

[CASE REPORT]

Antineutrophil Cytoplasmic Antibody-associated Vasculitis after COVID-19 Vaccination with Pfizer-BioNTech

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Abstract:

The extent of rare side effects of mRNA vaccines for coronavirus disease 2019 (COVID-19) remains unclear. Several cases of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) following COVID-19 vaccination have been reported. We herein report a 72-year-old man who presented with a fever after receiving the second dose of the Pfizer-BioNTech COVID-19 vaccine. He was diagnosed with acute kidney injury due to myeloperoxidase-ANCA-associated vasculitis and was treated with intermittent hemodialysis, high-dose prednisolone, and intravenous rituximab. His general symptoms and renal impairment subsequently improved. When systemic symptoms are prolonged or renal abnormalities appear after COVID-19 vaccination, the possibility of AAV should be considered.

Key words: ANCA-associated vasculitis, rapidly progressive glomerulonephritis, COVID-19 vaccine

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Introduction

Since December 2019, a coronavirus has caused cases of rapidly spreading severe pneumonia, resulting in a global pandemic. As of September 2021, over 200 million cases of coronavirus disease 2019 (COVID-19) have been reported, and 4 million people have died worldwide (1).

Various vaccines against COVID-19 have been made available in different countries. In Japan, the first vaccine (Pfizer-BioNTech) was authorized in February 2021, a second vaccine (Moderna) in May 2021, and a third vaccine (AstraZeneca) in August 2021. Vaccination began with priority among the elderly and healthcare workers. By September 2021, over 60% of the Japanese population had received at least 1 dose of the vaccine.

Large clinical trials of mRNA vaccines have demonstrated their efficacy and safety. Common side effects are often mild, such as local injection site reactions, fatigue, myalgia, a fever, chills, and headache (2, 3). Anaphylaxis has rarely been reported following vaccination. Cases of myocarditis and pericarditis following COVID-19 vaccination have in-

creased, especially among male adolescents and young adults (4). Side effects after the second vaccination may be more intense than those after the first vaccination. However, the extent of rare side effects remains unclear (5-7). Several cases have been reported recently in which nephritis, such as IgA nephropathy, minimal change disease, and antineutrophil cytoplasmic antibody-associated vasculitis (AAV) developed or recurred after COVID-19 vaccination.

We herein report a case of myeloperoxidase (MPO)-antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis with severe crescentic glomerulonephritis after COVID-19 vaccination.

Case Report

A 72-year-old man was admitted to our hospital in the beginning of July, because of an acute kidney injury. His medical history included prostatic hypertrophy, and he was being treated with tamsulosin. He had no allergies. He had previously been vaccinated against influenza without any complications. Routine laboratory tests performed two months prior to vaccination showed a normal kidney func-

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Table. Laboratory Data on Admission.

<u>Urinalysis</u>		<u>Biochemistry tests</u>	
Protein	1+	Total protein	5.2 g/dL
Glucose	-	Albumin	1.7 g/dL
Occult blood	3+	AST	31 IU/L
<u>Urinary sediment</u>		ALT	37 IU/L
Red blood cells	30-49 /HPF	ALP	258 IU/L
White blood cells	10-19 /HPF	LDH	196 IU/L
<u>Complete blood count</u>		Blood urea nitrogen	76.3 mg/dL
Red blood cells	346×10 ⁴ /μL	Creatinine	7.44 mg/dL
Hemoglobin	11.1 g/dL	Sodium	128 mEq/L
Hematocrit	33.6 %	Potassium	6.5 mEq/L
White blood cells	17.1×10 ³ /μL	Chloride	96 mEq/L
Neutrophils	90.3 %	<u>Serology</u>	
Lymphocytes	2.1 %	C-reactive protein	20.34 mg/dL
Monocytes	2.9 %	Rheumatoid factor	<5.0 IU/mL
Eosinophils	1.8 %	Antinuclear antibody	160 IU/mL
Basophils	2.9 %	Anti-GBM antibody	0.6 U/mL
Platelets	25.2×10 ⁴ /μL	PR3-ANCA	<0.5 IU/mL
<u>Venous blood gases (room air)</u>		MPO-ANCA	3,150 IU/mL
HCO ₃ ⁻	18.4 mEq/L	KL-6	143 U/mL
Base Excess	-5.9 mmHg		

ANCA: antineutrophil cytoplasmic antibody, GBM: glomerular basement membrane, MPO: myeloperoxidase, PR3: proteinase3

tion.

The patient had received his first dose of the Pfizer-BioNTech COVID-19 vaccine six weeks before admission and shown no symptoms after the first vaccination. He received the second dose three weeks after the first dose. After half a day, he had a fever of 38°C and developed an intermittent fever, progressive fatigue, and loss of appetite. The symptoms persisted for two weeks, so he visited a local clinic. Laboratory tests revealed a serum creatinine level of 5.0 mg/dL, high C-reactive protein level, and mild anemia, and a urinalysis showed microscopic hematuria and proteinuria. Chest radiography showed no pneumonia, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction was negative. Although he was treated with hydration and antibiotics, his kidney function and anemia deteriorated, C-reactive protein level remained elevated, and the fever persisted. An additional serological workup showed positive MPO-ANCA; therefore, he was referred to our hospital.

His blood pressure was 116/59 mmHg, pulse rate was 100 beats/min, and temperature was 37.2°C. He had no dyspnea or bloody sputum. No rales were audible in the lungs. Laboratory tests on admission showed no improvement in kidney function or urinalysis parameters. The titers of MPO-ANCA were remarkably high (Table). Chest computed tomography (CT) revealed a few nodular shadows (Fig. 1). The Birmingham Vasculitis Activity Score (BVAS) at presentation was 18, indicating extensive disease activity.

We clinically diagnosed the patient with rapidly progressive glomerulonephritis. He was treated with a pulse dose of corticosteroids (500 mg of intravenous methylprednisolone

for 3 days), followed by a 0.8 mg/kg daily dose of prednisolone (PSL). On the third day of admission, his serum creatinine level had worsened to 8.51 mg/dL, and intermittent hemodialysis was initiated (Fig. 2).

A kidney biopsy was performed six days after the PSL treatment. Almost all of his glomeruli showed cellular crescents, segmental necrosis, and destruction of the Bowman's capsule. Light microscopy revealed fibrinoid necrosis in the small vessels and proliferation of vascular endothelial cells, interstitial fibrosis, and atrophy of the renal tubules (Fig. 3). Immunofluorescence staining for IgG, IgA, IgM, and C3c revealed negative results. We made a diagnosis of pauci-immune crescentic glomerulonephritis due to MPO-ANCA vasculitis, and the patient was started on rituximab (375 mg/m²).

His renal function improved 1 week after admission, and hemodialysis was discontinued 11 days after the admission. Rituximab was administered twice because of cytomegalovirus-associated hepatitis and thrombocytopenia. His general symptoms disappeared, serum creatinine level stabilized at 2.2 mg/dL, and nodular shadows on chest CT reduced in size. His BVAS was 7 at the time of discharge from the hospital.

Discussion

Several vaccines to prevent SARS-CoV-2 infection are available for use in different countries. They represent different vaccine types, including nucleic acid, adenovirus-vectored, protein-based, and inactivated vaccines (8).

The mRNA vaccines, which are nucleic acid vaccines,

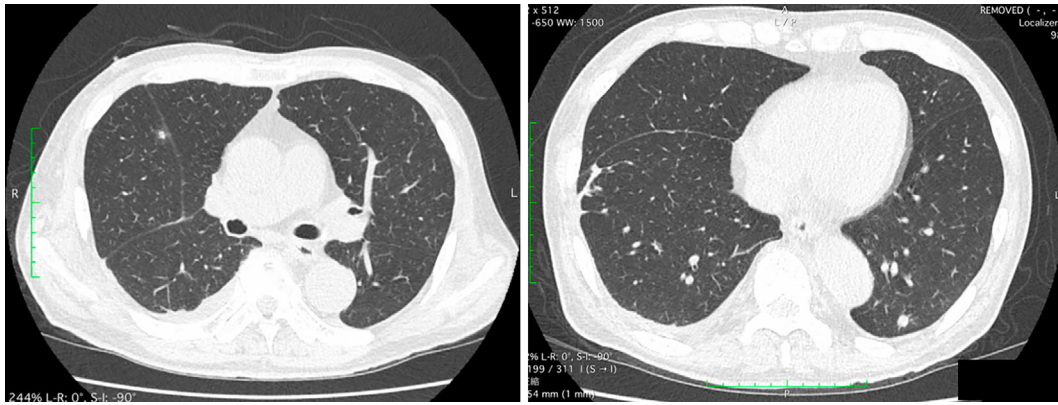


Figure 1. Chest computed tomography images obtained on admission show a few nodules.

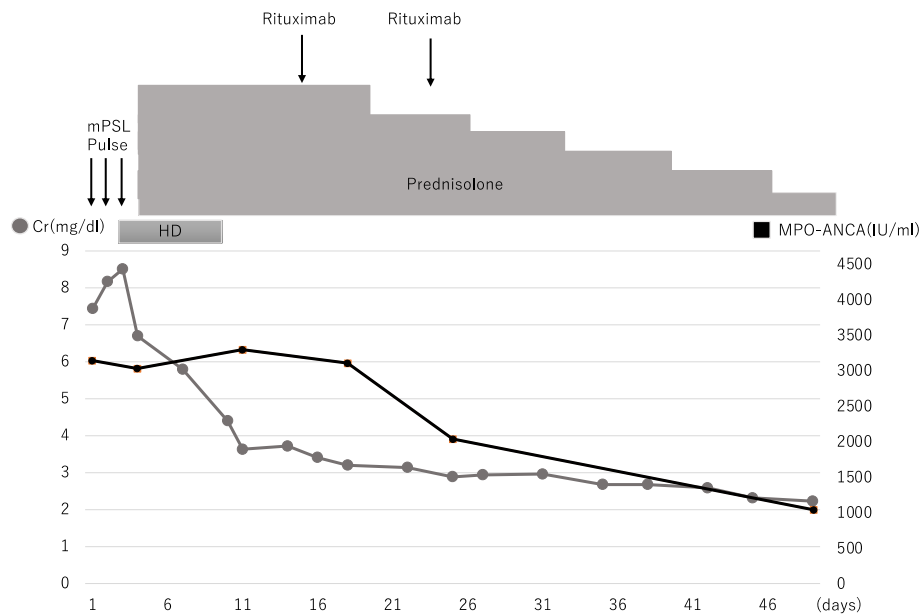


Figure 2. Clinical course. mPSL: methylprednisolone

have attracted considerable attention in terms of their preventive role against COVID-19. Moderna and Pfizer-BioNTech first developed their own mRNA vaccines, which are delivered in lipid nanoparticles to express a full-length spike protein. They have been designed to code for a receptor-binding domain of trimerized SARS-CoV-2 spike glycoprotein. The administration of these vaccines activates CD4+ and CD8+ T cells, and interferon- γ is secreted to protect against the virus (9).

The mRNA vaccines have been shown to be effective and safe. A clinical trial of these mRNA vaccines against COVID-19 reported 95% efficacy (10). Anaphylaxis (approximately 2.8-5 per million) and myocarditis/pericarditis (16 per million) emerged as severe complications following mRNA vaccine administration. However, there is no evidence of a significant causal relationship between vaccines and their side effects (4, 11). The mechanism of myocarditis/pericarditis following COVID-19 vaccination is supposed to be associated with the mRNA sequence that encodes the spike protein or the immune response that follows vaccina-

tion (12).

Renal-related autoimmune diseases, such as AAV, IgA nephropathy, and minimal change disease after COVID-19 vaccination (5-7), occur very rarely, and whether or not autoimmune diseases can be induced by vaccination remains unknown. AAV is an autoimmune disease characterized by vasculitis that causes vascular endothelial damage to small- and medium-sized vessels due to ANCA production (13). Patients with AAV have pathogenic autoantibodies that react to MPO or proteinase 3 (PR3) and exhibit necrotizing crescentic glomerulonephritis. Although the events causing AAV are not well understood, genetic factors, infectious agents, drugs, and environmental exposures may be responsible (14-17). Many case reports of autoimmune disease following influenza vaccination, including AAV, have been published (18-21).

Some mechanisms of vasculitis following influenza vaccination have been proposed. The first mechanism is molecular mimicry, in which a microbial antigen and a foreign antigen share structural similarities with self-antigens (20, 22).

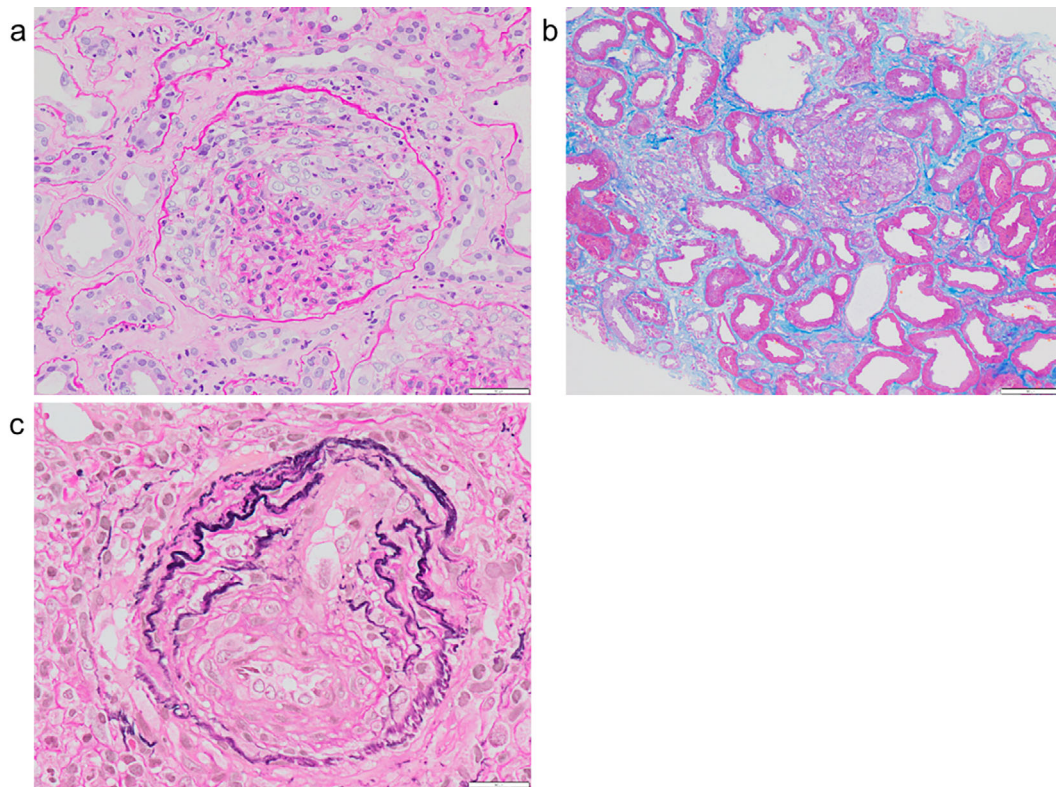


Figure 3. A renal biopsy performed one month after his second dose of the COVID-19 vaccine shows necrotizing and crescentic glomerulonephritis. (a) PAS-stained section shows cellular crescents of the glomeruli. 400×. (b) Masson-stained section shows interstitial fibrosis and atrophy of the renal tubules. 100×. (c) EVG-stained section shows the proliferation of the vascular endothelial cells and rupture of an elastic fiber. 1,000×.

The adjuvants contained in vaccines can provoke an autoimmune response. Viral RNA contained within the influenza vaccine reportedly stimulates the production of PR3-ANCA. Jeffs et al. studied the association between influenza vaccination and the onset of PR3-ANCA. They reported that specific influenza vaccines stimulated the production of PR3-ANCA *in vitro* and also found that the vaccines contained viral RNA, the natural ligand for human Toll-like receptor-7 (19).

These above mechanisms may be responsible for AAV developing after COVID-19 vaccine administration; however, AAV after SARS-CoV-2 infection has also been reported (23-25). The SARS-CoV-2 antigen and self-antigen have been suggested to be similar. In addition, it is believed that viral infection promotes the release of antigens that were originally isolated into the periphery or stimulates the natural immune response, resulting in an autoimmune response (22). This mechanism is non-specific to the antigen, and the COVID-19 vaccine may also trigger it.

Recently, a literature review of vaccine-associated AAV after COVID-19 vaccine that analyzed 29 cases was published (26). According to the review, most cases were secondary to mRNA vaccines (75.8%), with 24 patients developing new-onset AAV after vaccination (82.7%). Regarding ANCA subtypes of AAV, 15 cases were positive for MPO, 4 for PR3, and 3 for both (MPO and PR3). Of the 29 cases

reviewed, 27 had renal involvement (93.1%), and 10 had both lung and kidney involvement (34.4%). Most patients received immunosuppressive treatment, such as steroids, rituximab, or cyclophosphamide, and 10 of those 27 patients improved (37.0%), 9 showed partial improvement, and 5 were dependent on dialysis. They all responded relatively well to immunosuppressive therapy. In our case, the patient also responded favorably to corticosteroids and rituximab.

Whether or not AAV is induced by COVID-19 vaccination remains unclear; in this regard, we propose a connection between the vaccine and AAV. Recently, Asian reports of AAV after COVID-19 vaccination have been increasing in Japan, Taiwan, Nepal, and India (27-32). Because a third dose of the COVID-19 vaccine has been rolled out, clinicians should be aware of the possibility of new-onset AAV. It is also necessary to collect many cases of minor autoimmune diseases after vaccination for analyses.

In conclusion, when systemic symptoms are prolonged or renal abnormalities appear, clinicians should consider the possibility of AAV.

Informed consent was obtained from all individual participants included in the study.

The authors state that they have no Conflict of Interest (COI).

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