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Case Report

New-Onset of Membranous Lupus Nephritis after COVID-19 Vaccination: a Case Report and Literature Review

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Keywords

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- Adverse events
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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination is an important method to reduce the spread of Coronavirus disease 2019 (COVID-19). While most recipients experience only mild side effects such as fever, fatigue, and injection site pain, it has been found that SARS-CoV-2 vaccination is associated with a few autoimmune problems, including the development of immune thrombotic thrombocytopenia, autoimmune liver disorders, rheumatoid arthritis, IgA nephropathy (IgAN) and systemic lupus erythematosus (SLE). There have been several reports documenting the occurrence of lupus nephritis (LN) after administration of the SARS-CoV-2 vaccine. Considering the ability to activate the immune system, vaccines carry a series of risk inducing flares or exacerbating disease in patients with glomerulonephritises. Here we report a case of a new-onset membranous lupus nephritis (MLN) of a 37-years-old female after the shot of adenovirus vector based COVID-19 vaccine.

ABBREVIATIONS

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Coronavirus Disease 2019; IgAN: IgA Nephropathy; SLE: Systemic Lupus Erythematosus; LN: Lupus Nephritis; MLN: Membranous Lupus Nephritis; MCD: Minimal Change Disease; MN: Membranous Nephropathy; ANA: Antinuclear Antibodies; dsDNA: Double-Stranded DNA; ACL: Anti-Cardiolipin Antibodies; TPCR: Total Protein Creatinine Ratio; UACR: Albumin Creatinine Ratio; Anti-PLA2R Antibody: Phospholipase A2 Receptor Antibody; EDD: Electron Dense Deposits; EM: Electron Microscopy; EXT1/2: Exostosin 1/2; NCAM1: Neural Cell Adhesion Molecule 1

INTRODUCTION

Vaccines have been proven to be effective in reducing the transmission of infectious diseases and preventing severe illness, however, there have been a collection of instances displaying side effects brought on by immunizations. In recent years, the global severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination campaign has raised concerns about potential adverse events, including the development or exacerbation of auto-immune problems [1-3]. Studies showed that the SARS-CoV-2 vaccination is associated with increased risk of immune thrombocytopenic purpura, autoimmune liver diseases, Guillain-Barré syndrome, IgA nephropathy (IgAN), rheumatoid arthritis and systemic lupus erythematosus (SLE) [1,4-6]. Prior to the wide application of SARS-CoV-2 vaccinations, there were seldom reports of vaccine associated glomerular diseases. Recently, more and more reports showed that SARS-CoV-2 vaccination may carry a risk of initiating or exacerbating disease or inducing flares in patients with glomerular diseases, particularly IgAN, ANCA associated systemic vasculitis and minimal change disease (MCD) [7].

Evidence have shown that SLE patients are more prone to vaccine reactogenicity, including symptoms such as fever, vomiting, and injection site redness, following the administration of the SARS-CoV-2 vaccine [8]. Additionally, there have been cases reported in both adults and pediatric patients describing the onset of SLE after COVID-19 vaccination [9-12]. Besides, relapse or exacerbations of SLE, including the relapse of membranous lupus nephritis (MLN), after receiving the SARS-CoV-2 vaccine in the adult population was also documented [13]. However, cases of *de novo* MLN after SARS-CoV-2 vaccination are less reported.

Here we report a 37-years-old female who developed clinical symptoms of lupus two days after administration of the 3rd dose of the adenovirus vector based SARS-CoV2 vaccine. The kidney

biopsy was performed for her proteinuria and the diagnosis of MLN was made finally.

CASE PRESENTATION

A 37 years old female who presented with erythematous plaque in the injection site two days after the shot of the third dose of adenovirus vector based COVID-19 vaccine. Then the erythematous plaque became itchy, and the wound was difficult to heal after breaking open. She didn't ask for any medical help to deal with the wound. About 4 months later, she developed joint pain, fingertip and facial erythema, hair loss and foamy urine. She had not been previously infected by SARS CoV-2, and she denied any side effects after receiving the first two doses of the COVID-19 vaccine which was administered 8 months and 9 months, respectively, before the third one. She had no previous medical history of disease and was taking no medicines. Her family history was negative for autoimmune diseases.

Then she went to see a dermatologist and the dermatoscope examination of the skin erythema revealed cutaneous lupus. As she presented foamy urine, she was transferred to our department. After admission, her laboratory examination showed the total protein creatinine ratio (TPCR) was 2484.47mg/g, and albumin creatinine ratio (UACR) was 1765mg/g with weak positive urine occult blood. Positive antinuclear antibodies (ANA), double-stranded DNA (dsDNA), anti-Smith antibody and anti-cardiolipin antibodies (ACL) with low complement C3 and C4 level were presented. Otherwise, serum albumin, creatinine, blood routine examinations were all in normal range.

Then the renal biopsy was performed and the pathological findings showed diffuse thickening of capillary wall with mild mesangial expansion under light microscopy (Figure 1A). Interestingly, there was fuchsinophilic subepithelial deposits on trichrome staining (Figure 1B-F). One of 40 glomeruli had sclerosis, interstitial fibrosis was less than 10% without tubular atrophy. No diagnostic lesions were detected for vessels. Congo red staining was negative. Direct immunofluorescence revealed IgG (2-3+), IgG1 (2-3+), IgG2 (2+), IgG3 (3+), IgG4 (1+), IgM (2+), IgA (1-2+), C3 (3+), C1q (2-3+), C4 (2-3+), kappa light chain (2+), and lambda light chain (2+) were positive along the capillary wall and in the mesangial region (Fig. 1C, D). PLA2R staining was negative. Under electron microscopy (EM), scattered and bulky subepithelial and mesangial electron dense deposits (EDD) with very vague substructure were observed (Fig.1E, F). According to the biopsy, secondary membranous nephropathy (MN) was considered.

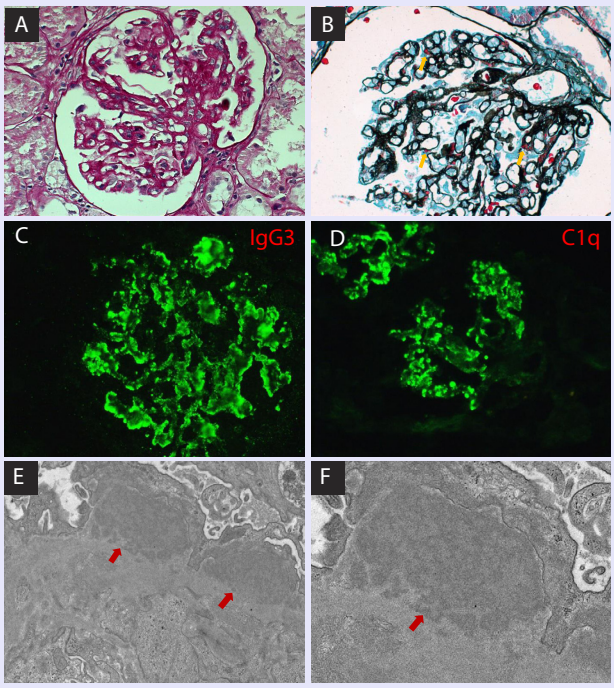

Figure 1 Renal pathological findings of this case.
(A) Diffuse thickening of capillary wall with mild mesangial expansion under light microscopy (Magnification: 400×).
(B) Conspicuously subepithelial "spkies" under sliver plus trichrome staining without obviously proliferative lesions (Magnification: 600×). Yellow arrows represented subepithelial deposits on trichrome.
(C) Positive staining of IgG3 (3+) along the capillary wall and mesangial space. (Magnification: 400×).
(D) Positive staining of C1q (2-3+) along the capillary wall and mesangial space. (Magnification: 200×)
(E) Scattered and bulky EDD observed under the subepithelial area by EM (Magnification: 5000×). Red arrow represented subepithelial EDD.
(F) The EDD exhibited a vague structure at higher magnification (Magnification: 10000×). Red arrow represented subepithelial EDD.
Abbreviations: EDD: electron dense deposits; **EM:** electron microscope

To further exclude primary MN, serum anti-PLA2R antibody, anti-thrombospondin type-1 domain-containing protein and neural epidermal growth factor-like 1 were analyzed and all of the three were negative. To our surprise, in kidney tissue Exostosin 1/2 (EXT1/2) and neural cell adhesion molecule 1 (NCAM1), both of which are reported to be autoantigens of MLN, were both negative.

Based on the clinical and pathological findings, the patient was ultimately diagnosed with MLN which was highly suspicious to associate with SARS-CoV-2 vaccination. The treatment approach for this patient involves a low-dose, multi-targeted regimen including hydroxychloroquine, prednisone, tacrolimus, and mycophenolate mofetil. A few months later, her urine protein decreased (Figure 2A), serum complement levels increased (Figure 2B), and the titers of autoantibodies (including dsDNA, ACL, etc.) decreased to normal range.

DISCUSSION

Systemic lupus erythematosus (SLE) is a chronic auto-immune disease characterized by the production of autoantibodies and immune complex deposition that can cause multiple organs damage, with lupus nephritis (LN) being a common and serious complication. With the widespread administration of COVID-19 vaccines, new-onset SLE has been reported after SARS-CoV-2 vaccination [10-12,14,15]. There are also some patients with a history of SLE who experienced worsening or relapse of their condition after receiving the COVID-19 vaccine [13,16]. New-onset of MLN after SARS-CoV-2 vaccination were less reported. Here we report a patient exhibited an initial presentation of MLN following the COVID-19 vaccine.

A recent study provides evidence that abnormal immune responses in susceptible individuals plays an import part in association with SARS-CoV-2 vaccine related renal damage, instead of direct deposition of spike protein and nucleoprotein of SARS-CoV-2 in the kidney [17]. The study group included 17 patients with *de novo* IgAN, MN, LN, MCD, focal segmental glomerulosclerosis and other diseases. 41.18% patients (7 patients) developed kidney disease after the first dose of SARS-CoV-2 vaccines, and 58.82% patients (10 patients) developed after the second dose. The spectrum and clinicopathological features of show a high degree of consistency among different types of SARS-CoV-2 vaccines.

The exact mechanisms underlying the development of MLN after COVID-19 vaccination remain unknown. The COVID-19 mRNA vaccines promote type I interferon excretion, which is also up-regulated in SLE and considered to be significant in the pathogenesis of SLE [18]. Molecular mimicry of the SARS-CoV-2 spike protein and the function of specific vaccine adjuvants may emerge to play a role in autoimmunity, which is a potential factor in the progress of SLE [19]. Furthermore, the disequilibrium of Th1/Th2 caused by vaccines may also be a pathogenic pathway involved when patients received adenovirus vector based COVID-19 vaccine. It has been shown that there is a dramatic Th1 response with an expansion of CD8+ T cells, with increases of cytokines such as interleukin-2, interferon gamma and tumor necrosis factor. However, no Th2 response has been found after adenovirus vector based COVID-19 vaccine administration [20]. Further research is needed to elucidate the pathogenic pathways involved.

In this case discussed above, combined with her clinic presentation, laboratory findings and "full house" patten shown by IF, subepithelial and mesangial EDD by EM, MLN was confirmed. She developed symptom of lupus two days after the third dose of SARS-CoV-2 vaccination. Strangely, as autoantigens of MLN [21], the expression of EXT1/2 and NCAM1 in the kidney tissue were nondetectable. This may suggest that the target antigens of vaccine-induced LN may represent a distinct phenotype of MLN compared to classic SLE. So far, there are no mechanisms

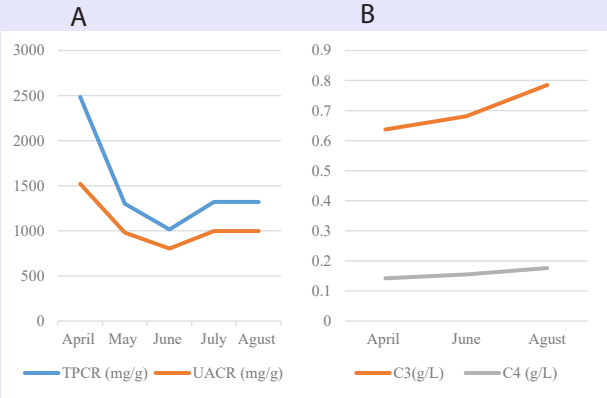

Figure 2: Clinical and laboratory progress.
A. The urine protein decreased following therapy
B. Serum complement levels improved
Abbreviations: TPCR: total protein creatinine ratio; **UACR:** urine albumin creatinine ratio

or triggers to support a direct causal relationship between SARS-CoV-2 vaccination and development of LN. In this case, it is plausible that the immune response stimulated by vaccination elicited SLE and LN in a genetically susceptible individual. It would be a rare adverse event of SARS-CoV-2 vaccine.

There are some limitations in our case. For example, the SARS-CoV-2 spike protein and nucleoprotein in serum and in kidney tissues were not quantified or quantitated. In summary, patients with LN after vaccination should be closely followed, and large epidemiologic studies are needed to assess whether this is more than just an association.

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