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Case Report

Successful treatment of new-onset diabetes mellitus and IgA nephropathy after COVID-19 vaccination: a case report

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Abstract: De novo glomerular injuries or relapse of nephropathy following COVID-19 vaccine has been reported. Here we present the first case of successful treatment of new-onset diabetes mellitus and biopsy-proven IgA nephropathy after COVID-19 vaccination. A 56-year-old man with no known medical history of renal dysfunction or diabetes mellitus developed both within 3 months after receiving a third dose of inactivated COVID-19 vaccine (Vero cells). His symptoms were characterized by brown urine, severe dry mouth, and excessive thirst. Randomly acquired blood glucose levels exceeded 33.3 mmol/L. A kidney biopsy showed IgA nephropathy. He was started on insulin for glycemic control. After glucocorticoid and cyclophosphamide treatment, oral tablets of repaglinide, combined with acarbose, controlled blood glucose and stabilized kidney function. This case is unique because the kidneys and pancreas were simultaneously affected by the vaccine. Successful treatment of the disease proved that cyclophosphamide combined with glucocorticoids were effective and that blood glucose was successfully controlled. This treatment option could be useful in similar cases in the future.

Keywords: COVID-19, COVID-19 vaccine, new-onset diabetes, IgA nephropathy

Introduction

COVID-19 vaccine has been administered in almost all countries as a critical measure used to control the pandemic. However, COVID-19 vaccination-related glomerular diseases have become a new concern. Both the mRNA vaccine and the inactivated vaccine can cause new-onset and relapsing glomerular disease [1]. These diseases typically occur after the first or second dose of vaccination. De novo glomerular disease is mainly IgA nephropathy (IgAN) or minimal change disease, which is mostly sensitive to steroids. Patients who experience relapse have a fair prognosis, and spontaneous remission occurs in some cases. The pathogenesis of these vaccine-associated diseases possibly includes humoral and cellular immune responses [2]. Some effects of the COVID-19 vaccine on glycolytic metabolism are known [3]. Here, we report a case of a patient with both new-onset diabetes mellitus and IgAN after COVID-19 vaccination. We also describe the dosing regimen used for successful treatment.

Case report

A 56-year-old man presented with new-onset severe hyperglycemia accompanied by hematuria and proteinuria. His blood sugar level was significantly elevated. Randomly acquired blood glucose samples revealed levels exceeded 33.3 mmol/L. Hypertension was the only previous condition noted in the medical history. The patient was never infected with COVID-19. He had no known COVID-19 exposures and did not experience flu-like illness throughout the COVID-

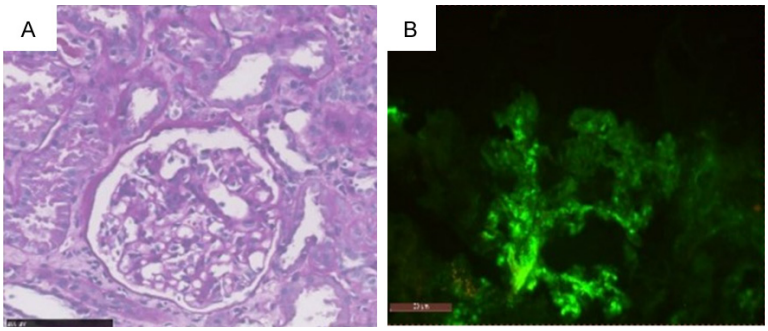

Figure 1. Immunofluorescence images acquired after renal puncture. A. Glomerular mesangial expansion and hypercellularity (hematoxylin-eosin, ×200); B. Strong glomerular mesangial deposits, revealed using IgA antisera (immunofluorescence study, ×200).

19 pandemic. He had no family history of kidney disease, including IgAN. He received the third SARS-CoV-2 vaccine (E202202002), manufactured by SINOVAC, and was asymptomatic during the 28-day interval between doses. However, about 3 months after receiving the vaccine, he developed brown urine, severe dry mouth, and excessive thirst.

The patient went to the hospital, where urinalysis showed proteinuria 3+ (ref: negative), 1,119 red blood cells per high-power field (ref: 0-3), and 156 white blood cells per high-power field (ref: 0-4). Serum albumin was 34.9 g/L. Serum creatinine was 109.7 μmol/L (ref: 57-97 μmol/L), and the estimated glomerular filtration rate (eGFR) was 79 mL/min/1.73 m^2. A randomly acquired urine protein-creatinine ratio was 2.15 g/g (ref: 0-0.2 g/g). Negative findings included lack of lower extremity edema, rash, abdominal pain, arthralgia, lymphadenopathy, and throat erythema. A kidney ultrasound showed mildly increased echogenicity with a normal size and cortical thickness. An additional serological work-up for glomerulonephritis was negative, including for hepatitis B and C, human immunodeficiency virus, and antinuclear and antineutrophil cytoplasmic antibodies. Erythrocyte sedimentation rate and C-reactive protein results were normal. Complement C3 (85, ref: 90-180 mg/dL) and C4 (24, ref: 10-40 mg/dL) results were normal. Creatinine phosphokinase was 82 U/L (ref: 0-190 U/L). Immunoglobulin A levels were elevated to 657 mg/dL (ref: 70-400 mg/dL). A kidney biopsy was performed. Light microscopy results revealed 12 glomeruli with mild mesangial expansion and hypercellularity, without endocapillary hypercellularity. Immunofluorescence results revealed 3+ diffuse granular mesangial staining for IgA (**Figure 1**). Other staining results found 2+ for C3; IgG and other immunoglobulin/complement antibodies were negative. The pathologic features were consistent with IgAN, with an Oxford MEST-C classification of M1E-0S0T0C0.

The patient was treated with intravenous cyclophosphamide (0.8 g qm), oral prednisone (initiated at 20 mg qd for a week, then tapered by 5 mg/d every week to 10 mg/d, then withdrawn after 1 month), and insulin (insulin aspart 10 U tid, and insulin glargine 20 U injected subcutaneously at 9:00 PM) therapy. After 1 week, randomly acquired blood glucose samples indicated that glucose levels were decreased. We thus began to discontinue the insulin given before sleep. After 2 weeks, because the randomly acquired blood glucose levels of this patient continued to decrease, we began to reduce the dose of insulin used in the daytime. After 4 weeks of therapy, the randomly acquired blood glucose level of this patient was successfully controlled using oral acarbose 50 mg tid combined with repaglinide 0.5 mg tid, without insulin injection (**Figure 2**). Reexamination results revealed that the urine protein-creatinine ratio was decreased to 0.208 g/g (**Figure 3**), kidney function remained stable, and serum creatinine did not increase (**Figure 4**). Blood glycated albumin decreased to normal levels (**Figure 5**). Serum albumin was obviously improved to 41.1 g/L (**Figure 6**). Hemoglobin was maintained within the normal reference range (ref: 120-160 g/L) (**Figure 7**). Glycosylated hemoglobin decreased from 12.9% to 6.4% (ref: 4.0-6.3%) (**Figure 8**). The number of erythrocytes in the sediment gradually decreased after two elevations to 147 cells/μl (ref: 0-17/μl) (**Figure 9**). After 4 months of therapy, proteinuria was absent, and all oral tablets used to control hyperglycemia were stopped.

Discussion

There are several case reports of various types of glomerulopathies following the administra-

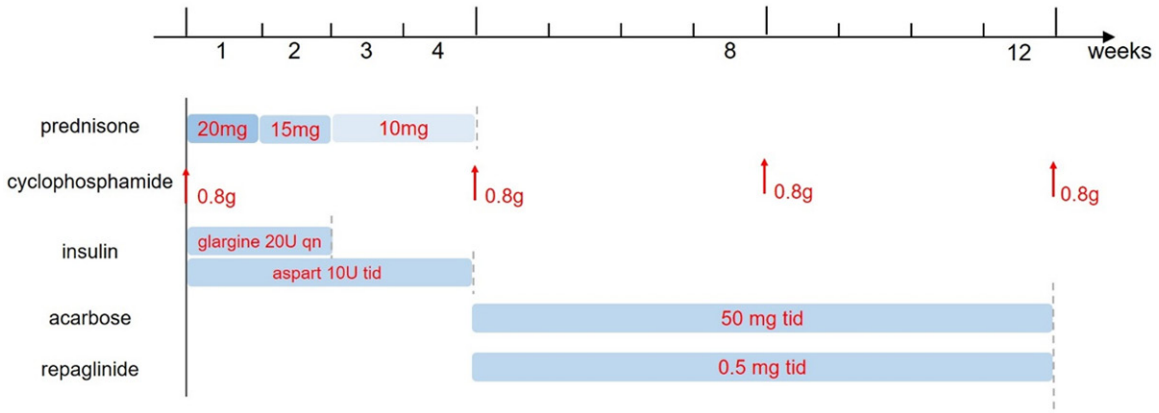

Figure 2. Clinical medication regimen and duration of the patient. The color bar length represents the duration of medication use. The red number represents the medication dose. The light dashed line represents discontinued use of the drugs. Prednisone was taken orally at 20 mg qd, reduced to 15 mg in the second week, 10 mg in the third week, and discontinued after 2 weeks. Cyclophosphamide was given via the intravenous route once a month, four times at 0.8 g each time. Insulin glargine 20 U qn injected subcutaneously for 2 weeks, and insulin aspart 10 U tid for 4 weeks. Acarbose 50 mg tid and repaglinide 0.5 mg tid were taken orally, starting in the second month and continuing for 2 months.

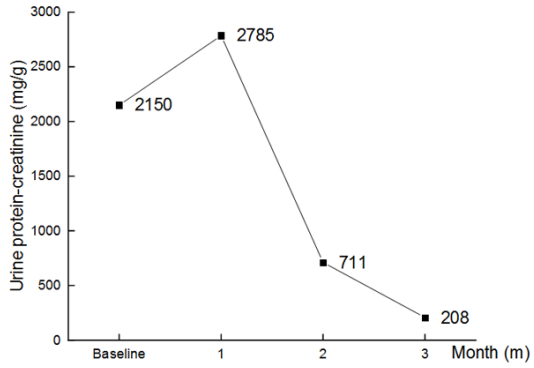

Figure 3. Changes in urine protein-creatinine ratios from baseline to 3 months.

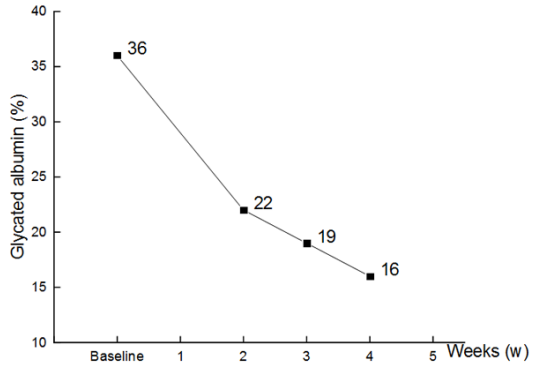

Figure 5. Changes in serum glycated albumin during 4 weeks of therapy.

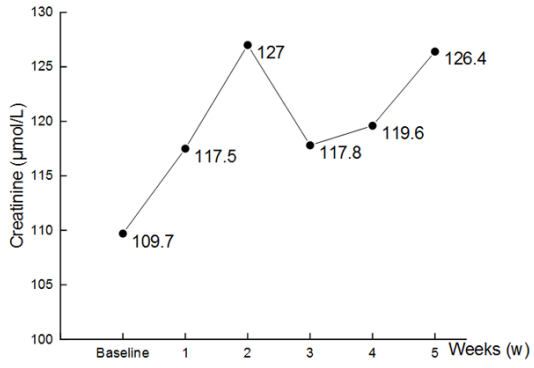

Figure 4. Changes in serum creatinine during 2 months of therapy.

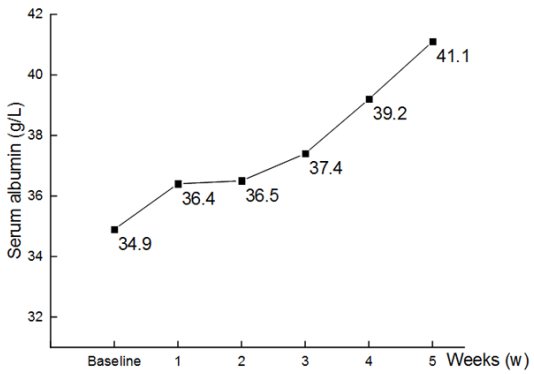

Figure 6. Changes in serum albumin from baseline to 2 months.

tion of COVID-19 vaccines produced by different manufacturers. In May 2021, Matthew Abramson et al. [4] first reported a case of IgAN after SARS-CoV-2 vaccination. A number of

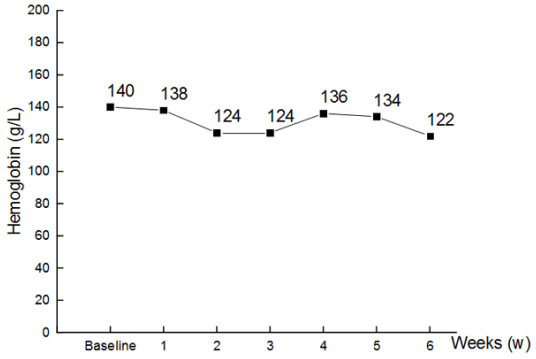

Figure 7. Changes in hemoglobin during a 6-week period.

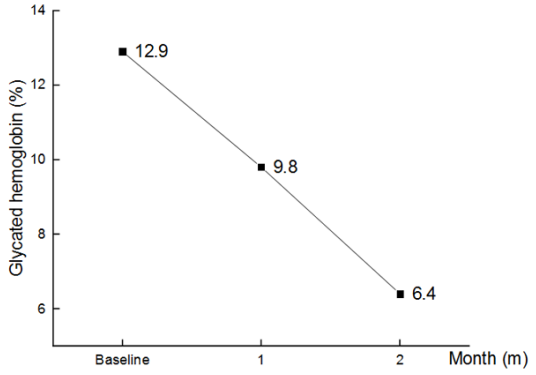

Figure 8. Changes in serum glycated hemoglobin during 2 months of therapy.

cases were subsequently reported. Roberta Fenoglio et al. [5] reported two cases of IgAN among 17 cases of biopsy-confirmed nephropathy after COVID-19 vaccination. One of the two patients developed acute renal failure. All 17 patients received immunosuppressive therapy. In this case, all other secondary causes were excluded, including those related to ANA, antineutrophil cytoplasmic antibodies, MPO, PR3, anti-GBM antibodies, signs of bacterial or viral infection, malignant tumors, and drug or poison usage. Therefore, the co-occurrence of new-onset diabetes mellitus and chronic glomerulonephritis should primarily be explained by immunological factors. This patient received the third dose of inactivated COVID-19 vaccine (Vero cells) during this period. We believe that there may be some relationship between the COVID-19 vaccine and the development of diabetes mellitus and chronic glomerulonephritis.

Inactivated and mRNA vaccines have the potential to cause new and recurrent glomerulopathy. Renal diseases can develop after the first or second dose. One study found that mRNA vaccines induce strong CD4+ and CD8+ T-cell responses, antibody responses, and cytokine release [6]. Glomerulopathy is closely related to podocyte injury mediated by T and B cells. Therefore, the humoral and cellular immune responses mediated by mRNA vaccines could be the cause of podocyte injury that results in new and recurrent glomerulopathy [7]. Inactivated vaccine-associated glomerulopathy is similar to minimal change disease caused by other inactivated vaccines (e.g., influenza); it is also related to the immune response elicited by the vaccine itself. Inactivated vaccines directly introduce antigenic proteins that stimulate the host immune response, which causes T and B cell responses and eventually results in podocyte injury.

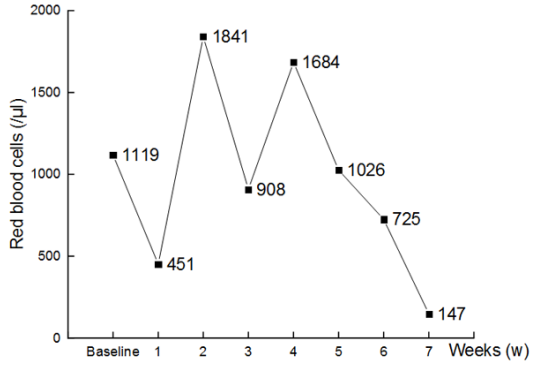

Figure 9. Changes in red blood cells in sediment during a 7-week period.

Diabetes mellitus type 2 is a chronic disorder characterized by high blood glucose levels during a prolonged period. Uncertainties about the exact mechanism involved remain, but the pancreatic angiotensin-converting enzyme 2 (ACE2) receptor has been implicated as the main enzyme related to COVID-19 pathophysiology. Some researchers mention potential mechanisms via which COVID-19 might cause new-onset diabetes type 2. Using a meta-analysis, Sathish T et al. [8] found a prevalence of COVID-19-associated new-onset diabetes mellitus of 14.4%. Dhan et al. [9] reported similar results. There are also some reported cases of hyperglycemia following COVID-19 vaccination. AbuRumaileh et al. [10] reported a case of new-onset diabetes type 2 that manifested as a hyperosmolar hyperglycemic state, after receipt

of a COVID-19 vaccine. Ganakumar et al. [11] whereas infection itself can be associated with severe hyperglycemia, including hyperglycemic emergencies. While the accelerated vaccine development and rollout have considerably decreased morbidity and mortality with reasonable safety, there are emerging reports of worsening of hyperglycemia in response to vaccination, with possible shared pathophysiology with COVID-19 infection-related hyperglycemia. We hereby report two young patients with type 1 diabetes (T1DM reported that two patients with type 1 diabetes developed diabetic ketoacidosis after receiving a COVID-19 vaccine. SARS-CoV-1 uses ACE2 receptors to damage pancreatic β-cells, resulting in acute diabetes [12]. Other mechanisms include cytokine storms and oxidative stress, overactivation of the renin-angiotensin-aldosterone system, and dysregulated release of stress hormones, such as cortisol and catecholamines; these conditions can lead to increased insulin resistance [13, 14]. There are emerging reports of worsening hyperglycemia in response to vaccination, which might have a pathophysiology similar to that of COVID-19 infection-related hyperglycemia. This response may be exaggerated following the post-vaccination immune response [15]. It is unclear how these vaccines cause these conditions, and further study is needed.

To our knowledge, this case report is the first to describe de novo diabetes mellitus type 2 and biopsy-proven IgAN that developed within 3 months after COVID-19 vaccination. Based on the vaccine-related mechanism of the immune reaction, we treated the patient with glucocorticoid and cyclophosphamide and controlled the diabetes mellitus within a short period. In general, glucocorticoids are considered a medication that can worsen diabetes and harm pancreas function, ostensibly leading to an increase in blood glucose levels. Given this response, glucocorticoids are rarely used to treat diabetes mellitus. However, in this case, it was strange that the patient's blood sugar level was dramatically high within a short period, without any history of diabetes or a propensity to the disease. Randomly acquired blood glucose levels exceeded 33.3 mmol/L. We suspected that the diabetes was caused by an immunological mechanism triggered by the COVID-19 vaccination. The pathology results of the kidney biopsy revealed an IgAN Oxford MESTC classification of M1E0S0T0C0 and mild mesangial expansion and hypercellularity without endocapillary hypercellularity. Therefore, we administered glucocorticoids combined with CTX therapy. The patient was very satisfied with the withdrawal of insulin and only required oral tablets to lower blood glucose levels.

Although correlation does not imply causation, the onset of symptoms of injury of two organs soon after vaccination should be considered as the inciting event. This patient received three doses of the inactivated COVID-19 vaccine (Vero cells). One explanation for the patient's IgAN and diabetes mellitus was production of antiglycan antibodies that cross-reacted with pre-existing under-galactosylated IgAN. It is also possible that the vaccine triggered and exacerbated the subclinical IgAN. Although most patients with COVID-19 vaccine-associated glomerular disease have a favorable prognosis, providers, doctors, and patients should be aware of this adverse effect. This outcome also highlighted the necessity for post-vaccination pharmacovigilance. However, it should be emphasized that while this type of response was likely a rare occurrence, use of the COVID-19 vaccine remains important and recommended during the pandemic, because the benefits of vaccination greatly outweigh the potential complications.

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Disclosure of conflict of interest

None.

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References

[1] Li NL, Coates PT and Rovin BH. COVID-19 vaccination followed by activation of glomerular diseases: does association equal causation? Kidney Int 2021; 100: 959-965.

[2] Xu S, Yang K, Li R and Zhang L. mRNA vaccine era-mechanisms, drug platform and clinical prospection. Int J Mol Sci 2020; 21: 6582.

[3] Santos AF, Póvoa P, Paixão P, Mendonça A and Taborda-Barata L. Changes in glycolytic pathway in SARS-COV 2 infection and their importance in understanding the severity of COVID-19. Front Chem 2021; 9: 685196.

[4] Abramson M, Mon-Wei Yu S, Campbell KN, Chung M and Salem F. IgA nephropathy after SARS-CoV-2 vaccination. Kidney Med 2021; 3: 860-863.

[5] Fenoglio R, Lalloni S, Marchisio M, Oddone V, De Simone E, Del Vecchio G, Sciascia S and Roccatello D. New onset biopsy-proven nephropathies after COVID vaccination. Am J Nephrol 2022; 53: 325-330.

[6] Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, Baum A, Pascal K, Quandt J, Maurus D, Brachtendorf S, Lörks V, Sikorski J, Hilker R, Becker D, Eller AK, Grützner J, Boesler C, Rosenbaum C, Kühnle MC, Luxemburger U, Kemmer-Brück A, Langer D, Bexon M, Bolte S, Karikó K, Palanche T, Fischer B, Schultz A, Shi PY, Fontes-Garfias C, Perez JL, Swanson KA, Loschko J, Scully IL, Cutler M, Kalina W, Kyratsous CA, Cooper D, Dormitzer PR, Jansen KU and Türeci Ö. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature 2020; 586: 594-599.

[7] Vivarelli M, Massella L, Ruggiero B and Emma F. Minimal change disease. Clin J Am Soc Nephrol 2017; 12: 332-345.

[8] Sathish T, Kapoor N, Cao Y, Tapp RJ and Zimmet P. Proportion of newly diagnosed diabetes in COVID-19 patients: a systematic review and meta-analysis. Diabetes Obes Metab 2021; 23: 870-874.

[9] Shrestha DB, Budhathoki P, Raut S, Adhikari S, Ghimire P, Thapaliya S, Rabaan AA and Karki BJ. New-onset diabetes in COVID-19 and clinical outcomes: a systematic review and meta-analysis. World J Virol 2021; 10: 275-287.

[10] Abu-Rumaileh MA, Gharaibeh AM and Gharaibeh NE. COVID-19 vaccine and hyperosmolar hyperglycemic state. Cureus 2021; 13: e14125.

[11] Ganakumar V, Jethwani P, Roy A, Shukla R, Mittal M and Garg MK. Diabetic ketoacidosis (DKA) in type 1 diabetes mellitus (T1DM) temporally related to COVID-19 vaccination. Diabetes Metab Syndr 2022; 16: 102371.

[12] Bindom SM and Lazartigues E. The sweeter side of ACE2: physiological evidence for a role in diabetes. Mol Cell Endocrinol 2009; 302: 193-202.

[13] Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A and Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol 2020; 8: 782-792.

[14] Kalupahana NS and Moustaid-Moussa N. The renin-angiotensin system: a link between obesity, inflammation and insulin resistance. Obes Rev 2012; 13: 136-149.

[15] Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, Boehm B, Amiel S, Holt RI, Skyler JS, DeVries JH, Renard E, Eckel RH, Zimmet P, Alberti KG, Vidal J, Geloneze B, Chan JC, Ji L and Ludwig B. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol 2020; 8: 546-550.