Coexistent Wegener's Granulomatosis and Goodpasture's Disease

To the Editor:

Wegener's granulomatosis (WG) and Goodpasture's disease are unique etiologies of pulmonary-renal syndromes. Given the similarity in clinical presentation, differentiating these diseases at the bedside can be challenging.

A 50-year-old woman was referred to the rheumatology clinic with a presumptive diagnosis of vasculitis. She presented with a 12-month history of recurrent epistaxis, nasal crusting, migratory arthralgias, and a 20-pound weight loss. She was also diagnosed and treated for an isolated episode of scleritis in the left eye. In the week prior to presentation, she developed sores on her tongue, mild dyspnea, and new onset hemoptysis.

Examination was remarkable for tongue ulcerations, nasal mucosal ulcerations, and splinter hemorrhages. Other findings included palpable purpura of the lower extremities, 3 joint effusions (both knees, left ankle), and 7 tender joints. Chest examination revealed fine crackles at bases; cardiovascular examination was normal.

Laboratory investigations revealed an elevated erythrocyte sedimentation rate of 60 mm/h, and urinalysis with 3+ blood and trace protein. Creatinine at presentation was 77 μmol/l. The cytoplasmic antineutrophil antibody (c-ANCA) was positive [proteinase-3 (PR-3)-positive, myeloperoxidase-negative] as was the anti-glomerular basement membrane (anti-GBM) antibody.

Chest radiograph revealed symmetric interstitial and airspace changes consistent with differential diagnosis of pulmonary hemorrhage, atypical infection, or acute noncardiogenic pulmonary edema. She underwent a computed tomography scan of the thorax, which demonstrated ground-glass opacity in keeping with pulmonary hemorrhage (Figure 1), while skin biopsy of her palpable purpura revealed a leukocytoclastic vasculitis.

She was diagnosed with Wegener's granulomatosis (WG) on the basis of clinical presentation and positive c-ANCA/PR-3 in the presence of biopsy-proven leukocytoclastic vasculitis. She was admitted to hospital and treated with intravenous methylprednisolone and cyclophosphamide. Following this, her symptoms resolved.

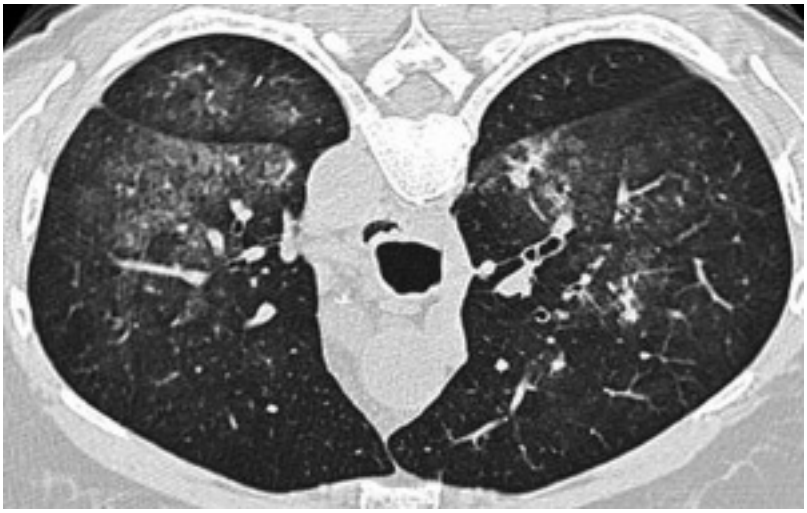

Figure 1. Computed tomography scan of the thorax shows diffuse ground-glass opacification of both lungs. The distribution is perihilar.

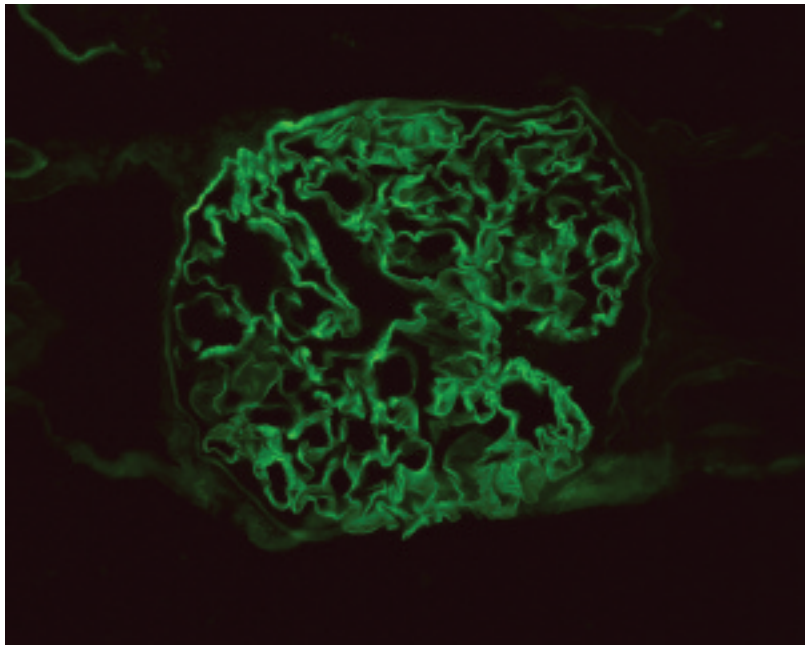

Figure 2. Renal biopsy revealed linear IgG immunofluorescence.

One month following treatment, her serum creatinine rose from 77 to 219 μmol/l. A renal biopsy revealed segmental necrotizing glomerulonephritis with crescents. There was also linear IgG immunofluorescence consistent with Goodpasture's disease (Figure 2). She was admitted for treatment with 5 cycles of plasmapheresis and intravenous methylprednisolone for Goodpasture's disease. This was followed by oral prednisone and intravenous cyclophosphamide (750 mg/m^2) every 4 weeks for a total of 6 cycles. Her renal function normalized and the anti-GBM became negative. She was switched to maintenance therapy with azathioprine (2 mg/kg).

One year after diagnosis, taking maintenance azathioprine, she is clinically in remission and her creatinine is 81 μmol/l. Her anti-GBM antibody remains negative, but c-ANCA and PR-3 remain positive.

Of note, our patient was found to be hepatitis C-positive (genotype 1). Her baseline viral load (hepatitis C virus RNA) was 2.38×10^6 IU/ml and a liver biopsy revealed stage 1 fibrosis. She did not require any antiviral therapy. She was negative for cryoglobulinemia throughout.

WG is a necrotizing systemic vasculitis of small and medium-size arteries and venules. It classically affects the upper airway (sinusitis, nasal ulcers), lower respiratory tract (alveolar capilaritis, cavitary pulmonary lesions, pulmonary hemorrhage), and renal system (segmental necrotizing glomerular nephritis). WG is often associated with the presence of ANCA, most commonly c-ANCA with PR-3. This condition affects men and women equally and typically occurs in the fourth or fifth decade of life. Untreated, the condition is usually fatal within one year. Acute treatment involves intravenous steroids and cyclophosphamide to induce remission, followed by maintenance therapy with an immunosuppressive agent, typically azathioprine or methotrexate.

Goodpasture's disease is an autoimmune condition characterized by rapidly progressive glomerulonephritis and alveolar hemorrhage. The inciting stimulus for this condition is unknown, but renal and pulmonary damage are mediated by IgG antibodies against type 4 collagen found in the glomerular and alveolar basement membranes. The presence of anti-GBM antibodies in the serum along with a renal biopsy demonstrating crescentic necrotizing glomerulonephritis and linear IgG immunofluorescence help to establish the diagnosis. This condition primarily affects the Caucasian population, with predominance in men. Goodpasture's disease progresses rapidly to endstage renal failure and death if left untreated. Patients are typically treated with several cycles of plasmapheresis until antibody titers are negative, followed by 2 to 3 months of steroids in combination with azathioprine or cyclophosphamide.

In recent decades, the presence of ANCA and anti-GBM antibodies in the right clinical setting has facilitated differentiation of these 2 diseases and their diagnosis. Our patient presented with classic clinical and laboratory features of Wegener's vasculitis, yet also had a positive anti-GMB antibody titer. The significance of anti-GBM antibodies during initial diagnosis was unclear; however, the development of renal insufficiency after therapy for vasculitis appeared to be the result of coexistent and undertreated Goodpasture's disease. Although it might seem rare to have 2 relatively uncommon conditions coexist, similar case presentations have been reported.

It is reported that ANCA and anti-GBM antibodies have coexisted in patients with glomerulonephritis and vasculitis. Levy and colleagues studied over 20,000 patient serum samples in a retrospective analysis, in which they found 5% of all ANCA-positive samples were also positive for anti-GBM antibodies[1]. Of the anti-GBM samples, 32% also had ANCA[1]. Both c-ANCA and PR-3 have been reported to be associated with anti-GBM antibodies (as in our patient), but less frequently than p-ANCA and MPO antibodies[1]. Although the presence of both antibodies in serum is interesting, the question is whether this translates to coexistent clinical disease and different clinical outcomes and prognosis in this group of patients. There have been several reports of coexistent vasculitis and anti-GBM renal disease. Wahls, *et al* described a man with lung biopsy-proven WG, followed 6 months later by renal failure and biopsy-proven anti-GBM disease[2]. Serratrice, *et al* reported a case of p-ANCA-positive vasculitis, followed later by anti-GBM-related acute renal failure[3]. The clinical outcomes and prognosis for this unique subset of patients have not been completely elucidated. Patients who are positive for both antibodies were shown to have worse renal outcomes if presenting with severe renal failure, compared to those patients with pure ANCA-related disease[1]. This was true despite treatment with immunosuppression and plasma exchange[1].

Given this observation, some investigators postulated that ANCA may in fact initiate renal damage that in turn exposes the glomerular basement membrane as an antigenic source, allowing the development of anti-GBM disease[4]. In a mouse model, Xiao, *et al* demonstrated that antimyeloperoxidase IgG was able to incite glomerular necrosis and crescent formation[5]. Their study showed definitive experimental animal evidence for the pathogenicity of ANCA. They concluded that their animal model offers strong support for the theory of direct ANCA pathogenicity in human vasculitis and glomerulonephritis[5].

Given our case and previous reports, clinicians should consider the possibility that vasculitis and Goodpasture's disease can coexist both serologically and clinically. This has significant implications for treatment and prognosis. Clinicians are familiar with Occam's razor, "among competing hypotheses, favor the simplest one"[6]. However, diagnostic parsimony may lead to inaccurate or only partially accurate diagnosis. In this particular case, Hickam's dictum, "A patient can have as many diagnoses as he darn well pleases," appears to be a principle not to be forgotten[6].

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