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An unusually "complex" glomerulonephritis

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ABSTRACT

A 53-year-old man with granulomatosis with polyangiitis presented with fever and acute kidney injury with nephrotic-range proteinuria following the second dose of the mRNA COVID-19 vaccine. Renal biopsy revealed an unexpected immune complex-glomerulonephritis (IC-GN) without vasculitis. Further workup found the patient to have HIV that was unmasked following the treatment of IC-GN. This case report explores the possible relationship between COVID-19 vaccines and the immune response in the setting of chronic HIV.

KEYWORDS COVID vaccine; glomerulonephritis; granulomatosis with polyangiitis; human immunodeficiency virus; immune complexes; type III hypersensitivity

Hypersensitivity reactions are inappropriate immune responses to an antigen and are classified into four types, I to IV.[1] Type III hypersensitivity reactions or immune-complex (IC) reactions occur when excess antigen-antibody complexes cannot be cleared and precipitate in tissues.[2,3] If deposited in the renal glomeruli, immune complexes can cause glomerulonephritis (GN). Common associations with IC-GN include infections (e.g., HIV), autoimmune diseases (e.g., systemic lupus erythematous), and vaccines (e.g., pneumococcal).[2,3] Vaccines enhance host defenses through immune activation against antigen, with some inducing IC formation important in B, T, and antigen-presenting cell activation.[4] Amid the pandemic, SARS-CoV-2 infection has been reported to cause IC diseases including GN,[5,6] and COVID-19 vaccines may induce de novo autoimmunity or flare underlying immune-mediated inflammatory diseases.[7–9] Here, we present an unusual case of IC-GN presenting shortly after COVID-19 vaccination in a patient with granulomatosis with polyangiitis (GPA) and HIV infection.

CASE DESCRIPTION

A 53-year-old man was diagnosed in 2008 with GPA based on fever, epistaxis, elevated C-anti-neutrophil cytoplasm antibodies (c-ANCA), erythrocyte sedimentation rate, C-reactive protein, and necrotizing lung granulomas with tissue histology consistent with ANCA-associated vasculitis. He had no prior renal involvement. Previous treatments included cyclophosphamide and rituximab (last dose in 2009). He had been in remission on methotrexate monotherapy for years. In February 2021, he received the Pfizer-BioNTech COVID-19 vaccines; the first dose caused arm soreness and fatigue. After the second dose, he noted low-grade fever (99.5°F), worsening fatigue, and mild shortness of breath that developed over the next few weeks.

On March 30, 2021, he presented for routine rheumatologic evaluation citing severe fatigue, epistaxis, gross hematuria, and shortness of breath. He had a temperature of 97.9°F, blood pressure of 156/96 mm Hg, and pulse of 94 beats/min. Exam noted dried blood in his nostrils and 2+ peripheral edema. The rest of his exam including the lungs was unremarkable. Laboratory studies showed a hemoglobin of 9.2 (baseline 12.6 g/dL), creatinine of 2.49 (baseline 0.9 mg/dL), and erythrocyte sedimentation rate of 110 (baseline 20–30 mm/h); urine studies revealed nephrotic-range proteinuria. Previous urinalysis was normal without evidence of proteinuria. His c-ANCA/PR3 levels were unchanged from baseline, and a COVID-19 test was negative. He was hospitalized for suspected GPA flare.

Additional evaluation with chest x-ray, chest computed tomography with angiogram, venous Dopplers, and cystoscopy were unremarkable. A renal biopsy was obtained.

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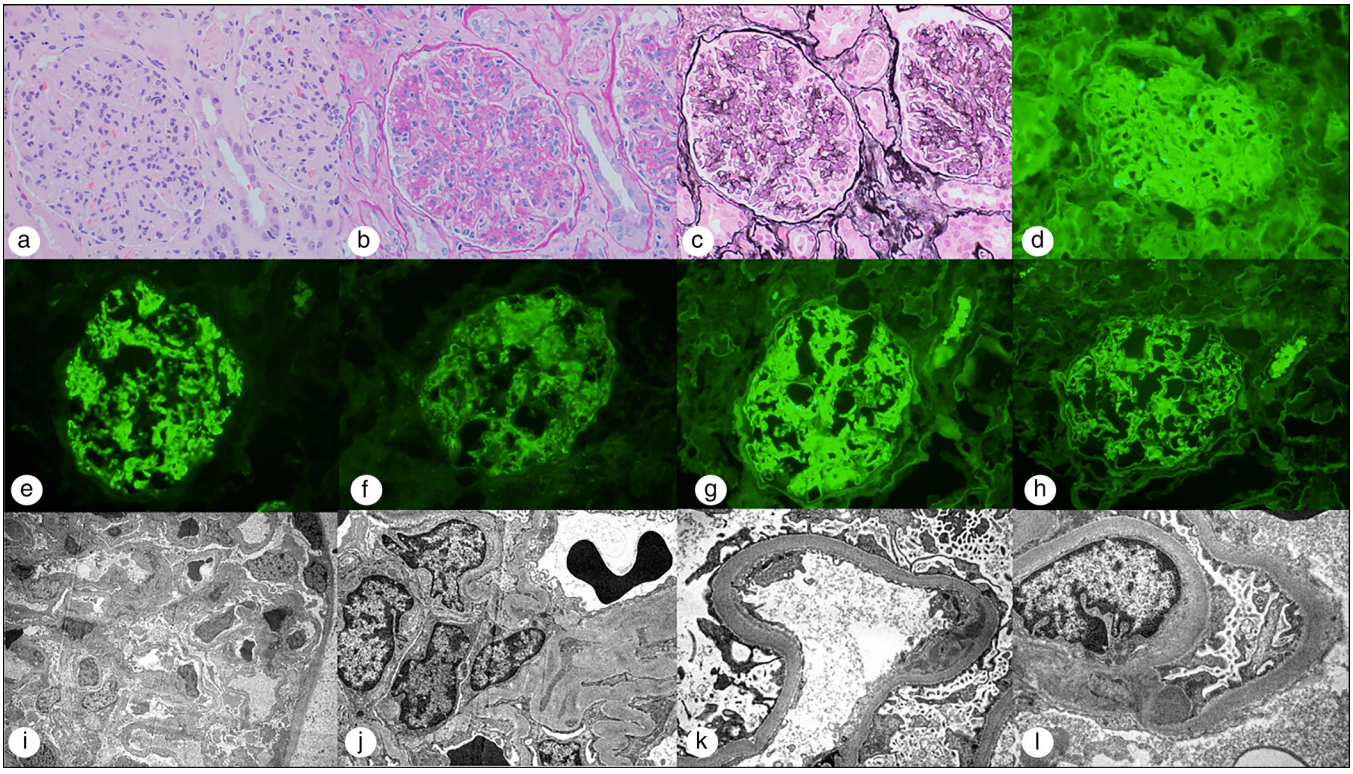

Figure 1. Glomerular hypercellularity evident with **(a)** hematoxylin and eosin stain, **(b)** Periodic-acid Schiff stain, and **(c)** Jones methenamine silver stain. Immune-complex deposition of **(d)** immunoglobulin G, **(e)** complement factor 3b, **(f)** complement factor C1q, **(g)** kappa, and **(h)** gamma light chains on immunofluorescence is also shown. Finally, a **(i)** panoramic view of glomerular hypercellularity, **(j)** mesangial hypercellularity, **(k)** subendothelial deposits, and **(l)** subepithelial deposits on electron microscopy are shown. Classic pathologic signs of granulomatosis with polyangiitis glomerulonephritis were not seen.

Pathology did not reveal vasculitis *(Figure 1a–1c)* but demonstrated IC-GN with granular deposits IgG, complements C3 and C1q, and lambda and kappa immunoglobulin light chains *(Figure 1d–1h)*. Subendothelial and subepithelial deposits were observed by electron microscopy *(Figure 1i–1l)*. Further testing for systemic lupus erythematosus, hepatitis, and glomerular basement membrane disease was unremarkable, but mixed serum cryoglobulins were present. The patient was treated with intravenous methylprednisolone 1000 mg/day for 3 days followed by rituximab. Symptoms and laboratory results improved, and he was discharged with a prednisone taper.

One month later, he reported cough and a fever of 101°F. A COVID-19 test was negative, but labs showed a white blood cell count of 1.0 (baseline 8.0/μL). Chest x-rays demonstrated bilateral pulmonary infiltrates. Additional testing revealed evidence of HIV with a viral load >100,000 and CD4 count <100. He responded to antibiotics for community-acquired pneumonia and was referred for HIV management. On follow-up, he responded well to antiretroviral therapy and had resolution of proteinuria in subsequent urine studies.

DISCUSSION

This is an atypical case of glomerulonephritis with unexpected findings, emphasizing the need for vigilance when diagnoses are disconnected. Initially, a GPA flare was suspected in this patient, but unexpectedly the renal biopsy demonstrated IC-GN rather than pauci-immune GN, as typical for ANCA-associated vasculitis.[10,11] Also, the timing from COVID-19 vaccination to symptomatic presentation raised suspicion of a vaccine-induced hypersensitivity immune reaction. Several cases of COVID-19 vaccine-induced de novo autoimmunity and immune-mediated inflammatory disease flares have been published since mRNA vaccine technology was introduced.[7–9,12,13] While COVID-19 vaccine-induced IC-GN has not been reported, other vaccines have been associated with IC-GN.[3] Likewise, COVID-19 has been reported as a cause of IC-GN[6] and pauci-immune GN.[5,14] While our patient did not have COVID-19, it was plausible the COVID vaccine might have induced de novo IC-GN.

However, HIV is the most likely cause of his IC-GN given that viral antigens are known to form immune complexes.[15] Our patient denied sexual relations for 6 years, and because his last HIV test 6 years ago was negative, the authors did not test for HIV at his initial hospitalization. It is probable the patient had long-standing HIV-associated IC-GN (or HIV immune complex kidney disease, HIVICK), and we suspect that the COVID vaccine may have exposed the disease. If true, this is the first case of COVID-19 vaccination uncovering HIVICK in a patient with GPA. This case serves a cautionary example to obtain HIV testing in individuals with new autoimmune issues and in those

undergoing immunosuppression. The patient has done well with antiretroviral therapy. His viral load is now undetectable, and his renal function has significantly improved while maintaining GPA remission. He received a booster dose of the mRNA vaccine without recurrence of IG-GN.

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