ANCA-Associated Vasculitis following the First Dose of Pfizer-BioNTech COVID-19 Vaccine

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Abstract
Coronavirus disease (COVID-19) vaccine can alter the body’s immunological balance leading to autoimmune disease in rare cases. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is one of the autoimmune diseases which have been rarely reported to appear post-COVID-19 vaccine. Herein, we report the case of a 47-year-old woman who developed acute renal failure few days after receiving the first dose of the Pfizer-BioNTech COVID-19 vaccine. Corticosteroids along with azathioprine were used for the management.

Introduction
The humongous medical, financial, and social impact of coronavirus disease (COVID-19) necessitated the rapid implementation of vaccination. Several types of vaccines were found using novel pathways such as mRNA delivered via lipid nanoparticles, viral vectors, inactivated virus, and protein subunits \cite{1}. These vaccines were significantly effective in reducing COVID-19-related mortality \cite{1}.

The induction of an autoimmune/autoinflammatory response, such as vaccine-induced immune thrombotic thrombocytopenia and immune-mediated myocarditis, are some of the rare side effects reported with different types of vaccines \cite{2, 3}. Interestingly, different types of vasculitides, including anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, were reported in the context of the Pfizer-BioNTech COVID-19 vaccine \cite{4}. As a consequence, multiple ongoing clinical trials are currently studying the safety profile of COVID-19 vaccines \cite{5}.

In this case report, we illustrate the case of a healthy woman who developed acute renal failure few days following the Pfizer-BioNTech COVID-19 vaccine. This patient was successfully treated with oral corticosteroids and azathioprine.

Case Report/Case Presentation
A previously healthy 47-year-old woman presented to the primary care clinic for bilateral flank pain, generalized weakness, and bilateral lower extremity swelling that started 3 days following the first dose of Pfizer-BioNTech COVID-19 vaccine. No shortness of
breath or hemoptysis was reported. Vital signs were within normal limits, including a blood pressure of 129/76 mm Hg. Physical examination was significant for bilateral lower extremity edema reaching the knees. No sacral edema was noted. Costovertebral angle tenderness was negative. Otherwise, the examination was unremarkable, including a regular rate rhythm, with normal S1 and S2, no murmurs, and palpable peripheral pulses.

Urinalysis was positive for proteins, red blood cells of 40–50/high power field, and white blood cells of 8–10/high power field. Urine protein/creatinine ratio was significantly elevated at 1,777 mg/g. Laboratory investigations were compatible with acute kidney injury as the serum creatinine was 2.91 mg/dL (baseline 0.8 mg/dL measured 7 months prior to presentation), urea was 208 mg/dL, and eGFR was 18 mL/min/1.73 m². In addition, bicarbonate was decreased at 17 mEq/L. The complete blood count was significant for leukocytosis (white blood count 14.99 × 10³/µL) with neutrophil predominance of 82.8%. Inflammatory markers were elevated with C-reactive protein of 2.34 mg/dL (normal range: 0.8–1.0 mg/dL). The extractable nuclear antigen profile was positive for anti-neutrophil cytoplasmic antibody (ANCA) IgG myeloperoxidase (MPO) at 2.8 units/mL (normal <1 units/mL). The IgG class ANCA directed to proteinase 3 (PR3) titers were within normal limits (normal <1 units/mL). Complement levels and other serologic tests were unremarkable. A CT scan of the chest was negative for any lung involvement. A kidney biopsy revealed changes of fibrous crescents with interstitial fibrosis and tubular atrophy with negative immunofluorescence compatible with a systemic disease mediated by ANCA (Fig. 1a, b). The patient was started on intravenous methylprednisolone for 3 days and prednisone 50 mg daily thereafter along with azathioprine 50 mg twice daily.

Serum creatinine trended down to 2.01 mg/dL 2 weeks after treatment initiation. Urine protein/creatinine ratio also trended down to 862 mg/g. In a follow-up visit to the clinic 3 months after initial presentation, the patient reported a better functional status. The lower extremity edema completely resolved. Serum creatinine was 1.23 mg/dL in the 3-month follow-up visit.

Discussion/Conclusion

Despite being rare events, vaccines have been long thought to induce autoimmune diseases, such as swine flu vaccine inducing Guillain-Barré syndrome [6]. ANCA-associated vasculitis (AAV) has been also reported in the context of vaccination. For example, multiple reports have illustrated a temporal relationship between AAV and influenza vaccination [7].

Besides the appearance of autoinflammatory/autoimmune phenomena in COVID-19 patients [8], different types of COVID-19 vaccines have been very rarely linked with several autoimmune diseases, such as rheumatoid arthritis [9] and lupus nephritis [10]. Vasculitis induction has been also reported in the context of COVID-19 vaccine. Both induction of vasculitis and a flare of a pre-existing vasculitis have been described post-COVID-19 vaccine [11–13]. One type of vasculitides, the AAV, has been also rarely illustrated to induce secondary to different types of COVID-19 vaccines, including the Pfizer-BioNTech vaccine (Table 1). Furthermore, a case series of 29 patients who developed glomerular disease post-severe acute respiratory syndrome coronavirus 2 immuni-
zation was reported in the literature [14]. Only two of these cases had a complete recovery. Out of all 29 cases, six had a crescentic glomerulonephritis. Four out of 10 ANCA-positive glomerulonephritis cases had the disease occurring after the Pfizer-BioNTech COVID-19 vaccine, none of which had a complete recovery, although the treatment is unclear. There was no overall increase in the incidence of biopsy-proven glomerular disease when compared to the era prior to the COVID-19 pandemic [14]. The glomerular disease secondary to COVID-19 vaccination was deemed to be rare, although it should be monitored as a potential adverse event [14].

Our case is unique in the rapid onset of symptoms and the onset post the first dose in particular [15–17]. It is important to note that the presence of fibrous crescents and interstitial fibrosis in the kidney biopsy might point to a chronic process. The AAV might have been silent in our patient and exacerbated after COVID-19 vaccination. A recent consensus statement on COVID-19 vaccination in patients with immune-mediated kidney disease high-

### Table 1. Positive ANCA and AAV cases following Pfizer-BioNTech COVID-19 vaccine

| Case          | Clinical presentation                                      | CBC and chemistry          | Serology                  | Biopsy                                 | Treatment                      | Outcome          |
|---------------|-----------------------------------------------------------|----------------------------|---------------------------|----------------------------------------|-------------------------------|------------------|
| Shakoor et al. [15] | Nausea, vomiting, diarrhea, and lethargy                        | Creatinine 3.54 mg/dL Urinary albumin-creatinine ratio 205 µg/mg | Anti-MPO 1.1 IU/mL Pauci-immune crescentic necrotizing glomerulonephritis | Steroids and rituximab | Creatinine 1.71 mg/dL | One month       |
| Dube et al. [16] | Asymptomatic Seven weeks Second dose                         | Creatinin of 9.1 mg/dL Urine albumin-creatinine ratio 653 µg/mg | Anti-MPO 71 IU/mL Pauci-immune crescentic glomerulonephritis | Steroids, rituximab, and cyclophosphamide | Creatinine 1.01 mg/dL | Ten weeks       |
| Hakroush and Tampe [17] | Generalized weakness and thigh pain Two weeks Second dose | WBC 22,900/µL Creatinin kinase levels 14,243 U/L Myoglobin >12,000 µg/L Creatinin 1.38 mg/dL Nephrotic range proteinuria | Anti-MPO >134 IU/mL Pauci-immune crescentic glomerulonephritis | Steroids and cyclophosphamide | Proteinuria 1.603 µg/mg | No specified period |
| Okuda et al. [18] | Pain, redness, and swelling in the left auricle Three weeks First dose | CRP 10.16 mg/dL Creatinine 0.62 mg/dL | Anti-MPO 494 IU/mL Anti-PR3 28.3 IU/mL | Not performed | Steroids | Negative CRP Nine days |
| Obata et al. [19] | Fever spikes, malaise, and cough Two weeks Second dose | WBC 12,600/µL CRP of 18.4 mg/dL Creatinine 1.22 mg/dL | Anti-MPO 112.8 IU/mL Focal necrotizing glomerulonephritis with cellular crescents Masson’s trichrome stain revealed fibrinoid necrosis with marked endothelial swelling | Steroids | Creatinine 1.35 mg/dL Anti-MPO 10.0 IU/mL | Eight weeks |
| Shirai et al. [20] | Severe vertigo and hearing loss Three weeks First dose | WBC 12,800/µL CRP 14.32 mg/dL | Negative anti-MPO Anti-PR3 259 IU/mL | Fibrin deposition in the small vessels and granulation tissue with intensive infiltration of inflammatory cells, predominantly neutrophils | Steroids and cyclophosphamide | NA |
| Current case | Bilateral flank pain, generalized weakness, and bilateral lower extremity edema Three days First dose | WBC 14,990/µL Creatinine 2.91 mg/dL Urine protein/creatinine 1777 µg/mg | Anti-MPO 2.8 IU/mL Pauci-immune crescentic glomerulonephritis | Steroids and azathioprine | Creatinine 2.01 mg/dL Negative CRP Negative ESR | Two weeks |

CBC, complete blood count; BUN, blood urea nitrogen; MPO, myeloperoxidase; WBC, white blood count; CRP, C-reactive protein.
lighted the rarity of induction/flare of immune-mediated kidney disease post-COVID-19 vaccination [21]. The consensus statement indicated that these rare cases respond to immunosuppression and mainly occur post-second vaccination dose.

Acute kidney injury has been rarely associated with severe acute respiratory syndrome coronavirus 2 infection [17] and COVID-19 vaccine [22, 23]. Although there is no recommendation to randomly check serum creatinine in COVID-19 patients or those recently vaccinated, an elevated serum creatinine or abnormal urinalysis in this population warrants further investigation keeping in mind a possible autoimmune process.

In conclusion, COVID-19 vaccines have substantial benefits. Rarely, autoimmune processes have been described post-vaccination. AAV is an example of an autoimmune disease that can be induced or flared up from a silent state by COVID-19 vaccines. A high index of suspicion regarding the presence of an autoimmune renal process is needed whenever a recently COVID-19-vaccinated individual presents for acute kidney injury.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature. The patient has given her written informed consent to publish this case (including publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Georges El Hasbani took care of reviewing the literature and writing this case. Imad Uthman generated the idea and provided the images.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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