodpasture´s syndrome is the alpha-3 chain of type IV collagen. The antigen target in PRS associated with systemic vasculitis is proteinase-3 and myeloperoxidase. Pulmonary-renal syndrome has been observed from the first to the ninth decade of life. The widespread adoption of serologic testing performed in an appropriate clinical context hopefully will limit diagnostic delay. The goals of treatment in PRS are to remove the circulating antibodies, to stop further production of autoantibodies, and to remove any antigen that stimulates antibody production. Treatment is based on plasmapheresis, steroids, and cyclophosphamide; however, infections are frequent contributors to death, and less toxic alternatives may improve outcome and prognosis resulting in a long-term survival. The degree of renal function and the percent of crescents on renal biopsy are better predictors of outcome. Renal transplantation can be safely carried out in PRS.

Introduction

The pulmonary-renal syndrome (PRS) or pulmonary-renal vasculitic disorders, which are defined as a combination of diffuse pulmonary hemorrhage and glomerulonephritis, is a severe syndrome with a bad prognosis and serious diagnostic and therapeutic consequences. In 1919, Ernest Goodpasture [1] described an 18-year-old patient presenting with a severe form of pulmonary hemorrhage and glomerulonephritis. In 1958, Stanton and Tange [2] used the term *Goodpasture's syndrome* (GPS) to describe other patients with similar characteristics. In 1967, Lerner *et al.* [3] described GPS associated with deposition of antibodies in a linear pattern on the glomerular and alveolar basement membranes. In addition, the pathogenicity of the autoantibodies has been demonstrated by passive transfer experiments and is related to disease severity [4]. Therefore, the diagnosis of GPS often relies on the use of immunoassay to detect circulating antiglomerular basement membrane (GBM) antibodies in serum samples. The antigen target has been identified as the non-collagenous domain of the alpha-3 (α3) chain of type IV collagen [5].

It is now clear that the PRS results from several diseases having different underlying pathogenic mechanisms, such as systemic lupus erythematosus (SLE), Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS), microscopic polyangiitis (MPA), or pauci-immune necrotizing and crescent glomerulonephritis (CGN). In recent years, antineutrophil cytoplasmic autoantibodies (ANCA) have been described in serum from patients presenting with PRS. Therefore, the eponymous GPS is only used for those cases of PRS induced by anti-GBM antibodies [6•].

Epidemiologic Aspects

Goodpasture's syndrome is infrequent and has an incidence of approximately 0.5 to 1 case per million people per year in European populations. Gender distribution is approximately equal, and the age at presentation can range from the first to the ninth decade of life. Goodpasture's syndrome has a bimodal age distribution, with a greater number of patients presenting at ages 18 to 30 and at ages 50 to 65. The disease appears more frequently in whites than in blacks, and is even more frequent in other ethnic groups, such as the Maoris of New Zealand [7].

Antineutrophil cytoplasmic autoantibody–associated vasculitis 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 may be challenging because of its relative infrequence, changing nomenclature, and variability of clinical expression. In patients presenting with PRS secondary to systemic vasculitis, pulmonary hemorrhage appears in

42% of WG cases and 29% of MPA cases, and it rises when renal involvement is severe [8]. Pulmonary hemorrhage in these disorders carries a mortality rate of 10%. Diffuse alveolar hemorrhage in SLE remains a devastating pulmonary complication; mortality rates are around 50%, and it occurs in less than 2% of patients with SLE. Evidence for glomerular involvement is also present in the great majority of cases [9].

Single-center experience suggests that 60% to 70% of cases with PRS are associated with ANCAs, and 20% are associated with anti-GBM antibodies [10,11].

What Is the Antigen in Goodpasture's Syndrome?

In GPS, the target antigen is the non-collagenous (NC1) domain of the α3 (IV) collagen chain, one of the six chains (alpha-1 to alpha-6 [α1 to α6]) that compose type IV collagen (α3 [IV] NC1) [12]. This target antigen is found primarily on the inert aspect of the lamina densa, which is the middle layer of the glomerular and alveolar basement membranes that serve as part of the support structures as a building block. Basement membranes, which are composed of type IV collagen, laminin, proteoglycans, entactin, and other proteins, form an anatomic barrier where cells meet connective tissue [13,14]. In the GBM, which is the main target of autoantibodies, the GPS epitopes are cryptic in the α3.α4.α5 NC1 hexamer complex. As a result, the epitopes are inaccessible for binding to autoantibodies unless the hexamer dissociates. A recent study suggests that the cryptic nature of the GPS autoepitope is the result of quaternary interaction of the α3, α4, and α5 NC1 domains of the hexamer complex. Three of the four GPS residues are hydrophobic and have a high propensity to the buried. This suggests that the cryptic nature of the GPS autoepitope is caused by one or more GPS residues participating in hydrophobic interactions with other NC1 domains in the hexamer complex, burying the epitope and making it inaccessible for binding to autoantibodies. Therefore, if pathogenic factors induce hexamer dissociation, the newly exposed GPS residues would then be perceived as "foreign" by the immune system, eliciting an autoimmune response. These finding provide critical information for understanding the etiology and pathogenesis of the disease, as well as for designing drugs that would mimic the epitope and, thus, block the binding of GPS autoantibodies to autoantigen [15••].

There are few data on the characteristics of the autoreactive T cells in GPS. A recent study shows that during acute disease there were increased frequencies of $CD4^+$ T cells reactive with α3 (IV) NC1, which decreased with time. The decrease in autoreactive $CD4^+$ T cell numbers during recovery may be the reason why recurrences are infrequent, and may explain the loss of pathogenic autoantibodies with time, because of the lack of T cell help [16••].

Evidence from animal model studies also supports a key role for α3 (IV) NC1. However, it has been difficult to establish the antigen that is detected by the anti-GBM antibodies. These animal models recognize the α3 (IV) NC1, and T cell involvement in the development of glomerulonephritis suggests that linear peptides are important. A recent study examines overlapping peptides covering the length of the target domain, and found that none of them would reliably produce glomerulonephritis in an experimental model of GPS. Two peptides produced mild nephritis in a minority of animals; several could provoke a T cell mitogenic response in animals that already had the syndrome. It appears that more than one antigen is necessary to produce glomerulonephritis, or that the antigen must undergo conformational change or post-translational modification in order to work its effect [17••].

Pathophysiology of Goodpasture's Syndrome

The GBM is in constant contact with blood by the fenestrations in the glomerular capillaries, which allow access for circulating antibodies to bind to the basement membrane. This binding activates the complement cascade, which causes polymorphonuclear leukocytes, antigens, and monocytes to infiltrate the glomeruli. Fibrinogen leaks into Bowman space and breaks down into fibrin by the prothombinase enzyme, which is associated with active monocytes. These monocytes generate crescents in the glomeruli. Interleukin-1 may attract fibroblasts from renal interstitium, which enhance the crescent formation [18••].

Alveolar capillaries do not have fenestrations, and the alveolar endothelium acts as a barrier to the anti-GBM antibodies. The etiology of lung involvement is unclear. Deposition of anti-GBM antibodies on alveolar basement membrane is related to an additional lung injury that increases alveolar-capillary permeability [13].

Many agents are associated with GPS, such as lithotripsy, kidney trauma, cigarette smoke, D-penicillamine, infections, and hydrocarbons. The association of GPS with specific human leukocyte antigens (HLA) types is very strong, and over 80% of patients carry HLA-DR15 or DR4 alleles and negative HLA-DR7 and DR1 associations, which suggests that these may confer some protection from disease [19].

What Is the Antigen in Pulmonary-Renal Syndrome Associated with Systemic Vasculitis?

Since the introduction of tests for ANCAs in patients who present with lung hemorrhage and nephritis, ANCAs has been found more often than anti-GBM antibodies. The reevaluation of anti-GBM antibodies, perinuclear staining (p)-ANCA, and granular cytoplasmic staining (c)-ANCA in 88 patients with evidence of lung hemorrhage and nephritis revealed that the major cause was ANCA-associated condition [11], the most common illness presenting as PRS is

systemic vasculitis. The group with ANCAs comprises more than two thirds of all patients and mostly contains patients with small-vessel vasculitides (SVVs). In these patients with SVVs, proteinase-3 (PR3) or myeloperoxidase (MPO) is targeted selectively by ANCAs [20].

Antineutrophil cytoplasmic autoantibodies are thought to contribute to the pathogenesis of SVVs, and activate cytokine-primed neutrophil and monocytes, which express PR3 and MPO on their surface. Neutrophils respond by adhering to cytokine-activated endothelial cells, generating a respiratory burst, releasing proteolytic granule contents, and secreting pro-inflammatory cytokines. Antineutrophil cytoplasmic autoantibodies also interfere with the normal processes of resolution of inflammation. Neutrophil apoptosis is dysregulated by ANCA activation of neutrophils and prevents apoptotic cell removal, which allows progression to secondary necrosis, a highly inflammatory event. Endothelial cells are important in localizing inflammation, and they develop an activated phenotype in ANCA-associated vasculitis with enhanced expression of adhesion molecules that promotes interaction with circulating inflammatory cells [21].

Studying the pathophysiologic role of ANCA in vivo, Brouwer *et al.* [22] reported an animal model for anti-MPO-associated pauci-immune necrotizing crescentic glomerulonephritis (NCGN). Recently, an animal model for anti-MPO associated pulmonary vasculitis was developed in analogy to the kidney model. In this model, rats were immunized with human MPO, and a single left lung perfusion with a neutrophil lysosomal extract was performed. The lesions were characterized by infiltration of polymorphonuclear leukocytes and monocytes and, in some rats, foci alveolar hemorrhage. These studies suggest a pathogenic role of MPO-ANCA in PRS associated vasculitis [23•].

Table 1. Classification of the pulmonary-renal syndrome (pulmonary hemorrhage and glomerulonephritis)

Goodpasture's syndrome or antiglomerular basement membranes
Immune complex–induced
Systemic lupus erythematosus
Rheumatoid arthritis
Systemic sclerosis
Antineutrophil cytoplasmic antibody–associated vasculitis
Microscopic polyangiitis
Wegener's granulomatosis
Churg-Strauss syndrome
Drug-induced vasculitis
Pauci-immune necrotizing and crescentic glomerulonephritis
Non–antineutrophil cytoplasmic antibody–associated vasculitis
Henoch-Schönlein purpura
Essential cryoglobulinemia
Behçet's disease
Immunoglobulin A nephropathy
Antiphospholipid syndrome
Others

Pulmonary-Renal Syndrome, Drugs, and Environmental Factors

There have been reports suggesting that hydralazine, propylthiouracil, and several other drugs may cause some cases of ANCA-positive vasculitis. The majority of these cases have been associated with anti-MPO antibodies. Penicillamine, propylthiouracil, and cocaine have been associated with PRS [24,25]. An interesting study supported the hypothesis that asbestos and silica exposition may induce PRS. Yashiro *et al.* [26••] described 14 patients with ANCA-related (anti-MPO) angiitis or nephritis identified within a 3-year period after the great earthquake of Kobe (Japan), and compared them with 15 patients with the same disease observed from 1990 to 1997 in Kyoto (poorly affected by the earthquake). Severe renal and pulmonary involvement was significantly higher in the Kobe group than in the Kyoto group. The asbestos and silica content after the earthquake produced acute and chronic lung damage with activation and induction of apoptosis from alveolar macrophages, T cells, and neutrophils, which are the main source of MPO. The surface expression of MPO during apoptosis may stimulate the immune response resulting in an amplified release of cytokines, oxygen radicals, lysosomal enzymes, and production of ANCAs (anti-MPO exposure to silica developed p-ANCA-associated vasculitis with pulmonary-renal syndrome (anti-MPO). Two siblings with similar environmental exposure to silica developed p-ANCA–associated vasculitis with PRS (anti-MPO). This is the first report of a family cluster of silica-induced, ANCA-associated systemic vasculitis and PRS with members sharing HLA antigens [27•].

Classification and Diagnosis of Pulmonary-Renal Syndrome

The term *nonspecific PRS* refers to pulmonary edema, pulmonary thromboembolism, or pulmonary infection, complicating the course of glomerular disease. Nonspecific PRS also refers to glomerular disease after pulmonary disease, which is mostly an infection. The term *specific PRS* denotes simultaneous or continuous pulmonary hemorrhage and glomerulonephritis. Therefore, *specific PRS* implies a much more restricted range of possibilities, and the most frequent is the SVV (Table 1).

Diagnosis of Pulmonary-Renal Syndrome

A diagnosis of PRS is best established by using a combination of clinical presentation, serologic results, and histologic results, although obtaining samples for the last may present practical difficulties in a critical care setting [28••].

Goodpasture's syndrome

The true diagnosis is usually made at late stages because of the vague symptomatology, such as weakness, fatigue, and flu-like illness, that may encompass the rapid progression of disease. Lung hemorrhage is manifested as blood-streaked sputum to massive, fatal pulmonary hemorrhage. Hemoptysis is generally episodic, and occasionally it is so extreme that it floods the lungs and produces asphyxia and, finally, death. Patients often complain of shortness of breath and cough, but no chest pain or pleurisy, because it occurs in pulmonary embolism. Chest radiograph shows alveolar-type shadowing with sparing of the upper lung fields secondary to lung hemorrhage. The diffusing capacity for carbon monoxide is increased in lung hemorrhage because of binding of hemoglobin to carbon monoxide. Computed tomography and magnetic resonance imaging are not necessary in the evaluation of lung involvement unless the diagnosis is questionable.

Most patients initially present with hematuria, erythrocyte casts, proteinuria (less than 3 g every 24 hours), elevated serum creatinine, and oliguria indicative of progressive renal insufficiency. This presentation usually occurs after the onset of pulmonary disease, as well as a rapidly progressive glomerulonephritis. Systemic features, such as arthralgias and myalgias, are usually absent, but they may be found in vasculitis causing PRS. Hypertension is uncommon except at endstage renal failure [18••,29•,30••].

The characteristic renal histologic finding in acute GPS is a necrotizing and proliferative glomerulonephritis that ranges from focal and segmental to diffuse glomerulonephritis.

More than 90% of patients have crescent formation. Crescents may contain mainly ordered layers of epithelial cells or disordered crescents with numerous macrophages, disruption of Bowman´s capsule often accompanied by a continuous periglomerular inflammation with a granulomatous appearance. Another glomerular lesions are foci of fibrinoid necrosis containing karyorrhectic debris and neutrophilic infiltration. The acute lesions evolve into sclerotic lesions, whereas cellular crescents evolve into fibrous crescents. Light microscopy does not differentiate GPS from other causes of crescentic glomerulonephritis; therefore, electron microscopy examination and immunofluorescence of the biopsy specimen are needed. Electron microscopy shows widening of subendothelial spaces of the glomerular capillaries, which are related to the binding of anti-GBM antibodies. Crescents are formed by parietal cells and macrophages in combination with GBM destruction. Immunofluorescence will exhibit linear deposits of immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin M (IgM) and C3 outlining the capillary loops [31]. Sometimes a lung biopsy is needed to exclude other diagnoses, such as infection or other PRS. Lung biopsy will demonstrate extensive nonspecific intra-alveolar hemorrhage, hemosiderin-laden macrophages, and, occasionally, linear immunofluorescence as seen in the kidney [18••].

The circulating antibodies to GBM are usually IgG and may be detected by enzyme-linked immunosorbent assay (ELISA) (greater than 20 U to be considered positive) and their specificity confirmed by western blotting. Testing for anti-GBM antibodies should always be combined with tests for ANCA, because the clinical presentation of small vessel may be similar, and the two types of autoantibodies can occur together. Less often, IgA and IgM have been reported [30••]. A circulating monoclonal and linear deposition of IgA-kappa antibody in the glomerular and tubular basement membranes has been shown in PRS [32]. Recently, Carreras *et al.* [33] reported a 69-year-old patient with Henoch-Schönlein purpura with kidney involvement followed by pulmonary hemorrhage. The presence of an IgA linear pattern on the kidney biopsy specimen and circulating anti-GBM IgA antibodies led to the diagnosis of GPS. In cases of glomerulonephritis with lung involvement, clinicians should not limit the search for anti-GBM IgG.

Although kidney disease may occur with or without lung involvement, isolated alveolar hemorrhage, as an incipient manifestation of the syndrome, is rare. A patient with anti-GBM disease who initially presented with anti-GBM–negative hemoptysis and normal urine has been reported. It was not until relapse of his condition that acute glomerulonephritis and anti-GBM were found [34].

Many standard techniques are available, and false-positive and false-negative results are found in some of these. Salama *et al.* [35] described three cases of GPS in which no circulating anti-GBM antibodies were detectable in serum by ELISA or western blotting techniques. The diagnosis of GPS was confirmed by renal biopsy with linear deposition of immunoglobulin along the GBM and crescentic glomerulonephritis. In addition, an alternative method of antibody detection using a highly sensitive biosensor system confirmed that circulating antibodies were present in sera from the patients that were tested. Optical biosensor technology allows the study of molecular interactions in real time, including interactions among proteins, nucleic acids, carbohydrates, and peptides, and does not generally require chemical modifications of the molecules studied, such as the addition of fluorescence, enzymatic, or radiolabels. Biosensor techniques detect anti-GBM antibodies and others in serum from patients with high sensitivity and without need for antibody purification [36••].

Pulmonary-renal syndrome–associated systemic vasculitis

Clinical features of PRS secondary to vasculitis are diverse and are characterized by manifestations of primary disorders—MPA, WG, CSS, SLE, Henoch-Schönlein purpura, or cryoglobulinemia. The cardinal manifestation of diffuse alveolar hemorrhage includes hemoptysis, diffuse alveolar infiltrates on chest radiograph, and anemia, disnea, and hipoxemia. Pulmonary capillaritis has been reported with variable frequency and severity in these disorders with a

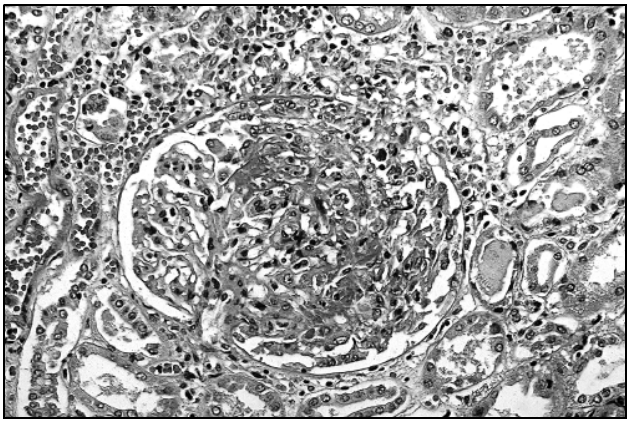

Figure 1. Necrotizing and crescentic glomerulonephritis in a patient with fulminant Wegener's granulomatosis.

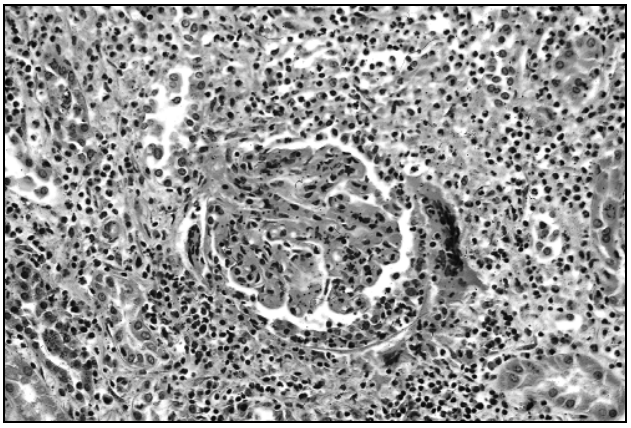

Figure 2. Glomerulonephritis with Bowman's capsule rupture and interstitial infiltration of giant cells (from the same patient as Figure 1).

similar frequency of positive cases for c-ANCA or p-ANCA. Although massive hemoptysis is a common manifestation of the diffuse alveolar hemorrhage, it may occur in the absence of hemoptysis. The detection of hemosiderin-laden macrophages in the sputum indicates that blood has been presented in the alveolar spaces long enough for it to be broken down by alveolar macrophages. Clinically significant pulmonary hemorrhage is usually sufficient to cause anemia; therefore, sequential determination of hemoglobin in peripheral blood is a good monitor for continued or recrudescent bleeding, even in the absence of hemoptysis [37].

The use of flexible bronchoscopy in 34 patients selected on the basis of concurrent hemoptysis and renal failure were reported. Pulmonary-renal syndrome was observed in only five patients (15%). The flexible bronchoscopy in hospitalized patients with hemoptysis and renal failure, and without radiographic findings, suggesting that neoplastic disease has a low yield and limited impact [38•].

There are several renal manifestations of PRS associated with SVV. The majority of patients present with rapidly progressive glomerulonephritis with hematuria, proteinuria, and serum creatinine that progressively rises over the course of days to weeks. The renal biopsy shows glomerular necrosis and crescent formation. Invariably, interstitial inflammation results in interstitial fibrosis [39].

Although the lung is the most common organ involved in WG, pulmonary hemorrhage is uncommon. In patients with WG and PRS, the pulmonary hemorrhage is often the initial presentation of this disease. The authors also described an autopsy finding of a 46-year-old man with WG and fulminant PRS (Figs. 1–4). The majority of patients with alveolar hemorrhage present with rapidly progressive glomerulonephritis and acute renal failure. Therefore, patients with PRS tend to have a fulminant variant of WG [37].

Microscopic polyangiitis is a systemic SVV primarily associated with necrotizing glomerulonephritis and pulmonary capillaritis. In a retrospective study of 29 patients with MPA, 27 were diagnosed with alveolar hemorrhage by the bloody aspect of bronchoalveolar lavage and its markedly elevated content of hemosiderin-laden macrophages. Patients with MPA had similar chest imaging features to those with pulmonary hemorrhage caused by GPS, WG, or SLE. The patients with MPA had a predominant p-ANCA antibodies (48%), but the percentage of patients with c-ANCA antibodies was higher (38%) than in previous reports. Pulmonary-renal syndrome developed rapidly within 6 weeks in 38% of MPA patients. However, a chronic course before diagnosis was not rare, with 28% of patients having symptoms for more than 1 year before diagnosis [40••].

Pulmonary hemorrhage is a rare complication of SLE (2%), and is associated with high mortality rates (60%). In the authors' experience, 32% of patients with pulmonary hemorrhage also had severe glomerulonephritis [9]. Acute alveolar hemorrhage in SLE usually occurs as a PRS. In most cases, the lung showed "bland" alveolar hemorrhage with little or no inflammation. Hughson *et al.* [41••] investigated the relationship between alveolar hemorrhages to immune complex deposition in the lungs of six patients with SLE, and correlated the findings with glomerular and vascular disease in the kidneys. Their findings indicated that alveolar hemorrhage in SLE, characterized by bland alveolar wall changes, was pathogenically similar to the lupus microangiopathy of the kidney. Therefore, the pathogenesis of the microvascular injury appears to be related to immune complex deposition and induction of apoptosis.

The concomitant occurrence of PRS has rarely been described in systemic sclerosis (SSc). Eleven patients have been reported to date [42•]. The average age of the patients with SSc-PRS was 46 years. Pulmonary-renal syndrome occurred with an average of 6.4 years after disease onset and was associated with prior fibrosing alveolitis or D-penicillamine treatment. Systemic sclerosis-PRS has a poor prognostic indication; that is, all patients died within 12 months of admission. An additional case of microscopic

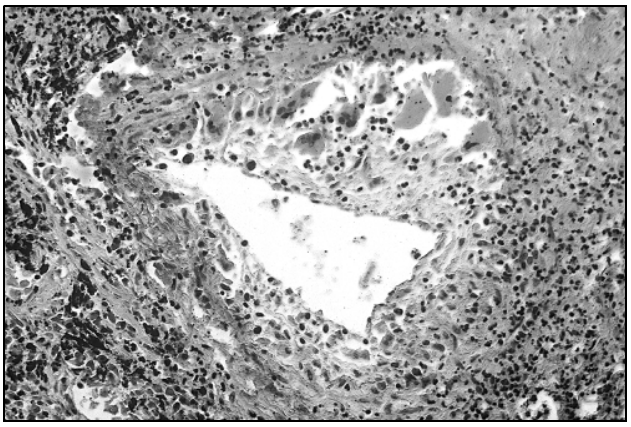

Figure 3. Pulmonary arteritis with giant cell infiltration (from the same patient as Figure 1).

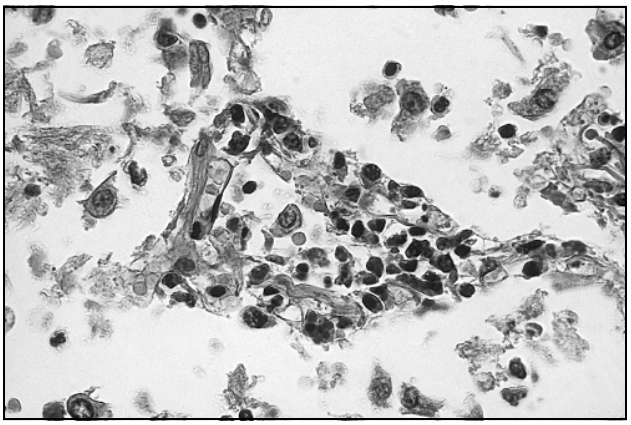

Figure 4. Pulmonary capillaritis (from the same patient as Figure 1).

polyangiitis presenting as PRS with long-standing diffuse cutaneous SSc and anti-MPO has been described [43]. Anticentromere antibody–positive PRS without clinical features of SSc or CREST syndrome (calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, and telangiectasias) was described in a fatal case in which the histologic findings reveled crescentic glomerulonephritis, including glomerular and pulmonary capillaritis, with granular immunoglobulins deposits and complement on the respectively capillary walls [44].

Outcome data for PRS remain confined to small studies with limited follow-up. Gallagher *et al.* [28••] studied 14 cases retrospectively from a single tertiary center over a 4-year period of follow-up. Thirteen patients had systemic vasculitis, and only one had SLE. Five patients were c-ANCA-positive, and seven patients were p-ANCA-positive; two of the latter patients also were positive for anti-GBM antibodies. Findings confirmed previous suggestions that PRS requiring intensive care treatment has high mortality rates and early survivors have good outcomes in the 1st and 2nd year.

The variety of histologic features of vasculitic lesions in MPO-ANCA–associated vasculitis was studied in 13 autopsy cases. These cases were classified into the following groups: 1) PRS characterized by capillaritis of lung and glomeruli; 2) glomerular capillaritis without pulmonary involvement associated with significant small-vessel arteritis; and 3) extensive distribution of small-vessel arteritis with no capillary involvement. Perinuclear staining ANCA may contribute to the pathogenesis in all cases [45•].

Pulmonary-Renal Syndrome in Childhood

Little is known regarding PRS in childhood. von Vigier *et al.* [46••] reported 21 pediatric patients with specific or nonspecific PRS. Three children had a systemic vasculitis associated with ANCA (WG, *n*=2; MPA, *n*=1) and two with SLE. Review of the literature disclosed 52 cases of specific PRS other than SLE—28 cases with WG, 13 with GPS, and 11 Henoch-Schönlein purpura. An additional report described the case of a 10-year-old girl with rapid and progressive loss of renal function and massive lung hemorrhage. The ANCA test with anti-MPO was positive, and the circulating anti-GBM showed an undetermined result [47].

Pulmonary-Renal Syndrome and Antiphospholipid Syndrome

Pulmonary involvement in antiphospholipid syndrome (APS) is infrequent and includes thromboembolic pulmonary hypertension, primary pulmonary hypertension, and pulmonary capillaritis. Diffuse alveolar hemorrhage with pulmonary capillaritis is a rare complication of APS [48]. Renal involvement in APS is also rare, and it has been recently recognized [49]. Henning *et al.* [50•] described the first three cases of PRS caused by APS. The patients presented dysnea, renal failure, and pulmonary infiltrates on the chest radiograph. Clinical findings, antiphospholipid antibodies, and histologic findings in transbronchial or renal biopsy proved the diagnosis of APS.

Treatment

Treatment of pulmonary-renal syndrome in Goodpasture's syndrome

The goals of treatment of PRS in GPS are to remove the circulating antibodies, stop further production of autoantibodies, and remove any antigens that stimulate antibody formation [18••]. Treatment consists of immunosuppression with oral steroids (starting at 1 mg/kg per day with a maximum dose of 60 mg, and subsequently lowering doses), cyclophosphamide 2.5 mg/kg per day rounded down to the nearest 50 mg, and in a reduced dose for patients over 60 years, and daily plasmapheresis (50 mL/kg, maximum 4 L) with a total of 14 sessions or until the anti-GBM antibody titer is undetectable [30••]. The most important risk of treatment is serious infection, which may accelerate the disease process. Fluid overload and smoking can trigger further pulmonary

hemorrhage. Some advocate for methylprednisolone pulses instead of plasmapheresis, although they have not been compared in a randomized trial.

Immunosuppressive treatment and plasmapheresis may be discontinued after 6 to 9 months [30••], and relapses are rare, but they may occur after 3 to 5 years [51]. Historically, the prognosis for GPS has been poor. With the advent of plasmapheresis in combination with prednisolone and cyclophosphamide, and improved serologic test for earlier recognition of the disease, the prognosis has improved dramatically resulting in long-term survival. However, the degree of renal function and the percent of crescents on renal biopsy are better predictors of outcome.

Long-term outcome of patients with kidney damage caused by GPS has been recently studied in 71 patients observed from 12 to 289 months (with an average of 90 months). All patients received plasma exchange, prednisolone, and cyclophosphamide. Patients whose kidney damage was less severe when they first sought care did better than those with more severe kidney damage. However, even patients with severe kidney damage could recover when treated. All patients who required immediate dialysis and had 100% crescents on renal biopsy remained dialysis dependent [52••].

Renal transplantation can be used in patients with end-stage renal disease. Patients with GPS who receive transplants have outcome comparable with patients with other causes of end stage renal disease [18••].

Treatment of pulmonary-renal syndrome in vasculitic disorders

Given the often-precipitous deterioration of the condition of patients with PRS, it is prudent to initiate early and aggressive therapy directed against the underlying disorder. Gallagher *et al.* [28••] described the treatment used in 14 patients with PRS. All patients were treated with corticosteroids, eight of 14 were treated with methylprednisolone pulses, also 13 of 14 were treated with cyclophosphamide and 12 of 14 underwent plasmapheresis. Patients were observed up to 22±9 months. Early reduction in cyclophosphamide dosage was required in nine patients because of neutropenia, seven patients were alive at the end of follow-up, but five patients (36%) died in the 1st month. Sepsis was the main factor of death. These findings confirm that PRS requiring intensive care treatment has high mortality rates. Cyclophosphamide-associated neutropenia and infection were frequent contributors to death, and less toxic alternatives may improve outcome in PRS.

Conclusions

Pulmonary-renal syndrome constitutes a significant diagnostic and therapeutic challenge in the overall management of patients with autoimmune diseases. The wide range of clinical manifestations makes it difficult to diagnose at early stages. Early suspicion of disease should prompt serologic tests and renal biopsy in order to obtain diagnosis and establish intensive care treatment.

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