Does withdrawal of immunosuppression in rheumatoid arthritis after SARS-CoV-2 infection increase the risk of vasculitis?

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SUMMARY
We describe a case of a 48-year-old woman who presented with acute respiratory failure due to diffuse alveolar haemorrhage and acute renal failure due to pauci-immune glomerulonephritis consistent with a new diagnosis of microscopic polyangiitis (MPA). The patient had a recent SARS-CoV-2 infection 6 weeks before MPA diagnosis and had stopped immunosuppression for her rheumatoid arthritis (RA) at that time. The patient was treated with pulse intravenous steroids, plasma exchange therapy and rituximab, which induced remission of her illness. This case highlights a timely dilemma of holding immunosuppression in a RA patient with low disease activity on combination therapy with SARS-CoV-2 infection, and the potential risk of developing an additional autoimmune disease, such as vasculitis, given their existing autoimmunity due to RA.

BACKGROUND
Rheumatoid arthritis (RA) is one of the most common diseases rheumatologists encounter in their practice. The latest data from the Global Rheumatology Alliance (GRA) registry reports that the most common rheumatic disease in which COVID-19 was documented was RA. Infection risk in RA is generally increased compared with the non-RA population. Studies have shown that high disease activity correlates with an increased risk of acquired infections. Acquiring infections can lead to flares of RA disease activity, which can potentiate the vicious cycle of infection, increase disease activity and alter the course of immunosuppressive therapy. Therefore, control of disease activity is the most important step in RA management during COVID-19.

The COVID-19 epidemic has led to an era of uncertainty concerning the treatment in patients with autoimmune disorders associated with their weakened immune response due to the use of immunosuppressive agents. Data on COVID-19 patients with underlying rheumatological diseases have been emerging mostly from small case series and GRA registry. Although immunosuppressed, RA patients are not particularly susceptible to the coronavirus infection and, if infected, do not have significantly worse outcomes than other patients. Current evidence to guide treatment decisions is lacking, and doubts remain about the continuation and initiation of immunosuppressants. Drugs like hydroxychloroquine (HCQ), dexamethasone, tocilizumab and baricitinib have been studied for the treatment of various manifestations of COVID-19. Recent guidance from the American College of Rheumatology (ACR) and National Institute of Health and Care Excellence recommends holding HCQ, chloroquine (CQ), conventional and biologic disease-modifying anti-rheumatic drugs (DMARDs) except sulfasalazine (SSZ), non-steroidal anti-inflammatories (NSAIDs) or interleukin-6 (IL-6) inhibitors in a documented or presumptive SARS-CoV-2 infected patients.

CASE PRESENTATION
A 48-year-old African-American woman with a history of RA, hypertension and recent SARS-CoV-2 infection presented to the hospital with worsening shortness of breath associated with trouble speaking due to rapid breathing, dry cough, body aches and two episodes of watery diarrhoea. She had tested positive for SARS-CoV-2 by nasal swab 6 weeks before this presentation with non-specific symptom of dry eyes only. The patient had stopped her immunosuppressive treatments for RA immediately after testing positive for SARS-CoV-2, which included clinical trial Janus kinase (JAK) inhibitor and methotrexate (MTX) 15 mg every week. Of note, the patient was counselled to stop the clinical trial therapy only, but elected to discontinue MTX as well. Five weeks after stopping immunosuppression, the patient was treated as an outpatient with azithromycin and amoxicillin clavulanic acid for 7 days for the diagnosis of community-acquired pneumonia, acute kidney injury and keratoconjunctivitis, which in retrospect may have been early manifestation of a brewing vasculitis. Physical examination on admission revealed the patient was in moderate to severe respiratory distress with a respiratory rate of 40–50 breaths/min and tachycardia, requiring non-invasive positive pressure ventilation (NPPV) by biphasic positive airway pressure bi-level positive airway (Respironics BiPAP Vision) at 80% FiO₂.

INVESTIGATIONS
Chest X-ray showed diffuse bilateral pulmonary airspace disease concerning for severe pulmonary oedema with a possibility of an underlying infectious process. Bedside ECG in the emergency room did not show evidence of acute heart failure. CT angiogram of the chest ruled out pulmonary embolism, aneurysm or dissection, but confirmed severe bilateral airspace opacities with air bronchograms, findings concerning for severe pulmonary oedema.
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with superimposed pneumonia and/or acute respiratory distress syndrome (figure 1).

Given worsening respiratory acidosis on NPPV by BiPAP, the patient required intubation and admission to the medical intensive care unit. Laboratory data showed wide anion-gap metabolic acidosis with an anion gap of 35, lactate of 14 mmol/L, BUN 55 mg/dL and creatinine 5.40 mg/dL. Nasal swab for SARS-CoV-2 nucleic acid amplification was not detected and Elecsys anti-SARS-CoV-2 was positive. The Elecsys assay is intended for use as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, indicating recent or prior infection. Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) confirmed serial aliquots of serosanguinous saline confirming diffuse alveolar haemorrhage (DAH). The cell counts of BAL fluid showed .0768x10^12/L red blood cells/UL, 3.1x10^9/L white blood cells/UL, with differential showing 99% neutrophils and 1% lymphocytes. Subsequent serologies confirmed perinuclear antineutrophil cytoplasmic antibodies (P-ANCA) titre of 1:320 with anti-myeloperoxidase (MPO) antibody level of 81.5 U/mL. Renal biopsy showed pauci-immune crescentic glomerulonephritis.

Differential Diagnosis

The primary differential diagnosis suspected before biopsy results was sepsis due to pneumonia, COVID-19 relapse, vasculitis and overlap syndrome. The nasal swab for SARS-CoV-2 reverse transcriptase PCR was negative on two separate occasions. Nucleic acid amplification test for multiple respiratory pathogens, such as mycoplasma, influenza A, influenza H1, influenza H3, influenza A virus H1 2009, influenza B, respiratory syncytial virus, parainfluenza virus type 1, 2, 3, 4, human metapneumovirus, rhinovirus/enterovirus, adenovirus, Cblamydia pneumoniae and Mycoplasma pneumoniae were negative as well. BAL smear was negative for Pneumocystis jirovecii and acid-fast bacilli. BAL specimen was negative for nucleic acid amplification for Mycobacterium tuberculosis. Urine antigens for Legionella and Streptococcus pneumoniae were negative. BAL stain for fungal elements was negative. Blood, urine and BAL cultures yielded no growth, thus ruling out most infectious culprits suspected for this presentation. Serologies were negative for anti-nuclear antibody, C3, C4, double-stranded DNA antibody, ribonucleoprotein, Smith antibody, Serum Amyloid A Antibodies (SSA) and Serum Amyloid B Antibodies (SSB) antibodies were negative. Echocardiogram was negative for any valvular disease and there was no evidence of elevated left ventricular end-diastolic pressure. Urine toxicology screen was negative for amphetamines and crack/cocaine.

TREATMENT

High-dose intravenous pulse glucocorticoid therapy was administered for DAH likely due to capillaritis. The patient also started on continuous renal replacement therapy for anuric acute kidney injury with refractory acidosis. After the finding of pauci-immune glomerulonephritis on renal biopsy, microscopic polyangitis (MPA) diagnosis was confirmed, intravenous steroids at 1 mg/kg were continued, five sessions of plasma exchange therapy were initiated and rituximab at 375 mg/m2 weekly for four doses was administered. The patient did require haemodialysis every 48 hours for 1 week until she had recovery in renal function.

OUTCOME AND FOLLOW-UP

At 4-week follow-up since discharge, the patient has completed four rituximab treatments and labs showing serum creatinine of 1.6 mg/dL with no electrolyte abnormalities, haemodynamic instability or respiratory difficulties. At this first assessment since hospital discharge, the patient’s vasculitis disease activity was in remission with Birmingham Vasculitis Activity Score of zero. The patient’s RA is very well controlled and her clinical disease activity index was 3 (near remission).

DISCUSSION

Rheumatologic diseases may be associated with an increased risk of severe infections associated with underlying diseases, chronic inflammatory processes and the use of immuno-suppressive drugs. However, concrete evidence is lacking if immunosuppressed patients with conventional or biologic DMARDs are at increased risk of SARS-CoV-2 infection. A recent observational study of the first cohort in Lombardy, Italy, shows the incidence of COVID-19 in patients treated with synthetic or biologic DMARDs is consistent with that of the general population. The GRA registry reports the most common comorbidities among RA patients with COVID-19 were hypertension (33%), lung disease, including chronic obstructive lung disease, asthma, interstitial lung disease (ILD) and others (21%), diabetes, cardiovascular disease and renal failure. RA patients with coexisting comorbidities, especially ILD and pulmonary artery hypertension, are at the highest risk for contracting SARS-CoV-2 infection when compared with the general population. However, hospitalisation has not been linked to RA disease.

The rare overlap of ANCA-associated vasculitis (AAV) in RA has been reported in the literature. In one retrospective analysis of a vasculitis database of RA patients diagnosed with AAV and case reports describing AAV and RA in the literature, there have been 14 cases due to Granulomatosis with polyangiitis (GPA), 11 due to MPA and 1 due to Eosinophilic granulomatosis with polyangiitis (EGPA) in RA patients. In these reports, vasculitic renal manifestations and rheumatoid factor positivity were frequent. Knowledge of these overlap syndromes is essential in early recognition of potential complications and differences in clinical courses and management pathways. Pulmonary vascular involvement due to RA, presenting as DAH, is a rare phenomenon,
suggests that COVID-19 disease can present in different and disease course of AAV is of great debate. New data on COVID-19 that may play a role in propelling vasculitis. We will briefly review the recently studied mechanisms of collagen vascular diseases. Other mechanisms of DAH, such as bland pulmonary haemorrhage and diffuse alveolar damage, have myriad etiologies. Anti-GBM diseases and SLE can induce both pulmonary capillaritis and bland pulmonary haemorrhage. Since pathological mechanisms of DAH and MPA-associated interstitial fibrosis overlap, it is difficult to diagnose the cause of DAH. When ANCA directed against proteinase-3 or MPO occur in RA accompanied by clinical findings compatible with vasculitis, the simultaneous occurrence of two separate diseases is also a strong possibility. Our patient lacked evidence of uncontrolled RA before the onset of MPA, and we suspect she may have had a trigger in autoimmunity due to the stoppage of immunosuppression in the setting of COVID-19 illness. Some other putative etiologies of DAH, such as infections, drug-induced, and toxin-induced, and cardiovascular etiologies, were excluded by investigations summarised in the case presentation. Cases of COVID-19-related vasculitis are reported in the literature and this could be a possible reason for our patient developing vasculitis in an otherwise stable RA disease pattern. We will briefly review the recently studied mechanisms of COVID-19 that may play a role in propelling vasculitis.

At the time of writing this report, how SARS-CoV-2 infection can affect the susceptibility, clinical presentation and disease course of AAV is of great debate. New data suggests that COVID-19 disease can present in different ways, and it does not necessarily affect the respiratory system. Vasculopathy may be a complication of COVID-19. Severe Kawasaki-like disease has been reported at the Italian epicentre of SARS-CoV-2 epidemic. The innate and adaptive immune response to SARS-CoV-2 infection leads to hyperstimulation of the immune system, which results in the majority of morbidity and mortality. Case reports have shown a mild form of the disease, and the use of tumour necrosis factor inhibitors seems to have had a protective effect on the evolution to severe forms, thereby preventing the damaging effects of the high levels of cytokines associated with the immunopathogenesis of SARS-CoV-2 infection. Of the JAK inhibitors, baricitinib has been the best studied in COVID-19. Baricitinib impairs the entry of SARS-CoV-2 by blocking viral endocytosis. Baricitinib in combination with remdesivir was approved by US Food and Drug Administration for treatment of suspected, or confirmed COVID-19 hospitalised adults and paediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation or extracorporeal membrane oxygenation. However, concerns about interferon response and viral infection risk remains due to the known increased risk of herpes zoster observed with JAK inhibition. It is unclear if JAK inhibitors compound thrombotic risk in COVID-19. Current prospective trials are ongoing to address these concerns. These features are an indication of the need to explore the exact pathology of this virus and consider vasculitis as a probable clinical presentation.

The majority of immunosuppressed patients are concerned about COVID-19 infection risk and many surveys worldwide have demonstrated 2.2%–13% of patients decreased or stopped taking immunosuppression due to the concern of acquiring infection. Our patient was on a JAK inhibitor and MTX for her RA disease control, which was stopped after an exposure to SARS-CoV-2 that resulted in infection. The use of immunomodulatory therapy in the setting of RA and COVID-19 remains controversial. The effect of the washout period of conventional synthetic DMARDs and certain biologic agents with long half-life (eg, MTX, leflunomide and certolizumab) in exposed or infected individuals need to be also considered in the clinical monitoring of exposed or infected patients. Currently, ACR recommends stopping HCQ/CQ, DMARDs, non-IL-6 biologics and JAK inhibitors temporarily, pending 2 weeks of symptom-free observation, in case of documented or presumptive SARS-CoV-2 infection. SSZ and NSAIDs may be continued. Emerging data suggest that some immunosuppressants, biologics and/or JAK inhibitors could theoretically mitigate the severe impact of COVID-19, favouring their continued use or initiation in the management of rheumatic disease.

Early and appropriate use of immunosuppression may help tackle the suspected cytokine storm, but their use after the storm has arrived may not be helpful. The non-infected patient can be safely continued on therapy to keep the disease activity under control. In those with disease flare, conventional DMARDs and biologics may be initiated. Holding immunosuppression in an exposed patient needs to be tailored to the individual patient, depending on their clinical presentation and in consultation with the treating rheumatologist.

Learning points

- Withdrawal of immunosuppressive therapies in patients exposed to SARS-CoV-2 or with mild proven SARS-CoV-2 infection should be considered carefully, as flares of autoimmune rheumatological conditions can be life-threatening.
- Immunosuppression may slow autoimmunity to SARS-CoV-2 infection; withdrawal may increase the risk of developing antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis during SARS-CoV-2 infection.
- Knowledge of rare overlap of ANCA-associated vasculitis in rheumatoid arthritis is important in the early recognition and management.
- Review of current guidance on the management of immunosuppression in rheumatic patients proposed by the American College of Rheumatology, Global Rheumatology Alliance and National Institute of Health and Care Excellence.

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Patient’s perspective

I am very grateful of the resolution of this illness and remain curious about the possibility of relapse in the future. I also wonder if I am immune to COVID-19 now.
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