Title

‘Granulomatosis with polyangiitis after Pfizer vaccination’: a case report

Authors

Essien, Francis
Evans, Jordan
Kyle, Andrew
et al.

Publication Date

2022

DOI

10.1177/26330040221130084

THERAPEUTIC ADVANCES in
Rare Disease

Case Report

'Granulomatosis with polyangiitis after Pfizer vaccination': a case report

Ther Adv Rare Dis

2022, Vol. 3: 1–7

DOI: 10.1177/26330040221130084

Francis Essien, **Jordan Evans**, **Andrew Kyle**, **Anatoly Urisman** and **Nicholas Adams**

***Abstract*:** The advent of COVID-19, caused by the SARS-CoV-2 virus, has resulted in over 541 million cases with 6.32 million deaths worldwide as of June 2022. The devastating consequences of this global pandemic resulted in the expedited generation of mRNA-based vaccines such as the Pfizer-BioNTech and Moderna vaccines. Although the vaccines have been effective, with recent data indicating greater than 95% effectiveness, rare complications have been reported, including manifestations of autoimmune phenomena. Herein, we report a rare case of Granulomatosis with polyangiitis (GPA) in an active duty military male soon after receiving the first dose of the Pfizer-BioNTech COVID-19 vaccine.

Plain Language Summary

A 27-year-old active duty marine was admitted to our hospital after being transferred from Hawaii with concern of new autoimmune disease after receiving the Pfizer vaccine. The patient initially presented to the emergency department with joint pain, fever, chest pain, hemoptysis, and a nose bleed. A comprehensive workup demonstrated elevated inflammatory markers, progressive renal dysfunction, and a positive antibody panel consistent with antineutrophil cytoplasmic antibodies (ANCA) vasculitis. Due to the limited capabilities in his deployed setting, he was transferred to our hospital for a higher level of care. We performed some additional tests to include computed tomography (CT) imaging of his lungs and a renal biopsy which came back consistent with GPA. The patient was started on high-dose prednisone and rituximab, and he achieved remission. He was discharged from the hospital with follow-up arranged with rheumatology and nephrology. He remained in remission on follow-up.

Keywords: ANCA vasculitis, COVID-19 Pfizer vaccine, granulomatous with polyangiitis, hemoptysis, pauci-immune glomerulonephritis

Received: 24 May 2022; revised manuscript accepted: 14 September 2022.

Correspondence to:
Francis Essien
Department of Internal Medicine, David Grant USAF Medical Center, Travis Air Force Base, 101 Bodin Circle, Fairfield, CA 94535, USA.
Franksophia15@gmail.com

Jordan Evans
Division of Nephrology, Department of Internal Medicine, David Grant USAF Medical Center, Travis Air Force Base, Fairfield, CA, USA

Andrew Kyle
Department of Internal Medicine, David Grant USAF Medical Center, Travis Air Force Base, Fairfield, CA, USA

Anatoly Urisman
Department of Pathology, University of California San Francisco, San Francisco, CA, USA

Nicholas Adams
Department of Radiology, David Grant USAF Medical Center, Travis Air Force Base, Fairfield, CA, USA

Introduction

Granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis) is a rare necrotizing vasculitis that predominantly affects small-sized arteries throughout the body, often manifesting in the upper and lower respiratory tracts as well as the kidneys.[1] It belongs to the classification of rare autoimmune diseases collectively known as the antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) which, in addition to GPA, also include eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg–Strauss syndrome) and microscopic polyangiitis (MPA).[1] The clinical

presentation of GPA is characterized by the formation of necrotizing granulomatous lesions within small vessels. The most common clinical manifestations occur in the nose and sinuses, lungs, and kidneys.[2] The pathogenesis of how exactly these ANCAs develop in some patients remains elusive, but there is increasing evidence of genetic and environmental factors playing a role.[3,4] Previous literature has suggested chronic nasal colonization with *Staphylococcus aureus* increases the incidence of GPA due to the production of autoantibodies generated by the unmethylated cytosine–guanine dinucleotide (CpG) motifs in the bacterial cell wall.[4] In those patients who may have underlying ANCA production, the compounding interaction results in hyperactivation of abnormal B and T cells, generation of reactive oxygen species, and production of neutrophil extracellular traps (NETs) which contain the respective antigens of PR3 and MPO.[4–6] Recently, there has been an increase in case reports in the literature of new onset AAV developing after either infection with the COVID-19 virus or exposure to COVID-19 antigens via the vaccines.[7–10] Herein, we present a rare case of GPA with pauci-immune glomerulonephritis that developed in a young active duty military male after receiving the COVID-19 vaccine.

Case report

A 27-year-old active duty Marine with no pertinent prior medical or significant family history received his first dose of the Pfizer-BioNTech mRNA vaccine in late September 2021 while stationed overseas in Japan. Four days after vaccination, the patient reported polyarthralgias, fever, and diffuse myalgias to his primary doctor. These symptoms were attributed to general immunization side effects, and patient was sent home with acetaminophen. Three weeks later, the patient presented to the emergency department (ED) with persistent arthralgias, severe positional chest pain and dyspnea on exertion. Based on his symptoms and laboratory evidence, he was diagnosed clinically with pericarditis and discharged on colchicine and celecoxib. In the following 10 days, patient had two additional ED visits with worsening chest pain, dyspnea, resting tachycardia, and sinus pain with epistaxis, palpable purpuric rash on the lower extremities, gingival bleeding, and elevated C-reactive protein. He was started on a short burst of prednisone 40 mg which alleviated his symptoms; however, upon cessation, all symptoms returned. His severe symptoms rapidly returned upon cessation of steroids.

The patient was restarted on high-dose oral prednisone and to transferred back to the United States for higher level of care with rheumatology specialists for expedited workup of a rapidly progressive multi-system inflammatory pathology. Once transferred, an extensive workup was conducted including the laboratory data which can be seen in Table 1. Of note, chart review into the patient's prior history showed that his baseline serum creatinine values had been 0.8 to 1 mg/dl for years and that he had never previously showed any evidence of proteinuria or hematuria on past urinalyses. Computed tomography (CT) scan of the chest was performed and showed confluent centrilobular ground glass opacities which were thought to represent either atypical infection or mild alveolar hemorrhage (Figure 1(a) and (b)). Transthoracic echocardiogram was performed, but was unremarkable with only trace pericardial effusion seen. Bronchoscopy and nasoscopy were also conducted and demonstrated diffuse erythema and inflammation, but there was no direct evidence seen of diffuse alveolar hemorrhage and no biopsies were taken. While the patient's symptoms did improve with oral steroids, his proteinuria and microscopic hematuria persisted, prompting nephrology consultation and eventually, renal biopsy. Pathology from the biopsy (Figure 2) demonstrated pauci-immune glomerulonephritis with early crescent formation, segmental fibrinoid necrosis, and mild acute tubular injury. Collective clinical, laboratory, and biopsy data were supportive of diagnosis of GPA with associated glomerulonephritis.

After discharge, the patient was started on induction therapy with rituximab 1000 mg IV for 2 doses on day 0 and 15, oral prednisone taper, and losartan. Within 1 month of induction, his clinical symptoms resolved, hemoglobin trended back to baseline, and urine protein to creatinine ratio significantly improved by >50% to 910 to 360 mg/g.

Discussion

With the spread of COVID-19 infections worldwide, there have also been increasing reports of autoimmune diseases flaring or developing *de novo* after either vaccination or infection with COVID-19. Reports cannot determine causation; they only convey temporal and clinical correlation. However,

Table 1. Summarized laboratory data during clinical evaluation.

Lab	Value	Reference
SARS-CoV-2 RNA PCR	Not detected	Not Detected
Eosinophil count	1.44 (H)	0–0.45 cellsx10^9/L
Hemoglobin	10.7 g/dl (l)	13–18 g/dl
C-reactive protein	6.2 mg/l (H)	<2.9 mg/L
Creatinine	1.22 mg/dl	0.7–1.2 mg/dl
Urine protein/creatinine ratio	909 mg/g (H)	
Serum albumin	2.6 g/dl (l)	3.5–5.2 g/dl
UA RBC	31–50/HPF (H)	<5 /HPF
Troponin I	<0.015 ng/ml	0.0–0.015 ng/ml
ProBNP	55 pg/ml	0–125 pg/ml
TSH	0.22 uIU/ml	0.27–4.2 uIU/ml
Immunologic		
Antiproteinase 3 Ab	>100 (H) U/ml	0.0–3.5 U/ml
Anti-GBM Ab	3 units	0–20 units
Myeloperoxidase Ab	<9.0 U/ml	0.0–9.0 U/ml
ANA	Negative	Negative
Rheumatoid factor	<10 IU/ml	0–20 IU/ml
Perinuclear Ab	<1:20	<1:20
C-ANCA	1:320	<1:20
Atypical ANCA	<1:20	<1:20
Anti-Histone Ab	0.4	<1.0
TPMT activity	24.2 units/ml RBC	15–24 u/ml RBC
Cryoglobulin	None detected	None detected at 72 hours
Beta-2 Glycoprotein IgG	<9 IgG Units	0–20 IgG Units
C3	102 mg/dl	82–167 mg/dl
C4	15 mg/dl	16–48 mg/dl
HIV	Not detected	Negative
Gonorrhea/Chlamydia	Negative	Negative
Hepatitis C core Ab	Non-reactive	Negative
Hepatitis B Surface Ag	Negative	Negative

ANA, Antinuclear antibody; c-ANCA, Antineutrophil cytoplasmic antibody; HIV, human immunodeficiency virus; RBC, red blood cells; RNA, ribonucleic acid; TPMT, thiopurine methyltransferase; TSH, Thyroid stimulating hormone; UA, Urinalysis.

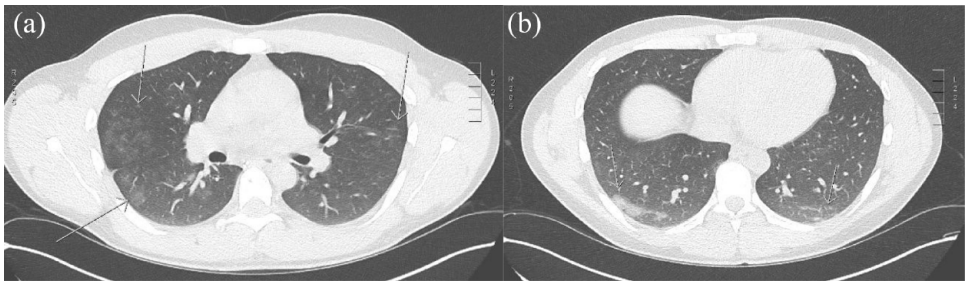

Figure 1. Peripheral subpleural consolidation, right greater than left (a) in the setting of confluent centrilobular ground glass opacities with peripheral sparing (b).

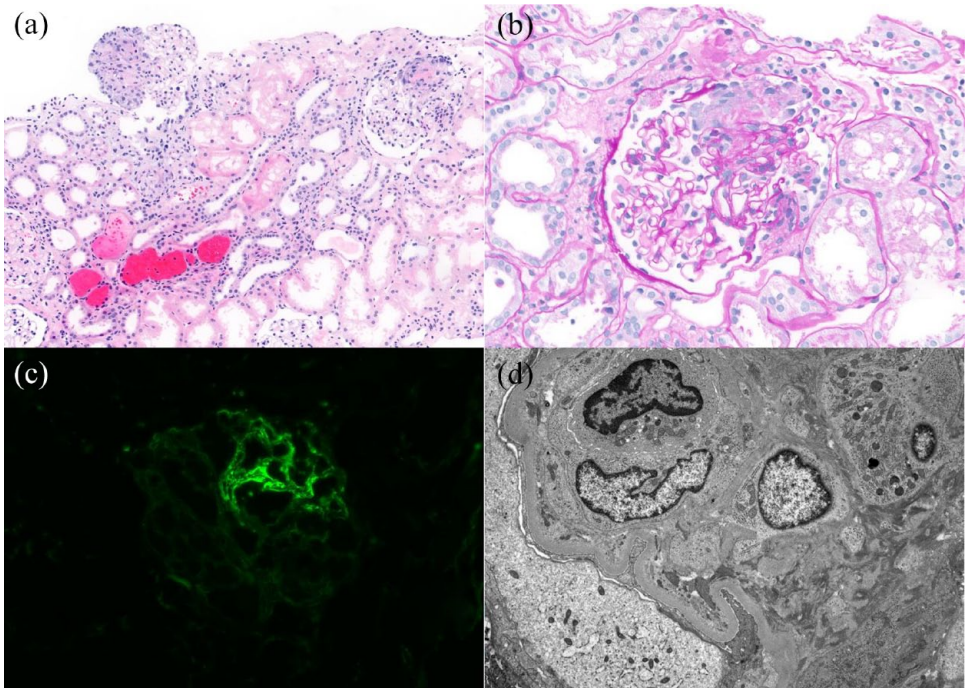

Figure 2. Biopsy findings: (a) histologic section stained with hematoxylin and eosin reveals blood and red blood cell casts in the tubular lumens. Two glomeruli demonstrate segmental fibrinoid necrosis surrounded by marked hypercellularity suspicious for crescents. Some tubules appear dilated and show features of acute tubular epithelial cell injury. No significant chronic changes are seen (200× magnification). (b) Periodic acid Schiff stain with one of the two glomeruli shown at higher magnification confirms a small crescent with fibrin adjacent to an area of segmental mesangiolysis (400× magnification). (c) Immunofluorescence stain for fibrin highlights a glomerular segment with fibrinoid necrosis (400× magnification). (d) Electron microscopy image shows a distended glomerular capillary lumen with endocapillary hypercellularity adjacent to an area of mesangiolysis and fibrin accumulation (bottom right). Diffuse podocyte foot process effacement is seen (4800× magnification).

as evidence for similar clinical or pathophysiologic presentations builds, the case for a true association builds. The Vaccine Adverse Events Reporting System (VAERS) is a joint venture by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) and is a mechanism by which these aggregate reports are passively submitted. Through VAERS, these regulatory bodies can further investigate potential adverse events that have sufficient evidence from individual reporters.[11] In a query of this database for 'vasculitis' and the 'Pfizer COVID-19 vaccine', a total of 6 reports were located which demonstrated sufficient evidence for an ANCA-associated

vasculitis.[12] More comprehensive publications of nearly 600,000 VAERS reports for all COVID-19 vaccines have demonstrated four common adverse events: cerebral thrombosis, Guillain–Barré syndrome, myocarditis, and pericarditis.[2] Although these are certainly not comprehensive representations of all pathology that may have occurred nationally, it does indicate that ANCA-associated vasculitis appears to be relatively rare post-vaccination for COVID-19.[2,12]

While the raw VAERS data can convey a rough estimation of the incidence of a specific symptom or disease, case reports contribute significantly more to the understanding of the specific clinical presentation of these patients. In addition to our case, others have been published in the past months. Selevaraj *et al.*[7] recorded a case of COVID-19 and GPA in 2020 who presented with clinical symptoms of vasculitis, worsening renal function, and positive c-ANCA/PR3 antibodies 1 month after infection with COVID-19. Hussein *et al.*[9] in 2020 reported a case in which a 37-year-old woman initially presented with alveolar hemorrhage determined to be due to GPA and was subsequently found to also be positive for COVID-19 infection at the time as well. In 2021, Lind *et al.*[13] reported a case in which a patient with suspected underlying GPA had a severe flare of his disease after COVID-19 infection causing alveolar hemorrhage. In addition to an association with COVID-19 infections, there have also been reports of AAV cases developing after COVID-19 vaccination. Shakoor *et al.* reported a case of new onset renal limited MPO-positive AAV after receiving the Pfizer-BioNTech vaccine. Hakroush and Tampe reported a rare combination of pauci-immune glomerulonephritis and rhabdomyolysis in a patient following Pfizer-BioNTech vaccination.[14,15] In early 2022, Shirai *et al.*[16] reported the case of a previously healthy woman who, after receiving the Pfizer-BioNTech COVID vaccine, developed vertigo, hearing loss, and sinusitis with a positive PR3-ANCA, clinically consistent with GPA.

Historically, the association between autoimmune or autoinflammatory diseases and vaccines or adjuvants has been of significant interest due to a concern of adverse events contributing to vaccine hesitancy. This challenges the medical community produce quality evidence regarding the incidence of such adverse events. One challenge in studying these clinical phenomena is the broad spectrum of clinical presentation concerning for autoimmune processes after vaccination. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) is an umbrella term that has been used to categorize and document some of these presentations that are temporally associated with vaccination.[17] In a recent review, Watad *et al.* studied 500 ASIA cases over a 3-year period reported in the ASIA registry and analyzed the frequency of different manifestations of autoimmune processes after vaccination. Results showed more than 40 separate autoimmune diseases after vaccination which occurred predominantly in women with a mean age of 43 years. The most common disease reported was undifferentiated connective tissue disease, which was associated with 14 different vaccines and six different foreign materials or adjuvants.[17]

In reviewing the data relevant to our case, only two of the 500 cases in Watad *et al.*'s review were ANCA-associated vasculitis.[17] In a separate publication, Watanabe reviewed the association between influenza vaccination and vasculitis. Data showed that while rare, 65 cases of vasculitis had been ported at that time with a significant temporal relation to influenza vaccination. This review also found the majority of cases presenting in females and in the elderly. Of 65 cases, 17 were ANCA-associated vasculitis, with seven being granulomatosis with polyangitis.[18] Our assessment of the incidence of ANCA-associated vasculitis following vaccination with Pfizer-BioNTech COVID-19 is similar to the incidence that occurs after vaccination in general. It is extremely rare but does occur.

In our presented case, compelling evidence implies at least an association between the administration of the COVID-19 vaccine and the onset of his AAV symptoms. Of course, causation in this case cannot be proven, but the patient had previously had no significant past medical history, no family history of AAV or autoimmune disease, no prior GPA symptoms, and no hematuria or proteinuria on multiple urinalyses over several years prior to the vaccination. The likelihood of GPA spontaneously developing in a young, healthy 27-year-old within a 1-month time window after getting the vaccine but with no relation to the vaccination seems improbable at best. There does remain the possibility of underlying low titers of ANCAs and PR3 antibodies being present in the serum prior to the vaccination that then flared up in production and the associated vasculitis complications as a result of the inflammatory response to the vaccination, but we do not

have any serologic data prior to the vaccination to prove or disprove this theory.

At this time, the pathogenesis of this novel clinical scenario remains unknown and undefined. It is known that the viral mRNA within the vaccine triggers an enhanced immune response which has been postulated for the development of AAV autoantibodies.[19,20] Toll-like receptors (TLR) used in antigen surveillance by leukocytes may also play a role in autoimmunity development.[20] TLR-2 activation, in cytotoxic lymphocytes, in response to the viral glycoprotein-encoding MRNA present in the vaccine has been described with a critical role in autoantibody formation.[20] The autoimmunity mechanisms may be further explained by molecular mimicry, formation of NETs leading to production of PR3 and MPO antigen, viral persistence, and epitope spreading.[19,20] Hussein *et al.*[9] suggest that subjects with COVID-19 infection who carry the TMEM173 gene variant are associated with an increased inflammatory reaction similar to the mechanism of action seen in Kawasaki vasculitis. The role of vaccination leading to autoimmune disease is an ongoing debate with many studies unable to reach a definite conclusion most likely due to the temporal relationship between the onset of disease and implementation.[19,20]

Conclusion

Since the onset of the COVID-19 pandemic, there have been rare reports of COVID-19 infection and vaccination being associated with de novo development and flares of AAV diseases. We present another such case of a biopsy-proven GPA with pauci-immune glomerulonephritis occurring within about 6 weeks of receiving the Pfizer-BioNTech COVID-19 vaccination that responded well to immunosuppressive therapy. The exact mechanism by which this occurs is not known. As the pandemic continues into its third year, we hope that this case and other similar cases will lead to further understanding of COVID-19 and its relation to AAV disease.

Declarations

Ethics approval and consent to participate

Ethical approval was not required for this case report. Written informed consent was obtained from the patient to publish as stated in the paper

Consent for publication

The patient gave written informed consent for the publication of the case report.

Author contributions

Francis Essien: Conceptualization; Data curation; Methodology; Writing – original draft; Writing – review & editing.

Jordan Evans: Data curation; Investigation; Writing – original draft; Writing – review & editing.

Andrew Kyle: Conceptualization; Data curation; Investigation; Writing – review & editing.

Anatoly Urisman: Data curation; Investigation; Writing – review & editing.

Nicholas Adams: Data curation.

Acknowledgements

None.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID iD

Francis Essien https://orcid.org/0000-0001-5337-2463

References

1. Yates M and Watts R. ANCA-associated vasculitis. *Clin Med* 2017; 1: 60–64.
2. Gallo K, Goede A, Mura C, *et al.* A comparative analysis of COVID-19 vaccines based on over 580,000 cases from the vaccination adverse event reporting system. *Vaccines* 2022; 10: 408.
3. Nakazawa D, Masuda S, Tomaru U, *et al.* Pathogenesis and therapeutic interventions for ANCA-associated vasculitis. *Nat Rev Rheumatol* 2019; 15: 91–101.

4. Kronbichler A, Lee K, Denicolo K, *et al.* Immunopathogenesis of ANCA-associated vasculitis. *Int J Mol Sci* 2020; 21: 7319.
5. Grygiel-Górniak B, Limphaibool N, Perkowska K, *et al.* Clinical manifestations of granulomatosis with polyangiitis: key considerations and major features. *Postgrad Med* 2018; 130: 581–596.
6. Alesaeidi S, Darvishi M, Dabiri S, *et al.* Current understanding and unknown aspects of the treatment of granulomatosis with polyangiitis (Wegener's granulomatosis): opportunities for future studies. *Curr Rheumatol Rev* 2020; 16: 257–266.
7. Selevaraj V, Moustafa A, Afriyie K, *et al.* COVID-19-induced granulomatosis with polyangiitis. *BMJ Case Rep* 2021; 14: e242142.
8. Bressler MY, Pathak N, Cervellione K, *et al.* New onset granulomatosis with polyangiitis associated with COVID-19. *Case Rep Dermatol Med* 2021; 2021: 8877292.
9. Hussein A, Khalil K and Bawazir Y. Anti-neutrophilic cytoplasmic antibody (ANCA) vasculitis presented as pulmonary hemorrhage in a positive COVID-19 patient: a case report. *Cureus* 2020; 12: e9643.
10. Chan-Chung C, Ong CS, Chan LL, *et al.* Eosinophilic granulomatosis with polyangiitis after COVID-19 vaccination. *QJM* 2022; 114: 807–809.
11. VAERS. About VAERS, https://vaers.hhs.gov/about.html
12. United States Department of Health and Human Services (DHHS), Public Health Service (PHS), Centers for Disease Control (CDC) / Food and Drug Administration (FDA), Vaccine Adverse Event Reporting System (VAERS) 1990-08/19/2022, CDC WONDER On-line Database, http://wonder.cdc.gov/vaers.html (accessed 28 August 2022).
13. Lind E, Jameson A and Kurban E. Fulminant granulomatosis with polyangiitis presenting with diffuse alveolar hemorrhage following COVID-19. *BMJ Case Rep* 2021; 14: e242628.
14. Shakoor MT, Birkenbach MP and Lynch M. ANCA-associated vasculitis following Pfizer-BioNTech COVID-19 vaccine. *Am J Kidney Dis* 2021; 78: 611–613.
15. Hakroush S and Tampe B. Case report: ANCA-associated vasculitis presenting with rhabdomyolysis and pauci-immune crescentic glomerulonephritis after Pfizer-BioNTech COVID-19 mRNA vaccination. *Front Immunol* 2021; 12: 762006.
16. Shirai T, Suzuki J, Kuniyoshi S, *et al.* Granulomatosis with polyangiitis following Pfizer-BioNTech COVID-19 vaccination. *Mod Rheumatol Case Rep*. Epub ahead of print 4 March 2022. DOI: 10.1093/mrcr/rxac016.
17. Watad A, Bragazzi NL, McGonagle D, *et al.* Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) demonstrates distinct autoimmune and autoinflammatory disease associations according to the adjuvant subtype: insights from an analysis of 500 cases. *Clin Immunol* 2019; 203: 1–8.
18. Watanabe T. Vasculitis following influenza vaccination: a review of the literature. *Curr Rheumatol Rev* 2017; 13: 188–196.
19. Jennette J and Nachman P. ANCA glomerulonephritis and vasculitis. *Clin J Am Soc Nephrol* 2017; 12: 1680–1691.
20. Duran T, Turkmen E, Dilek M, *et al.* ANCA-associated vasculitis after COVID-19. *Rheumatol Int* 2021; 41: 1523–1529.