

Cutting Edge Issues in Goodpasture's Disease

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Abstract Goodpasture's disease, or anti-glomerular basement membrane (anti-GBM) disease, is a systemic autoimmune disorder defined by anti-GBM antibody-mediated damage (mainly immunoglobulin G-1) resulting in progressive crescentic glomerulonephritis and, frequently, diffuse pulmonary alveolar hemorrhage. It may be regarded as a "conformeropathy" where the quaternary structure of the $\alpha345$ NC1 hexamer that constitutes GBM undergoes a conformational change, exposing pathogenic epitopes on the $\alpha3$ and $\alpha5$ chains, eliciting a pathogenic autoantibody anti-GBM response. Goodpasture's disease accounts for 20% of all patients presenting with a pulmonary-renal syndrome and may be associated with detectable perinu-

clear antineutrophil cytoplasmic autoantibody positivity in up to a third of patients. Associated triggers may include tobacco smoking, hydrocarbon solvent exposure, and cocaine abuse. Cough, hemoptysis, and dyspnea with fatigue are the commonest presenting features. It is critical to rapidly distinguish Goodpasture's disease from other causes of pulmonary-renal syndromes such as Wegener's granulomatosis. Early and intensive treatment with plasmapheresis and immunosuppression with systemic corticosteroids pending results of diagnostic testing, and later cyclophosphamide, is often beneficial, with 90% of patients surviving the acute presentation of Goodpasture's disease. The need for hemodialysis on initial presentation, a serum creatinine >5 mg/dL, and 50% to 100% crescents on renal biopsy, portend the necessity of long-term hemodialysis. Further elucidation of the molecular pathobiology of Goodpasture's disease, particularly the regulation of involved antigen-specific T cells, may improve early diagnosis, treatment, and outcomes in this rare but potentially lethal autoimmune disorder.

Keywords Goodpasture's · Plasmapheresis · Alveolar hemorrhage · Glomerulonephritis · Anti-GBM · Antibodies

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Case Illustration

A 52-year-old Caucasian female, current smoker (15 pack-years) was admitted to hospital complaining of progressive shortness of breath for 1 day prior to admission together with hemoptysis. She described the blood as bright red in color, of approximately one teaspoon per episode, mixed with scanty white sputum, with approximately 12 such episodes over a 24-h period. She also noted that her urine had become darker in color,

and that she was urinating less, estimating the daily urine volume to be approximately three cups. No complaints of fever, night sweats, joint pains, muscle aches, chest pain, or weight loss were elicited. She had not been abroad over the past 12 months nor had she been on any long vehicular rides of more than 30 min in duration. Her previous medical and surgical history was unremarkable; she was not on any regular medication and denied any illicit drug use.

Physical examination revealed hypertension (blood pressure 160/95 mmHg), with a heart rate of 98 beats/min, a respiratory rate of 30 breaths/min and a temperature of 37°C. Her oxyhemoglobin saturation on room air was 95% using finger oximetry. No skin rash was seen. Chest auscultation demonstrated a few crackles at the lung bases posteriorly, a soft abdomen without tenderness or guarding, and 2+ pitting peripheral edema in both lower extremities. The kidneys were not palpable. Cardiac examination was unremarkable.

Laboratory results included a hemoglobin level that was decreased at 10.6 g/dL, an elevated white blood cell (WBC) count of 14 K/mm³ and a normal platelet count of 230 K/mm³. The mean corpuscular volume was normal at 90 femtoliters/cell, as was the mean corpuscular hemoglobin at 29 pg/cell. Blood urea nitrogen and creatinine were elevated to 54 mg/dL and 4.8 mg/dL, respectively. The sodium and potassium levels were normal. International normalized ratio and partial thromboplastin time were also normal. Urine analysis revealed dysmorphic red cells, red blood cell and granular casts, 2+ proteinuria, and a red blood cell count of 40 cells per high power field (HPF) with eight WBC/HPF. Urine leukocyte esterase and nitrite were negative.

A chest radiograph (CXR) showed bilateral patchy infiltrates with sparing of both costophrenic angles. A computed tomographic scan of the chest revealed bilateral alveolar densities that spared the peripheries. Pleural effusions were absent (Fig. 1).

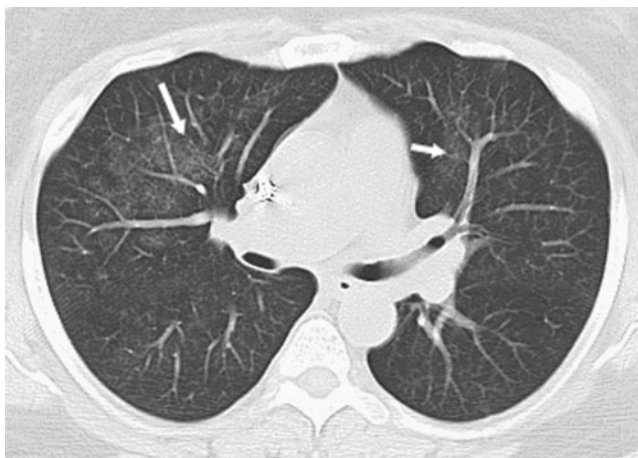


Fig. 1 CT scan of the chest revealing bilateral alveolar densities from diffuse alveolar hemorrhage (white arrows) that spare the peripheries

Pulmonary function tests revealed no airflow obstruction or lung restriction, but the carbon monoxide diffusion capacity (DL_{CO}) was elevated at 125% of the predicted normal range.

Serological testing did not demonstrate elevated antinuclear antibody (ANA) and rheumatoid factor levels. The erythrocyte sedimentation rate was elevated at 36 mm/h, and the perinuclear antineutrophil cytoplasmic autoantibody (p-ANCA) was also abnormal at 1:64 titers. The anti-glomerular basement antibody test (anti-GBM) was positive at 42 AU/ml by multi-analyte fluorescent detection, with a positive result defined as ≥ 26 AU/ml. The cytoplasmic antineutrophil cytoplasmic autoantibody (c-ANCA) titer was within normal limits.

A left kidney biopsy was obtained.

Introduction

In 1958, Stanton et al. published a manuscript entitled “Goodpasture’s syndrome (pulmonary hemorrhage associated with glomerulonephritis)” [1]. They described nine young men with a pulmonary-renal syndrome similar to that described in an earlier report by Ernest W. Goodpasture’s in 1919 of pulmonary hemorrhage associated glomerulonephritis [2, 3]. Since then, it has been established that immune-mediated injury to collagen IV disrupts the function of attached epithelia, leading to kidney and sometimes lung impairment [4]. This review defines patients with Goodpasture’s disease as those with the classic triad of detectable serum anti-GBM antibodies, crescentic glomerulonephritis, and diffuse alveolar hemorrhage (DAH), although retinopathy may occasionally also be found [5, 6]. On rarer occasions, DAH may occur in the absence of frank renal impairment, although some urine abnormalities may be found. Anti-GBM antibodies are still present. Therefore, the term “anti-GBM disease” is regarded as synonymous with Goodpasture’s disease for the purposes of this review. In contrast, Goodpasture’s syndrome describes the constellation of diffuse alveolar hemorrhage and glomerulonephritis from any cause [7, 8].

Epidemiology

In the case illustration above, this patient with Goodpasture’s disease presented with sudden onset of hemoptysis from DAH and concomitant progressive renal impairment that was subsequently shown to be due to a rapidly progressive crescentic glomerulonephritis in the presence of anti-GBM antibodies. Under these circumstances, both early recognition of the classical presentation

of Goodpasture's disease as the cause of this pulmonary-renal syndrome, and prompt and effective management, are of paramount importance in this potentially life-threatening disease [7]. If Goodpasture's disease remains unrecognized, the prognosis is often poor, with certain mortality in the past. However, with prompt diagnosis and treatment, mortality today is as low as 10% [8].

One retrospective study of 28 patients with Goodpasture's disease showed that 42% of cases (follow-up, >3 months; $n=24$) required long-term dialysis or renal transplantation [9]. The median age at diagnosis of the patients in this series was 23 years (range, 17–65 years), 68% were male and 89% were active smokers. Interestingly, 36% had been exposed to some other inhaled agent such as marijuana or cocaine. Other series suggest a similar age distribution, but a striking bimodal distribution was noted, with a peak incidence in the third and also sixth decades, and a slight overall male preponderance. Younger patients under 30 years of age were more likely male, and were more likely to present with a complete pulmonary-renal syndrome including alveolar hemorrhage. Conversely, older patients of 50 years or greater demonstrated a female preponderance, and an increased likelihood of presenting with isolated glomerulonephritis instead [10–12]. These patterns are reflected in Fig. 2.

This disease has also been described in siblings and both identical and discordant twins [8]. Overall, 30% to 40% presented with isolated renal involvement, 10% with DAH and 80% with the classic Goodpasture's triad [8, 11, 12]. This disease, albeit rarer than Wegener's granulomatosis, appears to be commoner in Caucasians such as the patient illustrated above (one to two cases per million population annually), and very rare in those of African origin [8, 13]. There is an apparent higher incidence of Goodpasture's disease in the spring and summer, and also localized clustering of the disease, perhaps suggesting an infectious relationship [8]. Anecdotal associations with urinary tract

infections and lithotripsy that may subclinically affect the glomerular basement membrane have also been reported [8, 13].

Pathobiology and Immunology

The 52-year-old woman discussed above was a current smoker and presented with both alveolar hemorrhage and acute renal failure from rapidly progressive glomerulonephritis. Patients can present with hemoptysis from DAH up to 1 year prior to the onset of renal manifestations of Goodpasture's disease. However, hemoptysis itself may be absent despite severe DAH. DAH has been noted to occur more frequently in smokers [6]. Lazor et al. showed that 89% of their patients with alveolar hemorrhage were active smokers [9], and Donaghy et al. demonstrated that alveolar hemorrhage was present in 100% of their patients who smoked, and only in 20% of nonsmokers with Goodpasture's disease. No significant difference in circulating anti-GBM antibody titers was found between smokers and non-smokers, suggesting that cigarette smoking may increase the permeability of lung capillaries and thus expose alveolar basement membranes to circulating anti-GBM antibodies [14, 15].

Other inhaled substances may also be associated with DAH in Goodpasture's disease, including cocaine (both alveolar hemorrhage as a direct cause and secondary to Goodpasture's disease) [9, 16], hard metals (inert tungsten carbide and cobalt) [17], smoke inhalation [15] and possibly volatile hydrocarbon solvents [18, 19]. It has been postulated that chemical injury to the lung or renal basement membrane may induce the production of anti-basement membrane antibodies and the potential for subsequent lung and renal damage [18]. Alternatively, these substances may damage capillary endothelia, allowing circulating anti-GBM antibodies to reach and damage the alveolar basement membrane [9]. While the role of inhaled hydrocarbon exposure in Goodpasture's disease remains unclear [6], it may act as a co-factor triggering an abnormal response [9]. In addition, group A type 12 streptococcal cell membrane shares some crossreactivity with human glomerular basement membrane, generating another hypothesis that infection may initiate anti-GBM antibody production [15, 20].

While the above patient's human leukocyte antigen (HLA) status was not investigated, it is recognized that Goodpasture's disease is a multigenic disorder that is strongly associated with several HLA genes, especially DRB1 alleles [4, 13]. Goodpasture's disease is characterized by autoimmunity to the NC1 domain of the $\alpha3$ -chain of type IV collagen ($\alpha3(\text{IV})\text{NC1}$) that is the primary component of GBM. Phelps et al. showed that DRB1*1501 and DRB*1502 alleles (corresponding to the serologically

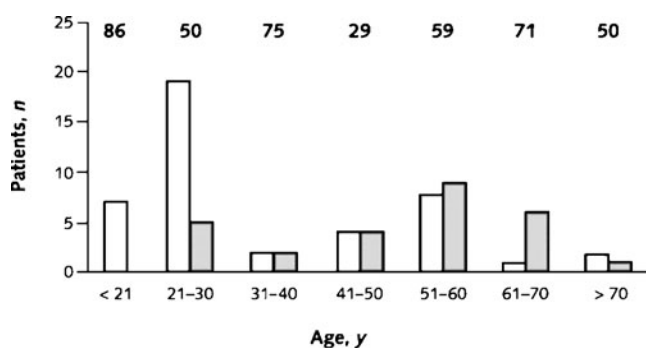


Fig. 2 Age and incidence of alveolar hemorrhage at presentation in patients with Goodpasture's disease. *White bars* represent patients with alveolar hemorrhage and *grey bars* represent patients without alveolar hemorrhage. The *numbers above the bars* represent the proportion of men in each age group. Adapted from Levy et al. [12]

defined HLA DR2 or DR15 genes) [8, 21] were strongly associated with the development of Goodpasture's disease (odds ratio (OR)=8.5) whereas both DRB*0701 and DRB*0101 were negatively associated with the development of this disease (OR=0.3 and 0.6, respectively). These latter two alleles also conferred dominant negative protection epidemiologically [13, 21].

Autoreactive T cells not only enhance B cell function and antibody production, but can directly elicit Goodpasture's disease. T cells react to the $\alpha 3(\text{IV})\text{NC1}$ domain, similar to anti-GBM antibodies [5, 22] in Goodpasture's disease patients. While the thymus expresses $\alpha 3(\text{IV})\text{NC1}$ peptides that can help eliminate autoreactive CD4⁺ helper T cells [23], this elimination is not complete, and some such T cells can escape to possibly help promote anti-GBM antibody production [4, 5, 13]. In a mouse model, regulatory CD4⁺CD25⁺T cells can inhibit autoimmune responses and attenuate the severity of crescentic glomerulonephritis [24]. The emergence and persistence of regulatory T cells may explain why Goodpasture's disease rarely follows a relapsing-remitting course typical of other autoimmune disorders (e.g. systemic lupus erythematosus). The development of "self-immunoregulation" and the re-establishment of tolerance have pathobiological and therapeutic implications [13, 25].

In rats, T-cell-mediated mechanisms are possibly associated with glomerulonephritis in the absence of antibody [4, 26]. The transfer of *in vitro* activated $\alpha 3(\text{IV})\text{NC1}$ -specific CD4⁺T cells into pertussis-toxin primed naïve syngeneic rats was sufficient to induce autoimmune anti-GBM glomerulonephritis [27]. T cells are also effectors of the inflammatory response, as the transfer of anti-GBM antibodies into mice deficient in $\alpha\text{-T}$ cell receptors failed to produce nephritis [4, 28]. CD-8⁺ T cells can function both as cytotoxic cells and also perform Th1- and Th2-like activities. Depletion of these cells can therefore suppress humoral and cell-mediated immune activity. The administration of anti-CD8 monoclonal antibody was found to be effective in both the prevention and treatment of experimental autoimmune glomerulonephritis in the rat model [29]. Reynolds et al. also demonstrated that early blockade of the CD154-CD40 T cell co-stimulatory pathway could prevent the development of glomerulonephritis, and that even delayed treatment could reduce disease severity in rats without significantly affecting antibody titers in established disease cases [13, 30]. Such T cell targeting strategies may be applicable in the future treatment of human Goodpasture's disease.

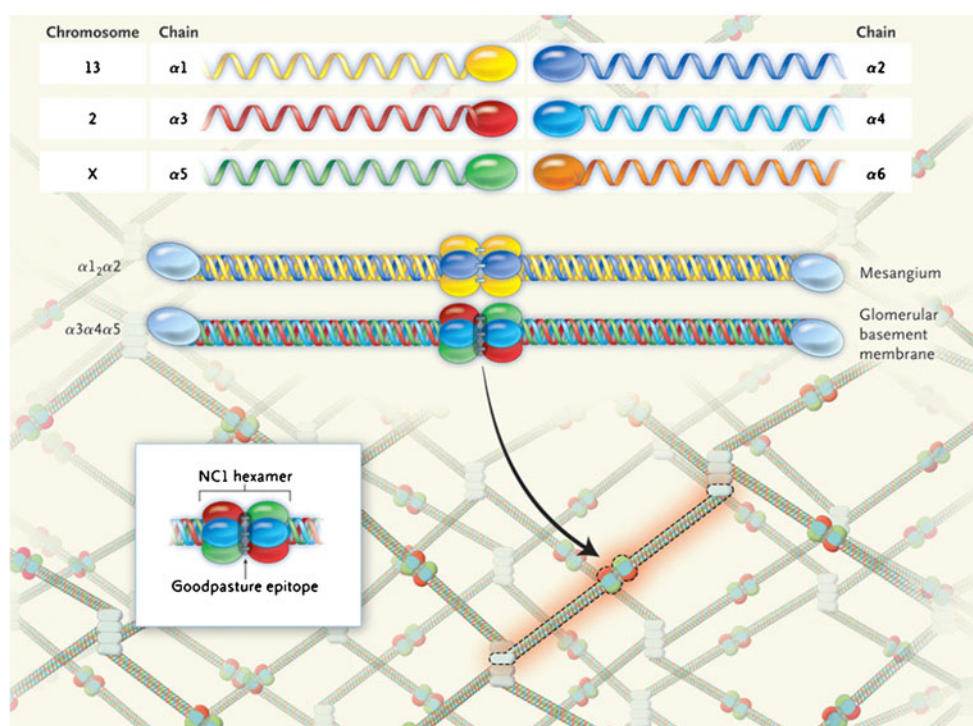
Anti-GBM antibodies are usually IgG, mainly of the IgG-1 subclass, but are sometimes IgM or IgA. These are directly pathogenic in themselves, are linked to the development of Goodpasture's disease, and their levels correlate to disease severity [11, 31]. They target the noncollagenous-1 (NC1)

domain of the $\alpha 3$ chain of type IV collagen, which itself is comprised of six α -chains ($\alpha 1$ to $\alpha 6$) encoded by three pairs of genes on chromosomes 2, 13 and X [4, 32–36]. Mature glomerular basement membrane is a lattice-like structure comprised in part by heterotrimers of $\alpha 3$, 4, and 5 chains that form a triple helix with short noncollagenous domains NC1 and NC2 [36]. This basement membrane, found in kidney, lung, cochlea and eye, comprises the surface on which epithelial cells rest; and hence immunological attack and injury to regions of the $\alpha 3(\text{IV})$ chain of collagen IV in mainly lung and kidney, disrupt epithelial function and integrity, predisposing to organ damage and dysfunction [4, 37]. Abbate et al. induced both glomerulonephritis and hemorrhagic pneumonitis resembling Goodpasture's disease in Wistar-Kyoto (WKY) rats after immunization with soluble $\alpha 3(\text{IV})\text{NC1}$ thus causally linking this self-antigen and antibody to Goodpasture's disease [35, 38].

The $\alpha 3\text{NC1}$ monomer is structured into the collagen IV network through the association of $\alpha 3$, $\alpha 4$, and $\alpha 5$ chains to form a triple helical protomer and oligomerization of these protomers via end-to-end associations and intertwining of triple helices [4, 35] (Fig. 3). Pedchenko et al. termed the development of Goodpasture's disease as an autoimmune "conformeropathy" where disturbance of the quaternary structure of the $\alpha 345\text{NC1}$ hexamer caused a pathogenic conformational change in the $\alpha 3\text{NC1}$ and $\alpha 5\text{NC1}$ subunits, thereby eliciting an autoimmune response [35]. Furthermore, elevated autoantibody titers to $\alpha 3\text{NC1}$ and $\alpha 5\text{NC1}$ monomers at diagnosis of Goodpasture's disease were found to be associated with eventual loss of renal function. These anti-GBM antibodies were seen to bind to specific epitopes that encompassed region E_A in the $\alpha 5\text{NC1}$ monomer, and regions E_A and E_B in the $\alpha 3\text{NC1}$ monomer, but no binding to the native crosslinked $\alpha 345\text{NC1}$ hexamer was found. This again supports the finding that it is dissociation of the NC1 hexamers from several possible causes, including environmental factors (hydrocarbons, viruses, and smoking), that expose the pathogenic epitopes on the $\alpha 3$ and $\alpha 5$ chains, precipitating the production of anti-GBM antibodies [4, 35, 39]. Salant suggests that the autoantibody itself may subsequently alter antigen conformation and expose further epitopes, causing an epitope spreading phenomenon [36].

In contrast, anti-GBM alloantibodies to the $\alpha 3\text{NC1}$ and $\alpha 5\text{NC1}$ domains in Alport post-transplantation glomerulonephritis bound epitopes that were already exposed on the native hexamer without the need for its dissociation [35]. This finding emphasizes the link between Goodpasture's disease and Alport syndrome (hematuria, proteinuria of less than 1 to 2 g/day, progressive renal failure, sensorineural deafness, lenticonus, and occasionally, mental retardation) [4, 40–42]. Alport syndrome is a mainly (80%) X-linked hereditary disease where mutations of the $\alpha 5$ chain of Type

Fig. 3 Type IV collagen structure and Goodpasture's epitope placement. The genes for the $\alpha 1$ and $\alpha 2$, $\alpha 3$ and $\alpha 4$, and $\alpha 5$ and $\alpha 6$ isoforms share common promoters on their respective chromosomes. Individual type IV collagen chains form a triple helix and contain short noncollagenous domains (NC1 and NC2) at each end. The fibers are laid down as a lattice, joined end-to-end by sulfilimine bonds between the NC1 domains and linked in bow-tie fashion by their NC2 domains. Mesangial type IV collagen is composed of $\alpha 1$ and $\alpha 2$ chains, whereas the collagen of the glomerular basement membrane contains $\alpha 3$, $\alpha 4$, and $\alpha 5$ chains. The Goodpasture antigen is sequestered in the hexamer made up by adjacent NC1 domains. Adapted from Salant [36]



IV collagen cause defective supramolecular organization of the $\alpha 3$, $\alpha 4$, and $\alpha 5$ chains in the basement membrane [8, 43]. The absence of expression of $\alpha 5$ and associated lack of $\alpha 3$ and $\alpha 4$ in the native kidney, and their expression instead in a renal allograft, engenders alloantibody production in response to this “foreign” $\alpha 345$ collagen network [44–46]. Although the presence of anti-GBM alloantibodies in the allografts of transplanted patients is relatively common, clinical anti-GBM disease is rare, occurring in 3% to 5% of patients with Alport syndrome who have undergone kidney transplantation [8, 35]. However, allograft loss usually occurs once Alport post-transplantation glomerulonephritis develops [47].

Renal injury in Goodpasture's disease also involves complement and protease activation after the binding of the anti-GBM antibody to basement membrane [48, 49]. Interleukin-12 and interferon- γ are also involved in epithelial crescent formation in the glomerulus [50, 51]. These mechanisms together with migration of macrophages and neutrophils into the kidney cause disruption of the filtration barrier, and Bowman's capsule, with resultant proteinuria, interstitial nephritis, and fibrosis [4, 52].

Clinical Features

The patient illustrated above noted both shortness of breath and hemoptysis, common symptoms (>70%) at presentation in patients with Goodpasture's disease. Fatigue (64%) and cough (64%) are also common recognized symptoms [9]. The

presence of myalgias, arthralgias, and weight loss, which the patient did not endorse, are systemic symptoms that may suggest an associated vasculitis [53]. Lazor et al. [9] reported a series of 28 patients with Goodpasture's disease and alveolar hemorrhage confirmed by bronchoalveolar lavage, which showed that 14% of patients had chest pain and 36% had macroscopic hematuria. Physical examination revealed crackles on chest auscultation in 50%, and peripheral edema in 32% (Table 1). The authors also found that the majority (57%) of their patients developed sub-acute symptoms between 1 week to 1 month prior to hospitalization, and that 39% developed symptoms over greater than a 1-month period. The median delay from onset of first symptoms to diagnosis was 5 weeks (range, 2–126 weeks), and the median delay from hospitalization to actual diagnosis was 6 days (range, 0–53 days). The development of acute symptoms over less than a 1 week time period requiring hospitalization was uncommon, occurring in 4%. The patient illustrated above, however, fit into this latter category. In addition, the patient's pulmonary function testing revealed an elevated DL_{CO} at >120% predicted, consistent with her acute diffuse alveolar hemorrhage. An elevated DL_{CO} was also found in a minority (25%) of patients in the series reported by Lazor et al. [9].

In other patients with Goodpasture's disease, DAH may not be immediately obvious radiologically and overt hemoptysis may not be present. Under these circumstances, an acutely decreasing hemoglobin level that is disproportionate to the degree of renal failure should alert the clinician to the possibility of Goodpasture's disease. In

Table 1 Clinical patient characteristics at time of diagnosis ($n=28$)

Clinical features	Percentage (%)
Dyspnea	79
Hemoptysis	75
Fatigue	64
Cough	64
Crackles at auscultation	50
Fever	43
Macroscopic hematuria	36
Flu-like illness	32
Edema	32
Nausea or vomiting	25
Weight loss	18
Arthralgia	18
Myalgia	18
Anuria >24 h	18
Chest pain	14

Adapted from Lazor et al. [9]

addition, an elevated DL_{CO} can be another sensitive indicator of alveolar hemorrhage [8]. Flexible bronchoscopy can also be performed to diagnose DAH. Serial bronchoalveolar lavages would show increasing red blood cell counts if DAH is present. Transbronchial biopsies would generally not be sufficient to establish this diagnosis [54, 55].

Anuria of <100 ml/24 h and lasting >24 h was not noted in this patient, but is seen in a minority (14%) of patients at presentation [9]. Such a finding suggests a poorer prognosis [4, 12]. Conversely, patients with Goodpasture's disease and normal renal function in terms of serum creatinine and/or creatinine clearance at the time of presentation appear to have a better prognosis, assuming nonprogression of disease, with less renal damage possibly from lower titers of anti-GBM antibodies and less complement deposition. Normal renal function may constitute up to 36% of Goodpasture's disease patients. [56].

Differential Diagnoses

Goodpasture's disease was strongly suspected in the patient illustrated above because of her presentation with a pulmonary-renal syndrome secondary to an acute and progressive glomerulonephritis together with diffuse alveolar hemorrhage. The pulmonary-renal syndrome is, however, more commonly described in ANCA-associated vasculitis (60% of cases), especially microscopic polyangitis and Wegener's Granulomatosis [7, 57]. Goodpasture's disease accounts for another 20% of pulmonary-renal syndrome cases [57].

Diffuse alveolar hemorrhage in systemic lupus erythematosus (SLE) is rare, and occurs in 4% of acute admissions for SLE, but is often associated with nephritis and often connotes a lethal prognosis [7, 55]. Catastrophic anti-phospholipid syndrome also portends a high mortality from associated microvascular thrombosis in the setting of pulmonary-renal disease [58]. Other causes for this syndrome include use of drugs such as cocaine, cytotoxics and carbimazole [7], or a current diagnosis of cryoglobulinemia, Henoch-Schönlein Purpura, rheumatoid arthritis and mixed connective tissue disease [59].

Diagnosis

Early diagnosis of the cause of a pulmonary-renal syndrome, and prompt treatment, especially in the intensive care unit (ICU), are critical to help prevent death from uremia due to acute renal failure and/or asphyxiation from massive hemoptysis. Diagnosis and management are best achieved by multispecialty care, including pulmonologists/intensivists, immunologists, nephrologists and pathologists, critical care nurses, and respiratory therapists [7]. The patient illustrated above demonstrated positive anti-GBM antibodies in her serum at a relatively high titer of 42AU/ml, consistent with her rapidly progressive disease [60]. The detection of these antibodies by enzyme-linked immunosorbent assay (ELISA) is based on the use of GBM preparations from various species and are of variable purity. Whole solubilized GBM, purified $\alpha 3(IV)$ collagen, the major structural component of GBM, chain and recombinant Goodpasture's antigen have been used. The sensitivity varied between 94.7% and 100%, with a specificity of 90.9% to 100% in one series [61]. A fluorescence immunoassay utilizing a recombinant antigen appeared to give better sensitivity and specificity [61]. Antibody specificity can be confirmed using the more sensitive and specific Western blotting method at a reference center. False positives can occur due to circulating antibodies to GBM antigens other than the Goodpasture's antigen ($\alpha 3(IV)NC1$) or due to high levels of polyclonal immunoglobulin in the sera [37, 60].

False-negative anti-GBM antibody results can also occur, especially in isolated and mild pulmonary disease, or when other immunoglobulins such as IgA or IgM are the cause of the disease rather than IgG [11, 60, 62, 63]. A small proportion of Goodpasture's disease patients (2% to 3%) have also been shown to be antibody-negative by ELISA and Western blot techniques. In such cases, biosensors, rather than ELISA and Western blot techniques, have been found to readily detect anti-GBM antibodies [60]. Optical biosensor techniques include the use of surface plasma resonance to determine antibody-antigen

interactions [64]. Use of indirect immunofluorescence to detect anti-GBM antibodies on normal human or primate kidneys is not adequately sensitive or quantitative [65].

Levy et al. reported that 32% of all anti-GBM-positive samples in their series were “doubly positive” due to concomitant ANCA positivity. Conversely, only up to 5% of samples with an initial positive serologic test for ANCA were also positive for anti-GBM antibodies [66]. A majority of the patients who were “doubly positive” demonstrated anti-myeloperoxidase specific p-ANCA. Nearly 70% of these patients were dialysis dependent at presentation, with none recovering renal function. Survival was 52% at 1 year, suggesting that “doubly positive” patients such as the patient illustrated above have a poor prognosis when they present with severe disease [66]. In contrast, other studies have found that this “doubly positive” phenotype may portend a better prognosis in which renal function may improve, perhaps because of a vasculitis-associated variant that responds well to treatment [4, 67]. Further studies are needed to reconcile these findings.

Critically ill patients with unstable vital signs (e.g., hypotension or hypoxemia) should be monitored in the ICU and may be too unstable to undergo a kidney biopsy. However, the “gold standard” in the diagnosis of Goodpasture’s disease remains a renal biopsy demonstrating immunoglobulin deposited in a linear fashion along the GBM in the presence of crescentic glomerulonephritis [60]. Life-saving plasmapheresis may need to be instituted prior to kidney biopsy if clinical suspicion is very high for Goodpasture’s disease. Renal biopsies are preferable to lung biopsies as the latter may demonstrate significant autofluorescence, rendering immunofluorescence staining and interpretation technically challenging [4]. While the patient illustrated above did not undergo lung biopsy, Fig. 4 demonstrates a representative surgical lung biopsy that is characteristic of Goodpasture’s disease affecting the lung. Extensive fresh alveolar hemorrhage is seen accompanied by intraalveolar hemosiderin-laden macrophages, interstitial edema, reactive type 2 cell hyperplasia, patches of neutrophilic interstitial inflammation (capillaritis), and variable airspace organization. In the absence of a vasculitic syndrome, medium or large-vessel vasculitis is not identified. Hyaline membranes can be present. The histopathology of pulmonary Goodpasture’s disease is indistinguishable from several other immunologically mediated diffuse alveolar hemorrhage syndromes (e.g., microscopic polyangiitis, the alveolar hemorrhage form of Wegener granulomatosis, and alveolar hemorrhage in systemic lupus erythematosus), making serum anti-GBM, ANA, and ANCA serologies critical to the final diagnosis.

The illustrative patient, however, did undergo a left kidney biopsy under ultrasound guidance without complication; two core samples were obtained. Light microscopy

of the renal biopsies demonstrated typical findings associated with Goodpasture’s disease dominated by segmental glomerular necrosis and crescentic glomerulonephritis. IgG immunofluorescence with a continuous linear pattern was identified, confirming the diagnosis of anti-GBM disease. The appearance of cellular crescents is believed to occur after destruction of the glomerular basement membrane by the immune injury. Over time, interstitial nephritis with fibrosis and tubular atrophy can occur [4]. The glomerular changes and IgG immunofluorescence in Goodpasture’s disease is shown in Fig. 5.

Prognosis and Current Treatment Strategies

Early and correct diagnosis of Goodpasture’s disease and appropriate management ensure that 90% of patients can survive the acute illness. Currently, 1-year survival is between 75% and 90%, especially in the setting of intensive monitoring in an ICU where services can be converged and concentrated. Recovery of renal function, however, is dependent on the level of renal function at the beginning of treatment [6, 8]. Oliguria, the need for dialysis, a serum creatinine concentration ≥ 5.7 mg/dL or 100% crescents on renal biopsy represent poor prognostic factors [4, 12]. Nevertheless, renal function may still be recovered in individual cases if treatment is initiated early. Age has not been found to be a predictor of either renal or patient survival [12].

Diffuse alveolar hemorrhage, mostly bland but occasionally demonstrating capillaritis [54, 68], is the most likely cause of death within the first 2 months after disease onset. Repeated episodes of DAH may result in interstitial pulmonary fibrosis [54]. However, alveolar hemorrhage responds rapidly to plasmapheresis, regardless of the severity of any concomitant renal disease, with control achieved in 90% of patients [8, 12, 69]. Plasmapheresis rapidly removes circulating anti-GBM antibodies. Daily or alternate day sessions are recommended (50 ml/kg; maximum of 4 L) for approximately 14 sessions or until anti-GBM antibody is undetectable. Plasma is replaced with 4.5% human albumin during the procedure and additional fresh frozen plasma (1 to 2 L) can be given to replace the albumin at the end of the exchange in case of significant bleeding, or recent biopsy, to help minimize depletion of coagulation factors. Any severe infection requires aggressive, appropriate therapy, and a single dose of intravenous immune globulin can be considered not to treat the syndrome, but rather as a method of augmenting humoral immunity [70]. Precipitating factors for alveolar hemorrhage such as tobacco smoking must be avoided, especially after successful plasmapheresis [6]. Every patient with alveolar hemorrhage from Goodpasture’s disease should

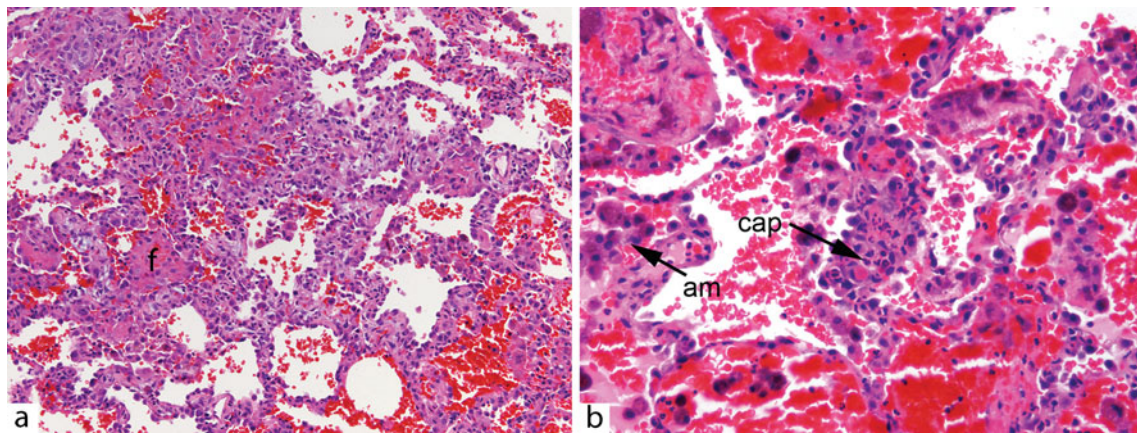


Fig. 4 Surgical lung biopsy. The surgical lung biopsy in Goodpasture's disease is dominated by fresh alveolar hemorrhage (**a**). The presence of fibrin (*f*) attests to active microvascular injury. Hemosiderin-laden alveolar macrophages (**b**, *am*) are required for the diagnosis, and typically signs of early organization are present (scattered tufts of immature fibroblasts in alveolar spaces). A critical indication for

emergent medical therapy is the presence of "capillaritis" (**b** (*cap*)), underscoring the real risk of massive hemoptysis in all patients with any form of immune-mediated pulmonary hemorrhage. Hematoxylin and eosin stain. **a** $\times 100$ original magnification; **b** $\times 200$ original magnification

additionally be treated with immunosuppression [8]. Lazor et al. showed that Goodpasture's disease patients with predominantly pulmonary involvement and a normal serum creatinine demonstrate excellent long-term renal survival. In addition, no long-term CXR abnormalities (especially fibrosis) were found in this subgroup of patients. Only a third of these patients demonstrated a moderate reduction in DL_{CO}, and a mild elevation in the alveolar-arterial oxygen difference of between 20 and 25 mmHg (median duration of follow-up 2.6 years (range, 0.4 to 17.6 years)) [9].

Concomitant immunosuppression with cyclophosphamide is important and has proven efficacy in both alveolar hemorrhage and glomerulonephritis in order to suppress further T cell activation and antibody formation by B

lymphocytes, and hence recurrence of disease. The use of cyclophosphamide to prevent further antibody synthesis and corticosteroids as an anti-inflammatory agent in conjunction with plasmapheresis has revolutionized the outcome in Goodpasture's disease [8, 71]. As Goodpasture's disease generally does not relapse, immunosuppression can be stopped after a few months of therapy. A detailed example of a recent plasmapheresis and immunosuppressive therapy protocol for Goodpasture's disease at the Hammersmith Hospital, London, UK is shown in Table 2.

Patients with Goodpasture's disease presenting with a creatinine level of less than 500 $\mu\text{mol/l}$ (5.7 mg/dL) demonstrated a 5-year renal survival rate of 94% after

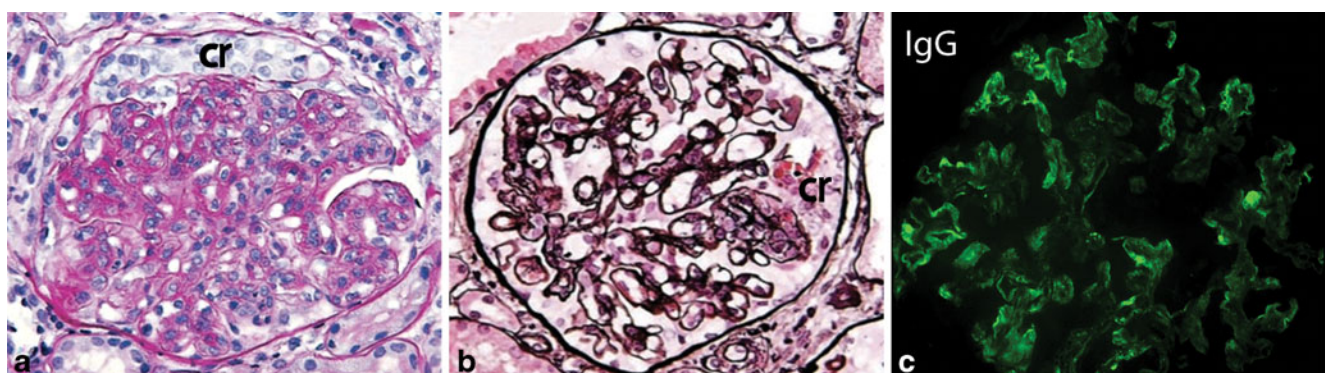


Fig. 5 Kidney biopsy. The renal injury in Goodpasture's disease is characterized by crescentic glomerulonephritis (**a**, periodic acid Schiff histochemical stain; **b** Jones silver impregnation method). Here, epithelioid cells (**a**, **b** (*cr*)) form aggregations that fill Bowman's space to a variable extent, and compress the glomerular capillary tuft. Neutrophils are seen within glomeruli, producing a necrotizing glomerulonephritis in patients with Goodpasture's disease. **b** Silver

impregnation techniques are helpful in outlining the relationship between capillary loops and the mesangial matrix in a variety of glomerular diseases. A focal cellular crescent is visible to the right (*cr*). **c** Continuous linear IgG immunofluorescence along capillary walls is diagnostic of Goodpasture's disease. **a–c**, $\times 400$ original magnification. Images courtesy of Dr. Maria Angeles Montero Fernandez, Hospital Vall d'Hebron, Barcelona, Spain

Table 2 A treatment protocol for Goodpasture's disease at Hammersmith Hospital, London, UK

Initial	
Plasma exchange	Daily, 4 L exchange for 5% human albumin solution; use 300- to 600-mL fresh frozen plasma within 3 days of any invasive procedure (e.g., biopsy) or in patients with pulmonary hemorrhage; continue for 14 days or until antibody levels are fully suppressed; withhold if platelet count $<70 \times 10^9/\text{mL}$, or hemoglobin $<9 \text{ g/dL}$; watch for coagulopathy, hypocalcemia, and hypokalemia
Cyclophosphamide	Oral dosing at 2 to 3 mg/kg/day (round down to nearest 50 mg; reduce to 2 mg/kg/day in patients over 55 years); stop if white cell count $<4 \times 10^9/\text{mL}$ and restart at lower dose when counts $>4 \times 10^9/\text{mL}$
Prednisone	Oral dosing at 1 mg/kg/day (maximum 60 mg); reduce dose weekly to 20 mg by week 6 and then more slowly; no evidence for benefit of intravenous methylprednisolone and can increase infection risk (possibly use if plasma exchange not available)
Prophylactic treatments	Oral nystatin and amphotericin (or fluconazole) for oropharyngeal fungus infection; ranitidine or proton-pump inhibitor for steroid-promoted gastric ulceration; low-dose cotrimoxazole for <i>Pneumocystis carinii</i> pneumonia prevention; consider acyclovir as cytomegalovirus prophylaxis; consider calcium/vitamin D for prevention of osteoporosis (but relatively short course of steroids)
Maintenance	
Prednisone	Reduce dose slowly from 20 mg at 6 weeks; stop completely by 6 months
Cyclophosphamide	Stop after 2 to 3 months; no further cytotoxic agents necessary

Adapted from Pusey [8]

undergoing intensive treatment as described above. A 5-year renal survival of 50% for patients presenting with a creatinine level of more than 500 $\mu\text{mol/L}$, suggests that this group of patients can also recover some renal function with similar intensive therapy [8]. Therefore all patients with Goodpasture's disease and renal impairment should be considered for treatment with plasmapheresis and immunosuppressive therapy (Table 2). The risk-benefit ratio in treating patients with Goodpasture's disease who require dialysis on presentation is less clear. Intensive therapy may be considered in younger patients with evidence of renal crescents on biopsy who are not anuric [8].

Kidney transplantation is feasible, and is considered after anti-GBM antibodies have been absent for at least 6 months because of concern about the risk of recurrence, albeit uncommon (3% to 10%) [4, 9, 72, 73].

Future Prospects for Therapy

Reynolds et al. assessed the effects of blockade of the T cell activation cascade, specifically the CD28-B7 interaction, in experimental autoimmune glomerulonephritis (EAG) in the WKY rat model. This EAG is associated with circulating and deposited anti-GBM antibodies and focal necrotizing glomerulonephritis with crescents. Blockade of CD28-B7 with native fusion protein CTLA4-Ig prevented any immune response and hence also prevented target organ injury as manifested by the lack of crescentic nephritis in EAG. Selective blockade of B7.1 molecules on antigen presenting cells using mutant CTLA4-Ig (Y100F-Ig) was almost but not quite as effective in preventing glomerulonephritis in this model, appearing to reduce only the Th1-dependent immu-

nological responses. These findings suggest that T cell costimulation is involved in EAG in the WKY rat model, and that it is likely a Th1-dependent disease with B7.1 preferentially stimulating a Th1-like response. Therefore, selective targeting of selected T cell costimulation may prove relevant in the future treatment of Goodpasture's disease [74].

Extracorporeal immunoadsorption to remove circulating IgG immunoglobulins without the need for protein substitution during daily treatments may also be beneficial in Goodpasture's disease. Anecdotal case reports suggest that it may be an alternative to plasmapheresis in patients with severe renal failure [75]. In one patient with 100% crescentic lesions, immediate initiation of immunoadsorption with sepharose-coupled sheep-antihuman IgG columns for 25 cycles coupled with pulsed cyclophosphamide and methylprednisolone immunosuppression resulted in stable creatinine levels of 2 mg/dL without the need for further hemodialysis. Such early treatments to remove pathogenic autoantibodies and immune complexes may be helpful in Goodpasture's disease, but future randomized controlled trials are necessary for further elucidation [75].

Lovic et al. found that plasma exchange efficiently lowered excess angiopoietin-2 (Ang-2) levels in critically ill patients with anti-GBM disease. Protein growth factor Ang-2 is significantly released from Weibel–Palade bodies in critically ill patients with anti-GBM disease and interferes with protective ligand angiopoietin-1/Tie2 cell surface receptor signaling in endothelial cells, leading to vascular inflammation and subsequent organ failure. Further studies are necessary to investigate whether or not removal of Ang-2 is critical in the amelioration of endothelial damage in such patients who have altered endothelial integrity [76].

Conclusions

Despite its rarity, Goodpasture's disease is often effectively treated with plasmapheresis and immunosuppression if diagnosed early and accurately. Further advances in the understanding of this disease at a molecular level, and also in the triggers of the autoimmune response that induce a conformational change in the α 345NC1 hexamer, may ultimately lead to more effective targeted therapies. Such therapies may include the use of decoy antigens to prevent antibodies binding to the GBM [36], co-stimulatory blockade of T cell activation [4, 74] or interleukin-4 and interleukin-10 immune modulation [77] amongst others. A combination of such measures may ultimately prove ideal, leading to even better therapeutic outcomes than are currently available.

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