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*Chronic Disease*

*Case Report*

# ANCA-associated vasculitis following the CoronaVac vaccination

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***Abstract*:** With the coronavirus disease 2019 (COVID-19) pandemic, vaccination has become one of the cornerstones to contain the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Large clinical trials have shown high efficacy and safety of SARS-CoV-2 vaccination against COVID-19. However, with the widespread use of SARS-CoV-2 vaccines worldwide, an increasing number of reports describe the onset of glomerular disease. Here, we report a case of a 70-year-old Chinese woman who developed new antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis within 4 h post the first dose of CoronaVac. CoronaVac is an inactivated SARS-CoV-2 vaccine developed by Sinovac Life Sciences (Beijing, China). Her clinical symptoms were nausea, fatigue, acute kidney injury, and proteinuria. Laboratory tests showed markedly elevated serum myeloperoxidase titers, and the renal biopsy showed microcellular fibrous crescent formation. Renal function of the patient responded favorably after treatment with steroids and cyclophosphamide. Although there is no direct evidence of a link between vasculitis and vaccination, similar complications should be monitored as potential adverse events with widespread vaccination globally.

***Keywords:*** ANCA-associated vasculitis, COVID-19, glomerulonephritis, SARS-CoV-2, vaccination

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## Introduction

With the pandemic of coronavirus disease 2019 (COVID-19) and the emergence of new variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), human health has been seriously threatened and global economic and social activities have been severely disrupted.[1] Rapid and large-scale COVID-19 vaccination is urgently needed to contain disease outbreaks through generating herd immunity. Large clinical trials have shown high efficacy and safety of SARS-CoV-2 vaccination against COVID-19. Common adverse reactions include injection site tenderness, fever, fatigue, and pain.[2,3] However, with the widespread availability of SARS-CoV-2 vaccines worldwide, an increasing number of reports describe the occurrence of new or relapsed glomerular disease.[4]

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of necrotizing vascular inflammatory diseases characterized by ANCA positive in the blood circulation and inflammation and damage of small and medium vessels.[5,6] AAV is a rare disease with an annual incidence of approximately 20 per million population in Europe and North America.[7,8] Kidney is one of the important target organs involved in AAV, known as ANCA-associated glomerulonephritis (AAGN).[5,6] Here, we report a case of newly diagnosed AAGN within 4 h post the first dose of CoronaVac vaccine, an inactivated SARS-CoV-2 vaccine developed by Sinovac Life Sciences (Beijing, China).

## Case report

A 70-year-old Chinese woman presented with poor appetite and nausea 4 h after receiving the first dose of CoronaVac vaccine on 17 May 2021. Poor appetite and nausea progressively worsened, followed by fatigue and foamy urine 10 days later. Her medical history included hypertension, hyperlipidemia, and kidney stones. She had penicillin allergy and no family history of ANCA-associated vasculitis.

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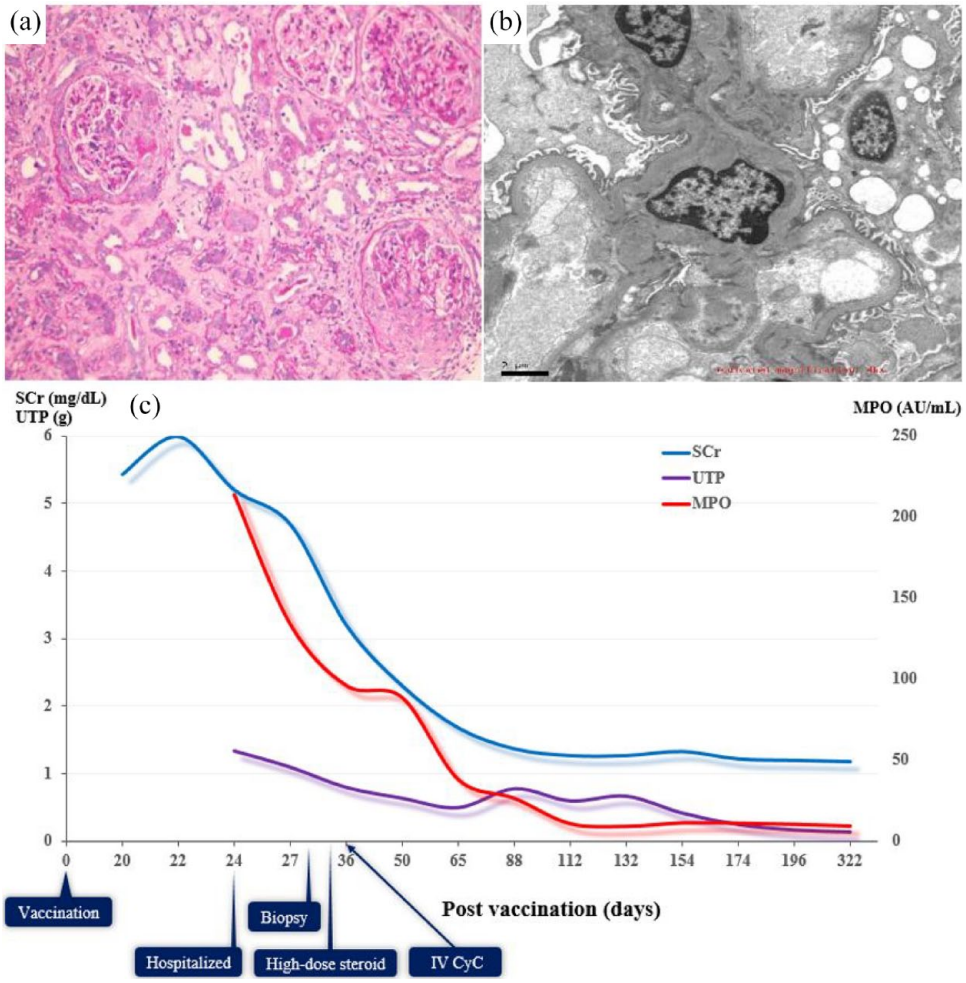


**Figure 1.** Histopathologic and clinical course. (a) Light microscope showing 6 glomerulosclerosis, 2 macrocellular, 8 macrocellular fibrous, 3 macrofibrous, 2 microcellular, and 2 microcellular fibrous crescent formations among the 34 glomeruli. (b) Electron microscopy showing capillary loops partial compression, parietal cells proliferation, and crescent formation. Immunofluorescence negative. (c) Time and clinical course of antineutrophil cytoplasmic antibody–associated glomerulonephritis after vaccination.
CyC, cyclophosphamide; MPO, myeloperoxidase; SCr, serum creatinine; UTP, 24-h urine protein.

Vital signs were stable on admission, and the physical examination was normal. The initial laboratory results at local hospital showed serum creatinine (Scr) of 5.43 mg/dl (baseline 0.54 mg/dl, 3 months ago), urine protein 2+ (baseline 1+, 3 months ago), and anti-myeloperoxidase antibody (MPO) 3+. Laboratory results in our hospital showed the Scr of 5.2 mg/dl, hemoglobin 10.3 g/l, MPO 214 AU/ml, perinuclear-ANCA + (1:10), and antinuclear antibodies + (H type 1:320). Urinalysis of 24-h urine protein was 1.33 g, and hematuria in urinary sediment was negative. Ultrasonography revealed normal renal. Computed tomography of the chest showed small pulmonary nodules. Additional serologic workup showed normal serum albumin, electrolytes, and C3/C4 levels. Anti-double-stranded DNA antibody was negative.

The kidney biopsy revealed 6 glomerulosclerosis, 2 macrocellular, 8 macrocellular fibrous, 3 macrofibrous, 2 microcellular, and 2 microcellular fibrous crescent formations under light microscope among 34 glomeruli (Figure 1(a)). Electron microscopy showed capillary loops partial compression, parietal cells proliferation, and crescent formation (Figure 1(b)). Immunofluorescences were all negative.

Combined with clinical features and biopsy findings, the diagnosis was ANCA-associated glomerulonephritis (AAGN). Treatment for AAGN was initiated immediately (high-dose i.v. glucocorticoids 0.5 g, followed by i.v. cyclophosphamide 0.2 g plus oral low-dose steroids maintenance therapy). Follow-up by 5 April 2022, the patient's renal function and urine output improved significantly. Figure 1(c) showed the clinical course since the vaccination.

## Discussion

With the widespread availability of SARS-CoV-2 vaccines worldwide, an increasing number of reports describe the occurrence of new or relapsed glomerular disease, including minimal change disease, membranous nephropathy, IgA nephropathy, and ANCA-associated glomerulonephritis.[4] Most reports are related to mRNA vaccines, and there are a few reports related to adenoviral vector vaccines and inactivated vaccines. To the best of our knowledge, this is the first domestic report of AAGN following CoronaVac vaccination so far.

The safety of the CoronaVac vaccine has been widely demonstrated[2]; however, in this case, environmental and genetic factors might have laid the foundation for the development of vasculitis. The relationship between AAV pathogenesis and COVID-19 vaccines is unclear, and molecular mimicry and cross-reactivity are thought to be triggers of auto-inflammatory disease.[9] It is reported that the spike protein of SARS-CoV-2 has homology to human tissues.[10] CoronaVac is developed using whole-virion inactivated Vero cells that retain SARS-CoV-2 antigenic components to induce antiviral neutralizing immunoglobulins.[11] Immunoglobulins may cross-react with human tissue antigens,[12] leading to cytokine storms caused by excessive immune response in susceptible individuals. Cytokine storm may promote the occurrence of autoimmune diseases. CoronaVac contains an aluminum-based compound adjuvant to improve inherently immunogenicity, which allows easier and more efficient recognition of 'non-self'.[13] This in turn allows triggering adaptive and innate immune responses, which may elicit post-vaccination adverse reactions known as 'autoimmune syndrome induced by adjuvants'.[14]

SARS-CoV-2 vaccination with different strategies and designs can initiate and enhance innate and adaptive immune responses by activating neutrophils, B cells, and T cells.[15] The development of AAV has been observed after SARS-CoV-2 infection and vaccination.[4,16] This evidence supports the hypothesis that immune responses to viruses and vaccines may generate ANCA in genetically susceptible individuals, leading to the development of AAV. Possible mechanisms include polyclonal activation, molecular mimicry, or systemic pro-inflammatory cytokine responses. The individuals with compromised immune systems are prone to reduced nucleic acids clearance of neutrophil extracellular traps (NETs).[17] Pro-inflammatory cytokines activate neutrophils, leading to the formation of NETs or the release of reactive oxygen species and lytic enzymes. NETs may be a double-edged sword. Although NETs play an important role in host defense, dysregulation of NETs can lead to vascular lesions and ANCA production.[6] NETs envelop a large number of damaging proteins (including MPO and anti-protease 3 antibody), which can directly damage the vascular endothelium and activate the alternative complement pathway to promote the development of vasculitis. NETs are also a key step in the pathogenesis of cytokine storm in ANCA-associated vasculitis triggered by COVID-19.[16]

Although we have not obtained direct evidence of a link between vasculitis and vaccination, the time of symptoms onset shortly after vaccination should be regarded as an induced event. Further studies are needed to elucidate the potential mechanism linking COVID-19 vaccine and AAV.

## Conclusion

In summary, CoronaVac has been proven to have great practicability and sufficient security advantages. The protection provided by vaccination exceeds the rare potential risk in the era of COVID-19 pandemic. We emphasize that people should continue to use vaccination, because AAV after vaccination is rare. Careful safety monitoring should be continued to assess the potential risks of vaccines.

## Declarations

### *Ethics approval and consent to participate*

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University with approval number No. [2021] 016. The authors declare that they have obtained a written informed consent from the patient discussed in the report.

### *Consent for publication*

All authors have all read and approved the final version of the manuscript and the patient provided their consent for publication.

### *Author contributions*

**Yaohui Ma:** Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Writing – original draft.

**Tianlun Huang:** Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Writing – original draft.

**Gaosi Xu:** Conceptualization; Project administration; Supervision; Validation; Visualization; Writing – review & editing.

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### *Competing interests*

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### *Availability of data and materials*

Not applicable.

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