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## Acute tubulointerstitial nephritis following COVID-19 mRNA vaccine: A case report

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### ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease-19 (COVID-19), still affects the world, as studies for vaccinations and treatments continue. One of the many types of COVID-19 vaccines is the messenger RNA (mRNA) vaccine. Several side effects of this type of vaccine have been reported in the literature, including renal complications. However, acute tubulointerstitial nephritis (ATIN) is a very rare complication of COVID-19 mRNA vaccine. Here we present a 50-year-old, previously healthy female who presented with renal failure following a COVID-19 mRNA BNT162b2 (Pfizer-BioNTech) vaccination and diagnosed as ATIN in the kidney biopsy. To the best of our knowledge, only two cases of ATIN following COVID-19 vaccine have been reported and one of them had an underlying kidney disease. This is the second case of ATIN following COVID-19 vaccine in a healthy individual.

### Implication for health policy/practice/research/medical education:

Side effects of COVID-19 vaccine have been reported in the literature, including renal complications. Acute tubulointerstitial nephritis (ATIN) is a very rare complication of COVID-19 mRNA vaccine. This is the second case of ATIN following COVID-19 vaccine in a healthy individual.

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### Introduction

Over the years, vaccines decreased the morbidity and mortality of various infections and also helped to eradicate fatal infectious diseases. Vaccines expose the body to a harmless antigen and by that way they provoke an immune response in the body. This immune response provided by the vaccine prevents the disease or makes the symptoms milder.

Coronavirus disease-19 (COVID-19), due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 (1). Currently, there is no specific medicine for this disease. COVID-19 vaccines have been rapidly developed towards the end of 2020 since, widespread use of these vaccines is still urgently needed for both disease prevention and control.

After the detection of this novel coronavirus, many studies on COVID-19 vaccines have been conducted. Several types of SARS-CoV-2 vaccines have been

developed, including live attenuated, inactivated and recombinant vector vaccines (2).

DNA and RNA vaccines are both nucleic acid vaccines, based on the viral genetic sequence. mRNA vaccines contain the selected sequence of the viral gene. This sequence is translated in the cytoplasm of the host cell and target antigen is produced (3, 4). The first mRNA vaccine for COVID-19 was mRNA-1273 (NCT04283461), developed by Moderna and the second mRNA vaccine for COVID-19 was BNT162 (NCT04368728) which developed by BioNTech/Pfizer (5).

Acute tubulointerstitial nephritis (ATIN) is associated with an immune-mediated infiltration of the renal interstitium by inflammatory cells. Patients often present with non-specific symptoms, which can lead to delay in diagnosis and treatment of the disease. Among the numerous causes of ATIN, the most common one is drug use. Patient's history of a previously diagnosed

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autoimmune condition, concomitant infections or recently administered drugs can help support a specific etiology of ATIN.

Imaging methods and urine analysis are of little diagnostic value. In sonographic or tomographic evaluation, kidneys affected by ATIN are usually normal or slightly increased in size. Urine cellularity and casts have been conducted to localize kidney inflammation. A definite diagnosis can only be established by a kidney biopsy that confirms and assesses the extent of interstitial inflammation. ATIN is a histologic diagnosis characterized by inflammatory cells in the interstitium and in the tubular epithelium.

Here we present the case of a 50-year-old, previously healthy female patient with histologically confirmed ATIN, following a COVID-19 mRNA BNT162b2 (Pfizer-BioNTech) vaccination. In this case, no apparent underlying cause for the etiology of ATIN could be found from patient history and diagnostic tests performed, except for the history of a COVID-19 mRNA BNT162b2 (Pfizer-BioNTech) vaccination prior to the onset of symptoms.

### Case Report

A 50-year-old previously healthy female patient presented to our nephrology department upon referral due to an acute kidney injury (AKI) diagnosis. She had persistent complaints of fatigue, headache, myalgia, nausea and vomiting following both doses of the Pfizer-BioNTech (BNT162b2) COVID-19 vaccine. Both episodes lasted about three weeks after vaccination. The patient applied to an internal medicine clinic with these complaints three weeks after the second dose of vaccination, where she was diagnosed with renal failure and referred to a nephrologist.

The patient appeared pale and unwell during our evaluation. Patient history was not remarkable for any disease or medication except for the current vaccinations. Physical examination revealed mild tachycardia. Primary laboratory workup results can be found in Table 1. The patient was admitted for further examination.

Ultrasonic Imaging of the urinary system was normal. Urinalysis results included normoglycemic glycosuria and proteinuria of 322 mg/d. Urine culture, hepatitis and HIV serology were negative. Anti-DNA, ANA (antinuclear antibody), anti-neutrophil cytoplasmic antibodies (p and c) tests were also negative. Urine sediment analysis on a phase contrast microscope revealed 4-6 renal tubular epithelial cells and plenty of leukocytes. A peripheral smear was conducted, for the workup of anemia, revealing a rouleaux formation of erythrocytes. Immune and hemoglobin electrophoreses were unremarkable. Computed tomography (CT) imaging of the thorax was obtained to exclude granulomatous diseases.

After administering 24 hours of intravenous fluid

therapy and two sessions of hemodialysis, renal biopsy was performed. Kidney biopsy was examined both under light microscopy and immunofluorescence microscopy. Biopsy contained fourteen glomeruli and was adequate for evaluation. In hematoxylin-eosin-stained sections, marked inflammatory cell infiltration was observed in the interstitial area, consisting of polymorphonuclear leukocytes, lymphocytes, plasma cells and histiocytes. Inflammatory infiltration was usually found concentrated around the tubules and occasionally infiltrating the tubules. No significant pathological changes were observed in the glomeruli other than mild expansion of the Bowman's space seen in nearly half of the glomeruli. The vascular structures also showed no pathological changes. Pathological features seen in the kidney biopsy are shown in Figure 1. In the immunofluorescence microscopy examination, no deposits were detected by antibodies to IgG, IgA, IgM, C3, C4 and C1q. The histopathological findings were consistent with ATIN.

Following pulse steroid treatment, the patient's serum creatinine level declined to 4.99 mg/dL. Through two months of follow-up, creatinine levels further declined to 1.6 mg/dL.

### Discussion

Adverse events that might be connected to several vaccines have been reported throughout the years. A combination of factors such as the number of people who experienced the event and the time between vaccination and development of potential side effects are important in the evaluation of these reports. It is crucial to acknowledge that although vaccination is by far the most effective approach to stop the COVID-19 pandemic, various adverse effects may accompany, as is the case with any other intervention.

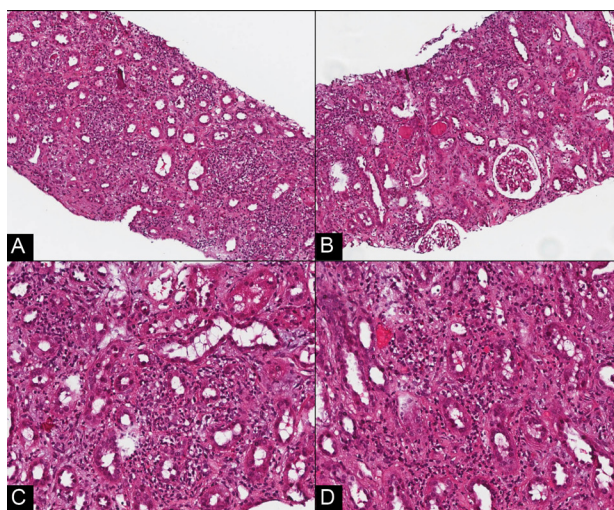
Kidney diseases such as COVID-19-associated nephropathy (COVAN), a new type of collapsing glomerulopathy associated with COVID-19, acute tubular injury, thrombotic microangiopathy, acute interstitial nephritis, focal and segmental glomerulosclerosis, membranous nephropathy, minimal change disease, immune complex-mediated glomerulonephritis/lupus nephritis, membranoproliferative glomerulonephritis, anti-glomerular basement membrane disease, IgA nephropathy, crescentic glomerulonephritis, light chain cast nephropathy, myoglobin cast nephropathy and acute pyelonephritis have been reported in native biopsies (6). In the study by May et al, the most common diagnosis in native biopsies was found to be collapsing glomerulopathy, present in 25.8% of the patients (6).

Different COVID-19 vaccines have been developed over the course of the pandemic, with the names Pfizer-BioNTech (BNT162b2) COVID-19 vaccine, Moderna (mRNA-1273) COVID-19 vaccine, Janssen (JNJ-

**Table 1.** Laboratory test results of the patient before vaccination, after vaccination and in the course of treatment

Parameters	Basal	After vaccination	After pulse steroid treatment	Second week of treatment	First month of treatment	Sixth week of treatment	Second month of treatment	Third month of treatment	Reference range /Unit
Leukocyte	5.9	9.82	12.87	17.7	9.88	11.86	14.23	10.92	4.5-11 ×10 <sup>3</sup> /μL
Hemoglobin	13.2	9.2	10	14.5	12.1	12.6	12	12.2	11.7-16 g/dL
Platelets	264	396	278	327	183	257	213	218	150-400 ×10 <sup>3</sup> /μL
Neutrophil	3.1	7.58	11.33	12.45	5.62	6.91	10.2	5.57	1.4-6.4 ×10 <sup>3</sup> /μL
Lymphocyte	5.9	1.29	0.91	3.61	3.54	4.22	2.97	4.59	1-4.8 ×10 <sup>3</sup> /μL
Eosinophil	0.3	0.19	0	0.11	0.14	0.03	0.07	0.13	0-0.17 ×10 <sup>3</sup> /μL
CRP	3.1	107.8	16.7	4.2	3.7	19.8	5.7	3.8	<8.5 mg/L
GFR (CKD-EPI)	80	4	9	12	13	33	37	42	mL/min/1.73m <sup>2</sup>
Total protein		7.4	6.4		6.6				6.4-8.3 g/dL
Albumin		3.8	3.5		4.1	4.4		4.2	3.5-5.2 g/dL
ALT	15				91	57		24	0-55 U/L
AST	19				40	22		16	0-32 U/L
Urea	20	117			44.7	54	51.4	42.6	<43 mg/dL
Creatinine	0.87	9.25	4.99	3.34	1.98	1.75	1.6	1.44	0.5-0.9 mg/dL
Uric acid		4.1			2.5	3.4			<5.7 mg/dL
Sodium		134	134	133	135	140		143	136-145 mmol/L
Potassium		4	3.7	5.5	4	4.2		4.4	3.5-5.2 mmol/L
Calcium		8.8	7.8	9.4	8.9	9.9		9.6	8.6-10.2 mg/dL
Phosphorus		4.8	3.3		3			3.8	2.7-4.5 mg/dL
Magnesium		1.7	1.9		1.85	1.99		2.04	1.6-2.6 mg/dL
SARS-CoV-2 PCR		Negative							
HBV, HCV, HIV		Negative							
ANA, Anti-dsDNA		Negative							
Anti-GBM		Negative							
ANCA		Negative							
RF		Negative							
Cryoglobulin		Negative							
C3		Negative							
C4		Negative							
SPEP		Normal							
Serum/urine IFE		Normal							
Diuresis		2.4	2.6						L/day
ESR		106			9	16			<20mm/h

SPEP, Serum protein electrophoresis, IFE, Immunofixation electrophoresis, ESR, Erythrocyte sedimentation rate, GFR, Glomerular filtration rate; CRP, C-reactive protein; ALT, alanine transaminase; AST, aspartate transaminase; ANCA, anti-neutrophil cytoplasm antibody; GBM, glomerular basement membrane.



**Figure 1.** Infiltration of polymorphonuclear leukocytes, lymphocytes and plasma cells in the interstitial area, more prominent around the tubules and occasionally infiltrating the tubules (Hematoxylin-Eosin $\times 100$ ) B: Mild expansion of the Bowman's space (Hematoxylin-Eosin $\times 100$ ) C-D: High-power view of the mixed interstitial inflammatory cell infiltration (Hematoxylin-Eosin  $\times 200$ ).

78436735) COVID-19 vaccine, Sinovac-CoronaVac and Oxford/AstraZeneca COVID-19 vaccine. Adverse effects regarding different organs and systems, including renal adverse effects, have been reported with each of these vaccines. Until now, recurrent and de novo IgA nephropathy, recurrent and de novo minimal change disease, membranous nephropathy, lupus nephritis, anti-neutrophil cytoplasmic antibody-associated vasculitis and granulomatous vasculitis have been reported as renal complications of different COVID-19 vaccines. It is important to keep in mind that a vast majority of COVID-19 vaccine recipients did not experience any renal adverse effects. In addition, potential relapses of a pre-existing diseases should always be kept in mind when dealing with post-vaccine kidney failure.

In our case, patient was diagnosed with ATIN as a result of clinical, laboratory and pathological findings. ATIN is a relatively rare complication of COVID vaccines, with two cases reported until now to the best of our knowledge. The case reported by de la Flor Merino et al from Spain presented with pre-existing chronic kidney disease and developed ATIN following the Pfizer-BioNTech (BNT162b2) COVID-19 vaccine (7). The patient was diagnosed with ATIN based on blood and urine tests, pathological and radiological examinations. After excluding drugs, autoimmune and infectious etiologies of ATIN, it was concluded that ATIN following BNT162b2 Vaccine was the reason of AKI in that patient. A slow clinical response was obtained following steroid therapy. Dheir et al, reported a case of ATIN after the first dose of Pfizer-BioNTech (BNT162b2) COVID-19 vaccine,

in a patient without any underlying disease (8). Steroid treatment was given and the clinical course gradually improved with complete recovery. The authors found no other etiology explaining the sudden onset of renal failure and attributed the clinical picture as the side effect of Pfizer-BioNTech (BNT162b2) COVID-19 vaccine. Similar to our case report, having excluded the causes that may have caused ATIN, the only possible cause was recent vaccination.

### Conclusion

Various renal complications have been reported due to various vaccines, although they are rare. Several renal complications of different types of COVID-19 vaccines have also been reported. However, ATIN is a very rare complication of COVID-19 mRNA vaccine, especially in otherwise healthy individuals.

### Authors' contribution

GK and EH were the principal investigators of the study. AS, BO and SA were included in preparing the concept and design. GK and EH revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

### Conflicts of interest

The authors declare that they have no competing interests.

### Ethical issues

This study was approved by Ministry of Health Platform of Scientific Study (2021-12-06T17-07-09). Written informed consent was obtained from the patient for publication of this case report and histopathological images. Additionally, Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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