CASO CLÍNICO

Gac Méd Caracas 2023;131(2):407-413
DOI: 10.47307/GMC.2023.131.2.17

Early nephrotic syndrome after vaccination for SARS-CoV-2 with Pfizer – BioNTech in a patient with bisalbuminemia

Síndrome nefrótico temprano postvacunación para SARS-CoV-2 con Pfizer – BioNTech en paciente con bisalbuminemia

Jaime Arturo Dulce[1a], Gustavo Aroca Martínez[2b], Riguey Mercado Marchena[3c], Yohana Mantilla Morales[4d], Daniel Herrera Martínez[5e], Raúl García Tolosa[6*]

SUMMARY

Background: *Nephrotic syndrome (NS) is a clinical syndrome defined by massive proteinuria greater than 3.5 g/24h, responsible for hypoalbuminemia (less than 30 g/L), with resulting hyperlipidemia, edema, and various complications. It is caused by increased permeability through the damaged basement membrane in the renal glomerulus. Etiologies include primary and secondary causes, among which are systemic, metabolic, genetic, infectious, neoplastic, and pharmacological diseases. Among the complications to be considered, the state of hypercoagulability, susceptibility to infections, and an increase in cardiovascular risk should be highlighted.* **Case presentation:** *A 69-year-old female patient, without any relevant pathological history, consulted due to a clinical that began a week after the application of the Pfizer-BioNTech vaccine that generated progressive edema of the lower limbs with the first dose and later until anasarca after receiving the second dose. Among the requested paraclinical tests, proteinuria in the nephrotic range, hypoalbuminemia, and hyperlipidemia were obtained. Infectious and autoimmune causes were ruled out, and protein electrophoresis was requested in which bisalbuminemia with distortion in the gamma zone was reported. Renal biopsy reports endocapillary glomerulonephritis.* **Conclusions:** *The etiology of nephrotic syndrome is diverse, various systemic, infectious, and neoplastic pathologies must be ruled out. The reported case shows that this happens early after the application of the Pfizer-BioNTech vaccine. It is important to report that it occurs in the context of*

DOI: https://doi.org/10.47307/GMC.2023.131.2.17

ORCID: 0000-0003-1542-2786[1]
ORCID: 0000-0002-9222-3257[2]
ORCID: 0000-0002-7511-9642[3]
ORCID: 0009-0000-9441-421X[4]
ORCID: 0009-0007-7027-9739[5]

[a]Especialización en Medicina Interna, Universidad del Sinú, CTG, BOL, CO.1; E-mail: jadulcem@gmail.com

[b]Departamento de Nefrología, Clínica de la Costa, BAQ, ATL, CO. Gustavo J. Aroca-Martínez, MD, PhD. 2; E-mail: garoca1@unisimonbolivar.edu.co;

[c]Especialización en Medicina Interna, Universidad Libre, BAQ, ATL, CO.2; E-mail: rigueyc-mercadom@unilibre.edu.co;

[d]Especialización en Medicina Interna, Universidad Libre, BAQ, ATL, CO.2; E-mail: yohanas-mantillam@unilibre.edu.co;

[e]Especialización en Medicina Interna, Universidad Libre, BAQ, ATL, CO.2; E-mail: danielal-herreram@unilibre.edu.co

Correspondencia: Riguey Mercado Marchena. E-mail: rigueyc-mercadom@unilibre.edu.co Tel: 3105692927.

Recibido: 3 de mayo 2023
Aceptado: 12 de mayo 2023

bisalbuminemia, which is not triggered by nephrotic syndrome but is observed with some degree of frequency in these patients.

Keywords: *Nephrotic syndrome, Pfizer-BioNTech COVID-19 vaccine, bisalbuminemia, adverse effect.*

RESUMEN

Introducción: *El síndrome nefrótico (SN) es un cuadro clínico definido por proteinuria masiva mayor de 3,5 g/24h, responsable de hipoalbuminemia (menor de 30 g/L), con la consiguiente hiperlipidemia, edema y diversas complicaciones. Es causada por el aumento de la permeabilidad a través de la membrana basal dañada en el glomérulo renal. Su etiología es debido a causas primarias y secundarias entre las que se encuentran las enfermedades sistémicas, metabólicas, genéticas, infecciosas, neoplásicas, farmacológicas. Entre las complicaciones a tener en cuenta se deben resaltar el estado de hipercoagulabilidad, la susceptibilidad a infecciones y un incremento en el riesgo cardiovascular.* **Presentación del caso:** *Paciente femenina de 69 años de edad, sin ningún antecedente patológico de importancia, quien consulta por cuadro clínico que inició una semana posterior a aplicación de vacuna con Pfizer – BioNTech que generó edema progresivo de miembros inferiores con la primera dosis y posteriormente hasta anasarca luego de recibir la segunda dosis. Entre los paraclínicos solicitados se obtuvo una proteinuria en rango nefrótico de 19,3 g/24h, hipoalbuminemia de 1,8 g/dL e hiperlipidemia. Se descartaron causas infecciosas y autoinmunitarias, se solicitó electroforesis de proteínas en las que se reporta bisalbuminemia con distorsión en zona gamma. La biopsia renal informa glomerulonefritis endocapilar.* **Conclusiones:** *La etiología del síndrome nefrótico es diversa, se deben descartar diversas patologías sistémicas, infecciosas, neoplásicas. El caso reportado muestra que este sucede de una forma temprana posterior a la aplicación de la vacuna Pfizer-BioNTech. Es importante relatar que sucede en el contexto de una bisalbuminemia, la cual no se desencadena por el síndrome nefrótico, pero es observada con algún grado de frecuencia en estos pacientes.*

Palabras clave: *Síndrome nefrótico, vacuna Pfizer-BioNTech COVID-19, bisalbuminemia, efecto adverso.*

INTRODUCTION

Nephrotic syndrome (NS) is a clinical syndrome defined by massive proteinuria, hypoalbuminemia, hyperlipidemia, edema, and various complications in which symptoms such as dyspnea occur. It is caused by increased permeability through the damaged basement membrane in the renal glomerulus, especially infectious or thrombo-embolic. It results from an abnormality of glomerular permeability that may be primarily due to an intrinsic renal disease in the kidneys or secondary due to congenital infections, diabetes, systemic lupus erythematosus, neoplasia, or certain drug use. The diagnostic criteria are shown in Table 1 (1,2).

Table 1. Diagnostic criteria for nephrotic syndrome.

Component	Findings
Proteinuria	Proteinuria 24h > 3-3.5 g Proteinuria/creatinuria ratio > 3-3.5 mg/mg
Hypoalbuminemia	Albuminemia <2.5 g/dL
Edema	Peripheral edema, pleural effusion, ascites
Hyperlipidemia*	Total cholesterol > 350mg/dL

* Not necessary for diagnosis.

The incidence of nephrotic syndrome in North America is estimated to be approximately 3 per 100 000 person-years based on data from the Kaiser Permanente integrated care delivery system, in turn, it was estimated in this cohort that patients with primary NS are 20 times more likely to of developing end-stage renal disease (ESRD) and are at high risk of developing cardiovascular outcomes and death (3). NS is the third cause of end-stage renal disease, after diabetes mellitus and arterial hypertension (4). It continues to remain among the ten leading causes of death in the United States (5). According to systematic reviews, the worldwide incidence of primary glomerulopathies is estimated to be between 0.2-0.8 for minimal change disease, 0.3-1.4 for membranous disease, and 0.2-1.1/per 100 000 people/year for focal and segmental disease (6).

The NS can be classified according to the etiology between primary, corresponding to 75 % of the cases, and secondary in 25 % of these (4). Common primary causes of nephrotic syndrome

are intrinsic kidney diseases, such as membranous nephropathy, minimal-change nephropathy, and focal glomerulosclerosis. Secondary causes include systemic diseases, such as lupus erythematosus, diabetes mellitus, amyloidosis, metabolic, immunological, neoplastic, infectious (bacterial, viral, parasitic), allergic, genetic, drug-related, and others such as Castleman's disease, preeclampsia, sarcoidosis, and malignant hypertension (1). Cases have also been described that are due to post-vaccination states (7,8).

The pathophysiological mechanism by which NS occurs is not fully elucidated; however, the glomerular changes that may lead to proteinuria are damage to the glomerular basement membrane, the endothelial surface, or the podocytes, this leads to an increased permeability of plasma proteins such as albumin (9). Secondary to this, hypoalbuminemia results in a decline in plasma colloid osmotic pressure, in turn causing increased transcapillary filtration of water in the body. Subsequently, this process leads to the development of edema. In addition, a decrease in circulatory volume is generated, so there is the activation of the renin-angiotensin system (RAS) and sodium and water retention. Due to protein losses such as antithrombin III, proteins C and S, as well as increases in acute phase reactants, a hypercoagulable state occurs (10).

Among the main complications that occur in the context of this syndrome are end-stage renal disease, acute kidney injury, thromboembolism, cardiovascular disease, infections, and neoplasms (11).

Since December 2019, the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its associated disease, COVID-19, was reported for the first time in Wuhan, China, has caused a devastating pandemic worldwide and the World Health Organization (WHO) decided to classify it as a pandemic (12). Since then, there have been various ways in which this infectious process has been tried to be managed and, in the same way, how to avoid the complications resulting from this infection has been studied. Among these actions, more than a year after the virus outbreak, various scientific research units and vaccine companies have worked to successfully develop a variety of COVID-19 vaccines. The vaccines can be classified by different technological platforms into whole virus vaccines, subunit vaccines, viral vector vaccines, and gene vaccines (13). One of them, the Pfizer - BioNTech vaccine contains a nucleoside-modified mRNA that encodes the SARS-CoV-2 spike glycoprotein and is delivered in lipid nanoparticles for more efficient delivery into host cells (14).

Although vaccination is a safe method to control the spread of the COVID-19 pandemic, some side effects have been reported. A study in the United States revealed some adverse effects among individuals who were administered the BNT162b2 mRNA COVID-19 vaccine. The unpleasant effects included general pain, fatigue, muscle pain, headache, chills, and fever. Other reported side effects were joint pain, nausea, muscle contractions, sweating, dizziness, flushing, loss of appetite, swelling at the injection site, insomnia, itching, tingling, diarrhea, nasal stuffiness, and sensation of heartbeats (15). Both COVID-19 infection and COVID-19 vaccination can be associated with nephrotic syndrome.

A case is presented in which nephrotic syndrome occurs days after the application of the first and second doses of the Pfizer - BioNTech vaccine. It was characterized by massive proteinuria, hypoalbuminemia, hyperlipidemia, and edema up to anasarca, the etiology of NS in a post-vaccination state is discussed.

CASE PRESENTATION

A 69-year-old female patient, mixed race, housewife, from Rioacha, Guajira (Colombia), who presents a 1-month evolution clinical picture consisting of progressive edema of the lower limbs one week after the application of the first dose of vaccine for SARS-CoV-2 Pfizer-BioNTech, a month later the second dose is applied, with which there is a progression of the edema that leads to anasarca and dyspnea, for which she decides to consult. The review by systems did not refer to any additional symptoms. On admission, the patient with normal vital signs, weighing 70.4 kg, with dyspneic facies, auscultation of the lungs with decreased vesicular murmur in the bases, abdomen with a positive ascitic wave, extremities with grade 3 edema of the lower limbs, preserved muscle strength, deep tendon reflexes without alterations.

The paraclinical tests on admission (Table 2), report elevated nitrogen levels with creatinine at 2.6 mg/dL, ionogram without changes, transaminases and bilirubin in normal ranges, total protein 4.2mg/dL and albumin 1.8 mg/dL (markedly decreased), complete blood count with normal leukocytes, WHO grade II normochromic normocytic anemia, platelets without alterations, coagulation times at target, partial proteinuria 3.2 g/dL, uroanalysis with proteins 300mg/dL, blood +, urinary sediment 5-7xc, leukocytes 8-10xc.

Table 2. Evolution of paraclinical tests during the hospital stay.

Laboratories	Hospitalization	Day 2	Day 3
Creatinine (mg/dL)	2.6	2.6	2.6
BUN (mg/dL)	40	37	38
Urea (mg/dL)	85.6	79	81
glycemia (mg/dL)	92	81	
Na (mmol/L)	140	140	140
K (mmol/L)	3.5	2.7	3.1
Cl (mmol/L)	110	113	113
Mg (mg/dL)	2.4	2.4	
P (mg/dL)	4.9	4.7	
Total proteins (g/dL)	4.2		4
Albumina (g/dL)	1.8		1.7
Globulins (g/dL)	2.4		2.3
LDH (U/L)	321		
leukocytes	5 400	4700	5 400
Neutrophils (%)	77	40	36
Eosinophils (%)	0.2	3.4	2%
Lymphocytes (%)	16	44.8	51%
Hemoglobin (g/dL)	9.5	8.2	10.5
Hematocrit (%)	28	24	31.4
Platelets	429k	373k	384K
PT (Seg)	10.5	9.9	
PTT (Seg)	35	30.9	
B. Total (mg/dL)	0.2		
B. Direct (mg/dL)	0		
TGO (U/L)	31		23
TGP (U/L)	17		15
Alkaline phosphatase (U/L)	65		
GGT (U/L)	22		
Partial proteinuria (mg)	3 243		
HbA1c		4.98	
Proteinuria 24h (mg/dL)		19 335	

The infectious, autoimmune, and metabolic profiles are normal (Tables 3 and 4). In the diagnostic images, an abdominal ultrasound has been reported to show kidneys without any type of alteration, presence of ascites, and bilateral pleural effusion. The chest CT confirmed the same effusion with passive pulmonary collapse, without condensation, or cardiovascular alterations. Figure 1 describes the main chronological events of the case. Given the clinical findings and complementary tests, it is contextualized as nephrotic syndrome under study for which a renal biopsy is scheduled. She was discharged with management with a RAS inhibitor, statin, and diuretic.

Table 3. Autoimmune and infectious profile and lipid profile.

Laboratories	Day 2
VDRL	(-)
HIV	(-)
HBsAg	(-)
Anti-VHC	(-)
CMV IgG	97.8
CMV IgM	(-)
EB IgG	11.4
EB IgM	0.39
ANAS	(-)
ANTI RO	0.19
ANTI LA	1.18
ANCAS	(-)
AAC	0.87
Anticardiolipin	2.94

CMV: Cytomegalovirus, EB: Epstein Barr, ACC: Anti-citrulline antibodies

Table 4. Lipidic profile

Laboratories	Day 3
Total cholesterol (mg/dL)	369
Triglycerides (mg/dL)	291
LDL (mg/dL)	369
HDL (mg/dL)	57

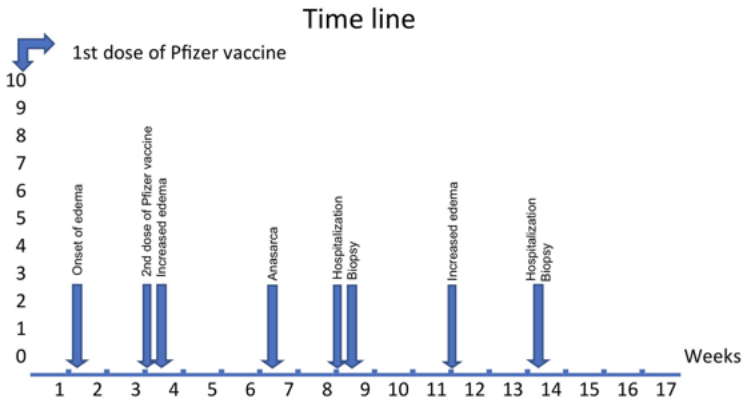

Figure 1. Chronology of events during the clinical course.

Attends control referring persistence of edema and protein electrophoresis report with bisalbuminemia and biopsy reporting glomerular lesion pattern with mesangial proliferation with a probability of diffuse podocytopia, negative immunofluorescence (Figure 2). Hospitalization is admitted again for biopsy which reports a pattern of exudative diffuse endocapillary proliferative glomerulonephritis-like glomerular lesion with scarring changes (Figure 3).

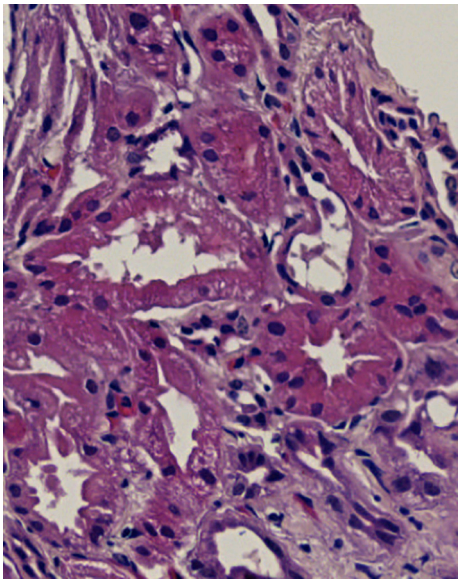

Figure 2. Renal biopsy 1. Hematoxylin-eosin staining. A slight increase in glomerular size is observed with a reduction in Bowman's space, interstitial edema, and vascular congestion, with tubules appearing normal.

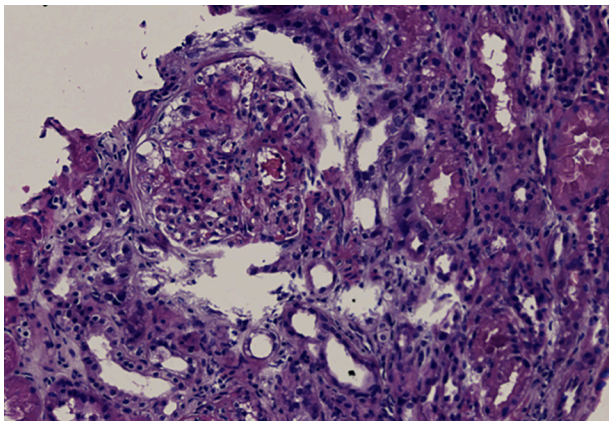

Figure 3. Renal biopsy 2. Hematoxylin-eosin staining. The phenomenon of glomerulomegaly with hypercellularity is observed, with immunohistochemistry corresponding to endocapillary proliferation, areas of mesangial smearing, remnants of neutrophils, and cellular debris.

DISCUSSION

According to the Johns Hopkins Center for Systems Science and Engineering (CSSE). epidemiology group, to date, more than four hundred million COVID-19 cases have been reported, and more than eighteen billion doses have been applied (16). The battle that has been tried to wage against COVID-19 through vaccination has been frontal, thanks to the impact it has had on the disease, it has been possible to reduce morbidity and mortality.

The reported case shows a temporal association between the mRNA-based vaccine and the appearance of progressive edema that led to anasarca meeting the diagnostic criteria for nephrotic syndrome. In the reported biopsy, signs of diffuse podocytopathy were evident. There have been few cases of glomerulopathies that have been reported after the application of the vaccine, however, they have been constantly growing (17-22).

Currently, due to the high vaccination rates, several reports of de novo glomerular disease have been observed in mRNA-based vaccines such as Pfizer or Modern, which have chronological confirmation after their application (8,23). Among the most frequent glomerulopathies according to the reported findings are IgA glomerulopathy and minimal change glomerulopathy (24).

The mechanisms involved in the pathogenesis of post-vaccination glomerular disease have not yet been fully clarified, it is probably related due to the release of interleukin-2, TNF-α, interferon γ that produce a direct lesion in the podocyte (25,26). These are the injury mechanisms that have been previously described in the development of podocytopathies (27). There are still insufficient data on other genetic factors that are related to post-vaccination glomerulopathies. It is under discussion whether genetic analyzes remain in certain patients that could predict the appearance of post-vaccination glomerulopathy, this is due to the protective effect of the vaccine and its impact on mortality, which is why it is necessary to continue with the application of these vaccines. Especially at present when the dominant variant for SARS-CoV-2 is Omicron, whose main characteristic is its high transmission and therefore the high risk of complications associated with COVID-19.

Whether there is a direct SARS-CoV-2 renal infection remains controversial, and data remain limited (28,29). Despite the increasing number of cases with glomerulopathies, the risk of idiosyncratic reactions and therefore recurrence in patients who already have minimal change glomerulopathy is still unknown. Therefore, clinicians need to consider the possible association between nephrotic syndrome and COVID-19 infection or vaccination so that they can be vigilant to the presence of signs and be prepared to give the appropriate management.

In conclusion, nephrotic syndrome is a possible complication of both COVID-19 infection and the COVID-19 vaccine and should be considered in patients exhibiting sudden onset edemas or deterioration in kidney function (29). While most cases respond to standard treatment, clearer guidelines will need to be developed once more data is available.

Financing. This research did not receive external funding.

Conflicts of interest. The authors declare they have no conflict of interest.

REFERENCES

1. Kodner C. Diagnosis and management of nephrotic syndrome in adults. Am Fam Physician. 2016;93(6):479-485.
2. Shin J Il, Kronbichler A, Oh J, Meijers B. Nephrotic Syndrome: Genetics, Mechanism, and Therapies. Biomed Res Int. 2018;2018:1-2.
3. Go AS, Tan TC, Chertow GM, Ordonez JD, Fan D, Law D, et al. Primary Nephrotic Syndrome and Risks of ESKD, Cardiovascular Events, and Death: The Kaiser Permanente Nephrotic Syndrome Study. J Am Soc Nephrol. 2021;32(2):2303-2314.
4. Politano SA, Colbert GB, Hamiduzzaman N. Nephrotic Syndrome. Prim Care - Clin Off Pract. 2020;47(4):597-613.
5. Heron M. Deaths: Leading Causes for 2018. Natl Vital Stat reports from Centers Dis Control Prev Natl

Cent Heal Stat Natl Vital Stat Syst. 2021;70(4):1-115.

6. McGrogan A, Franssen C, De Vries C. The incidence of primary glomerulonephritis worldwide: A systematic review of the literature. Nephrol Dial Transpl. 2011;26:414-430.
7. De Serres G, Billard MN, Gariépy MC, Roy MC, Boucher FD, Gagné H, et al. Nephrotic syndrome following four-component meningococcal B vaccination: Epidemiologic investigation of a surveillance signal. Vaccine. 2019;37(35):4996-5002.
8. Thappy S, Thalappil SR, Abbarh S, Al-Mashdali A, Akhtar M, Alkadi MM. Minimal change disease following the Moderna COVID-19 vaccine: first case report. BMC Nephrol. 2021;22(1).
9. D'Amico G, Bazzi C. Pathophysiology of proteinuria. Kidney Int. 2003;63(3):809-825.
10. Goldman L, Ausiello D, Schafer A. Goldman-Cecil. Tratado de medicina interna. 26th edition. Sciences EH, editor. Barcelona, España; 2021.p.2657.
11. Yamamoto R, Imai E, Maruyama S, Yokoyama H, Sugiyama H, Nitta K, et al. Incidence of remission and relapse of proteinuria, end-stage kidney disease, mortality, and major outcomes in primary nephrotic syndrome: The Japan Nephrotic Syndrome Cohort Study (JNSCS). Clin Exp Nephrol. 2020;24(6):526-540.
12. Triggle CR, Bansal D, Ding H, Islam MM, Farag EABA, Hadi HA, et al. A Comprehensive Review of Viral Characteristics, Transmission, Pathophysiology, Immune Response, and Management of SARS-CoV-2 and COVID-19 as a Basis for Controlling the Pandemic. Front Immunol. 2021;12.
13. Motamedi H, Ari MM, Dashtbin S, Fathollahi M, Hossainpour H, Alvandi A, et al. An updated review of globally reported SARS-CoV-2 vaccines in preclinical and clinical stages. Int Immunopharmacol. 2021;96:107763.
14. Patela R, Kakia M, Potluria VS, Kaharb P, Khanna D. A comprehensive review of SARS-CoV-2 vaccines: Pfizer, Moderna & Johnson & Johnson. Human Vaccines & Immunotherapeutics. 2022;18(1): e2002083.
15. Kalyan Kadali RA, Janagama R, Peruru S, Gajula V, Madathala RR , Nikhita Chennaiahgari N, et al. Non-life-threatening adverse effects with COVID-19 mRNA-1273 vaccine: A randomized, cross-sectional study on healthcare workers with detailed self-reported symptoms. J Med Virol. 2021;93(7):4420-4429.
16. University JH. Coronavirus resource center. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE). 2022.
17. Hanna J, Ingram A, Shao T. Minimal Change Disease After First Dose of Pfizer-BioNTech COVID-19 Vaccine: A Case Report and Review of Minimal Change Disease Related to COVID-19 Vaccine. Can J Kidney Heal Dis. 2021;8:1-5.
18. Kobayashi S, Fugo K, Yamazaki K, Terawaki H. Minimal change disease soon after Pfizer-BioNTech COVID-19 vaccination. Clin Kidney J. 2021;14(12):2606-2607.
19. Tan HZ, Tan RY, Choo JCJ, Lim CC, Tan CS, Loh AHL, et al. Is COVID-19 vaccination unmasking glomerulonephritis? Kidney Int. 2021;100(2):469-471.
20. Timmermans SAMEG, Busch MH, Abdul-Hamid MA, Frenken LAM, Aarnoudse AJ, van Paassen P. Primary Podocytopathies After COVID-19 Vaccination. Kidney Int Reports. 2022:3-5.
21. Dormann H, Knuppel A, Amann K, Erley C. Nephrotic syndrome after vaccination against COVID-19: Three new cases from Germany. Dtsch Arztebl Int. 2021;118:662-663.
22. Lebedev L, Sapojnikov M, Wechsler A, Varadi-Levi R, Zamir D, Tobar A, et al. Minimal Change Disease Following the Pfizer-BioNTech COVID-19 Vaccine. Am J Kidney Dis. 2021;78(1):142-145.
23. Li NL, Coates PT, Rovin BH. COVID-19 vaccination followed by activation of glomerular diseases: Does association equal causation? Kidney Int. 2021;100(5):959-965.
24. Klomjit N, Alexander MP, Fervenza FC, Zoghby Z, Garg A, Hogan MC, et al. COVID-19 Vaccination and Glomerulonephritis. Kidney Int Reports. 2021;6(12):2969-2978.
25. Bomback AS, Kudose S, D'Agati VD. De Novo and Relapsing Glomerular Diseases After COVID-19 Vaccination: What Do We Know So Far? Am J Kidney Dis. 2021;78(4):477-480.
26. Izzedine H, Bonilla M, Jhaveri KD. Nephrotic syndrome and vasculitis following SARS-CoV-2 vaccine- true association or circumstantial? Nephrol Dial Transpl. 2021;36:1565-1569.
27. Kopp JB, Anders HJ, Susztak K, Podestà MA, Remuzzi G, Hildebrandt F, et al. Podocytopathies. Nat Rev Dis Prim. 2020;6(1):1-24.
28. Lau WL, Zuckerman JE, Gupta A, Kalantar-Zadeh K. The COVID-Kidney Controversy: Can SARS-CoV-2 Cause Direct Renal Infection? Nephron. 2021;145(3):275-279.
29. Cancarevic I, Nassar M, Medina L, Sánchez A, Parikh A, Hosna A, et al. Nephrotic Syndrome in Adult Patients With COVID-19 Infection or Post COVID-19 Vaccine: A Systematic Review. Cureus. 2022;14(9): e29613.