Fulminant granulomatosis with polyangiitis presenting with diffuse alveolar haemorrhage following COVID-19

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SUMMARY

A 40-year-old man developed granulomatosis with polyangiitis (GPA) following a mild case of COVID-19. Initially, he experienced mild migrating joint pain for 2 months prior to testing positive for SARS-CoV-2 but dramatically worsened following resolution of his infection. The pain continued to progress until he suddenly develope haemoptysis, prompting him to present to a local hospital. The diagnosis of diffuse alveolar haemorrhage secondary to GPA was confirmed with labs, imaging and histopathology. Precipitous deterioration of GPA with concurrent COVID-19 infection indicates a possible temporal relationship. Since the onset of the pandemic, SARS-CoV-2 has been anecdotally associated with the development of various connective tissue disorders. The overlapping clinical presentations and similar appearance on lung imaging present clinicians with a diagnostic challenge. This underscores the importance of having a high index of suspicion of autoimmune diagnoses in patients who present with new or worsening findings following a COVID-19 infection.

BACKGROUND

Granulomatosis with polyangiitis (GPA) is a rare small vessel vasculitis that occurs most frequently in Caucasians ages 40–65, affecting roughly 1 in 100 000 people annually.[1] The disease characteristically affects the kidneys and lungs, however, a constellation of nonspecific symptoms including fatigue, fever, arthralgias and myalgias, sinusitis and cough commonly occurs as well. The significant overlap in symptoms of viral illnesses, including COVID-19, and autoimmune diseases presents a diagnostic challenge. This may lead to a delay in diagnosis until more severe life-threatening signs emerge, putting patients at risk of irreversible end-organ damage.

Our case demonstrates the importance of considering an autoimmune diagnosis in individuals presenting with nonspecific symptoms following infection with SARS-CoV-2. We aim to add to a growing body of literature describing post-COVID autoimmune disease. This emphasises the necessity for further research to elucidate any causal relationship between autoimmune disease and COVID-19.

CASE PRESENTATION

A 40-year-old man with no significant previous medical history initially developed shoulder pain 2 months prior to the diagnosis of COVID-19. The pain eventually spread to his knees, feet and carpophalangeal joints, though it remained mild enough that he did not seek evaluation.

In early December, the patient developed diffuse myalgias, fever, chills, congestion and anosmia, prompting him to receive a SARS-CoV-2 PCR test, which was positive. Previously described shoulder and knee pain abated somewhat in the days following his COVID-19 diagnosis. Roughly 10 days after the diagnosis of COVID-19, the pain dramatically worsened to the point that he sought evaluation by his primary care physician. The diagnosis at that time was presumed to be reactive arthritis. Four weeks following his recovery, the patient awoke in the night with a fever of 104 F and experienced significant haemoptysis. He presented to a local hospital and was subsequently transferred to a tertiary referral centre.

INVESTIGATIONS

Pertinent lab results included aspartate aminotransferase 91 (10–40 IU/L), alanine aminotransferase 159 (10–40 IU/L), anti-proteinase-3 (anti-PR3) >8 (<0.3 AI), erythrocyte sedimentation rate 81 (0–10 mm/hour), C-reactive protein 127.5 (<5 mg/L), rheumatoid factor 21 (<3.5 IU/mL), C-antineutrophil cytoplasmic antibodies (C-ANCA) titre elevated at 1:640 (<1:20), myeloperoxidase-antineutrophil cytoplasmic antibodies <0.2 (<0.3 AI), COVID-19 IgG antibody (+).

Urinalysis was mildly inflammatory showing 30 proteins, 4 white blood cells, and 9 red blood cells.

Contrast enhanced CT angiogram of the thorax showed multifocal opacities in all lung lobes concerning for multiple pathologies including diffuse alveolar haemorrhage (figure 1).

Bronchoscopy showed minimal bloody secretions present in the vocal cords, trachea, main carina, left and right lungs that were easily removed. Bronchoalveolar lavage of the lingula with 120 mL of saline showed progressively bloody sequential aliquots consistent with diffuse alveolar haemorrhage.

Renal biopsy demonstrated focal crescentic glomerulonephritis (figures 2 and 3).

Differential diagnosis

Diffuse bilateral lung opacities in the setting of recent diagnosis of COVID-19 raise the possibility of viral or secondary bacterial pneumonia, persistent SARS-CoV-2 pathology or interstitial lung disease. However, obtaining positive C-ANCA and anti-PR3 titers led us to a diagnosis of GPA,

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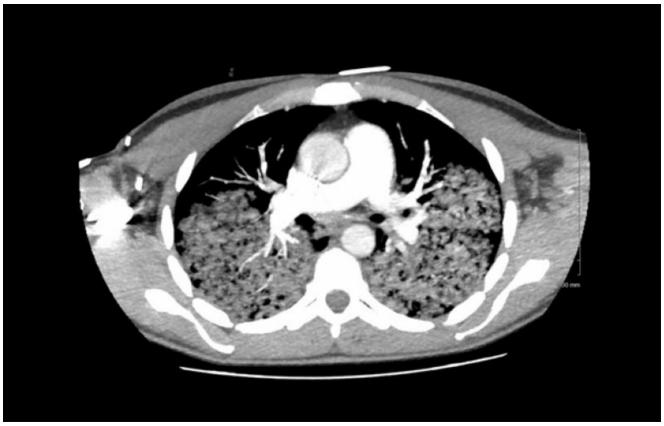

Figure 1 Mid-thorax CT on admission showing diffuse alveolar haemorrhage (chest window).

which was then confirmed by a renal biopsy showing focal crescentic glomerulonephritis.

TREATMENT

Due to the mild nature of his SARS-CoV-2 infection, the patient did not receive any treatment for COVID-19.

Four weeks following resolution of his acute infection, treatment for GPA was initiated with high-dose intravenous methylprednisolone for 3 days, then high-dose prednisone for 10 days with a plan to continue at a reduced dose for 6 months. In addition to high-dose intravenous steroids, the patient received 1 g of intravenous rituximab prior to discharge, with plans to continue a maintenance regimen at an outpatient centre.

OUTCOME AND FOLLOW-UP

The patient has continued to improve clinically in the months following discharge and has not required any further hospitalisations.

DISCUSSION

The pathogenesis of GPA is complex but consists of inflammatory cytokines priming neutrophils, leading to migration of PR3 to the surface of the cell membrane.[2] Once, on the cell surface, the anti-PR3 auto-antibody binds to the PR3 antigen causing activation and subsequent neutrophil degranulation.[3] Increased Il-17, interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) levels lead to formation of inflammatory granulomatous lesions.[4] In addition, the release of oxygen radicals incites necrotising injury followed by fibrinoid necrosis, which, in the lungs, causes loss of capillary wall integrity. This manifests clinically as diffuse alveolar haemorrhage, a life-threatening complication of the disease.[2]

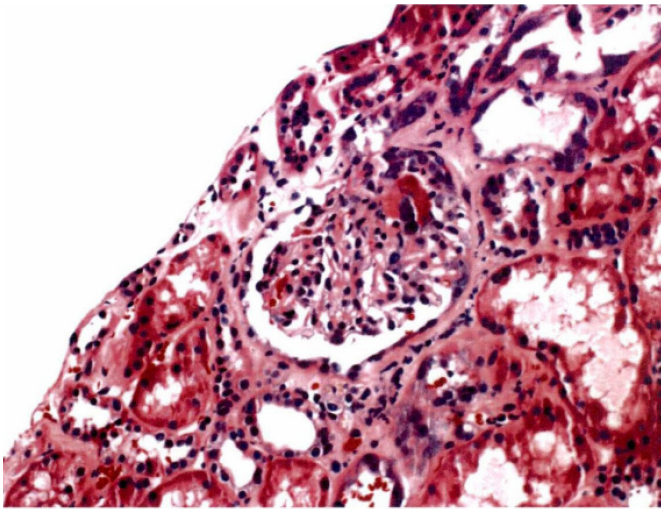

Figure 2 Glomerular necrosis and crescental lesions.

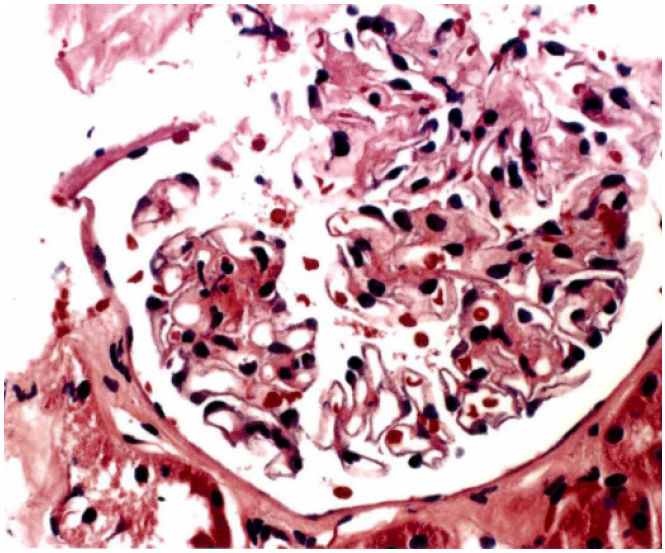

Figure 3 Glomerular necrosis.

Recent studies have shown that hyperactivation of immune cells in patients with COVID-19 leads to elevated levels of various autoantibodies and inflammatory cytokines including IFN-γ and TNF-α.[5 6] Others have demonstrated a relationship between coronaviruses and the increased incidence of rheumatoid arthritis and multiple sclerosis.[7] In a case similar to our patient, a middle-aged man developed symmetric polyarthritis and diffuse myalgia a week before testing positive for SARS-CoV-2 . Six weeks later, his symptoms dramatically worsened. On rheumatological evaluation, he was found to have an elevated ESR and anti-CCP, which led the authors to speculate that an autoimmune disease had been precipitated by COVID-19.[8]

While there have been several reported cases of COVID-19 occurring in patients receiving immunosuppressant treatment for GPA, there is a paucity of literature describing fulminant GPA following COVID-19. Our case illustrates several challenges associated in caring for patients who have recently recovered from COVID-19, including the diagnosis of autoimmune diseases such as GPA. In our patient, GPA was not diagnosed despite numerous early encounters in the healthcare setting. Even after admission, CT findings showed significant overlap with common features of COVID-19 as well as other lung pathologies such as postviral pneumonia. The nonspecific nature of both the subjective and objective findings makes the diagnosis of GPA challenging in the postviral period. Furthermore, since SARS-CoV-2 may be detected via PCR for 90 days or longer, a positive test may result in misdiagnosis long after a resolved infection.

Second, the temporal relationship with COVID-19 and the acceleration of GPA symptoms indicates a possible connection. As described by Garlapati *et al*, numerous viruses have been shown to unmask underlying propensity towards GPA via increased serum levels of inflammatory mediators. It is also known that SARS-CoV-2 increases levels of the same mediators, several of which play a role in the pathogenesis of GPA.[2 3 5] Therefore, it is conceivable that the presence of excessive inflammatory mediators provided substrate for the priming of neutrophils and ANCA-induced degranulation, resulting in the fulminant onset of GPA in our patient whose symptoms had previously been smouldering for several months.

Additionally, it is worthwhile to consider the role of SARS-CoV-2-induced alteration of the nasopharyngeal and pulmonary microbiota plays in the presentation of GPA in patients with post-COVID. It is well documented that SARS-CoV-2 changes the microbiome and that microbial dysbiosis is significantly correlated with an increase in TNF-α, a key mediator in formation of granulomatous lesions.[4 9 10] Specifically, SARS-CoV-2 binding to abundant angiotensin-converting enzyme 2 receptors in the respiratory tract causes cytokine release that alters local microbiota leading to increased mucus production and decreased ciliary clearance putting the host at risk of bacterial superinfection and acute respiratory distress syndrome.[10] This could cloud the diagnostic picture of a patient who presents with cough or haemoptysis post-COVID-19.

Treatment of GPA in a patient with post-COVID-19 requires careful consideration of the consequences of immunosuppression. This should be accounted for when deciding to use rituximab or cyclophosphamide for induction of GPA remission. The drug-induced depletion of B cells could have a devastating consequence in individuals who have not yet mounted an antibody response. Indeed, a recent study found that patients who received anti-CD-20 therapy had significantly lower rates of SARS-CoV-2 IgG seroconversion.[11] Therefore, it would be prudent to consider the COVID-19 IgG antibody status of the patient. The lack of antibody production could have numerous consequences including persistent disease or reinfection with SARS-CoV-2, difficulty in obtaining accurate serology to assess for immunity and prevent an adequate response to vaccination. Treatment options when immunosuppression cannot wait for an immune response include monoclonal antibody therapy or high-titre convalescent plasma to help promote clearance of SARS-CoV-2.

Learning points

- This is a classic presentation of a rare disease that was diagnosed during the patient's third encounter with the healthcare system, in part due to the similar sequala of COVID-19.
- Consider rheumatologic diagnoses, particularly vasculitides, in patients who present with joint pain, fever, cough/haemoptysis in the post-COVID period.
- The time course suggests that the viral infection possibly accelerated the autoimmune disease process. If true, due to the sheer number of COVID-19 infections at present, the virus could be responsible for a substantial amount of disease burden among individuals predisposed to developing autoimmune disease.
- The choice of immunosuppression should take into consideration a patient's immune response to COVID-19. A B-cell depleting agent prior to adequate immune response could have potential deleterious effects.
- If immunosuppression must take place prior to adequate antibody production, antibody supplementation with monoclonal antibody therapy or convalescent plasma may prove beneficial.

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