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IgA vasculitis nephritis (Schönlein-Henoch purpura with nephritis) following COVID-19 vaccination

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ABSTRACT

IgA vasculitis nephritis (Schönlein-Henoch purpura nephritis) is an autoimmune circumstance characterized by palpable purpura involving the lower limbs, arthralgia, abdominal pain and kidney involvement. It is possible that a cytokine storm following coronavirus disease 2019 (COVID-19) could lead to an immunological dysregulation responsible for IgA vasculitis nephritis in these cases. Reactivation or first onset of IgA vasculitis nephritis is uncommon; however, there have been increasing reports of this disease, as a complication of COVID-19 vaccination. It is possible that COVID-19 mRNA vaccination may trigger several auto-inflammatory and autoimmune cascades. Previous research has shown that Toll-like receptors play a role in the development of IgA vasculitis nephritis. Following injection of a COVID-19 mRNA vaccine, the uptake of double-stranded RNA by-products will trigger Toll-like receptors, leading to a series of intracellular cascades starting an innate immunity-driven process of cell-mediated and humoral-mediated immunity.

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

COVID-19 mRNA vaccines provoke IgA vasculitis nephritis (Schönlein-Henoch purpura nephritis); though a coincidence disease should also be envisaged.

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Introduction

Although pulmonary infection along with alveolar injury and acute pulmonary illness has been described as the characteristic presentation of severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2), involvement of other vital organs including the kidney and heart have been reported (1). In the past three years coronavirus disease 2019 (COVID-19) has afflicted many people in a

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global pandemic throughout the world. This outbreak led to the development of COVID-19 vaccines. Following the widespread administration of COVID-19 vaccinations, a reversion to normality has taken place that relies on the use of these vaccines (2). Vaccines are believed to be the most effective tool to end the pandemic and several studies have also demonstrated that vaccination can decrease the rate of hospitalization (3). In the initial trials the reported adverse reactions included rare cases of anaphylaxis. Overall, the risk of harmful side effects has remained low following vaccination of many people worldwide however, with vaccination of increasing numbers and booster doses, new cases of adverse effects are emerging (4,5).

Subsequent the COVID-19 vaccination, there is the likelihood that the vaccines may aggravate prior autoimmune diseases or provoke new-onset autoimmune disease (5,6). One such disease which we have sought to review is IgA nephritis (Schönlein-Henoch purpura nephritis). IgA nephritis is a small vessel vasculitis that systematically affects organs including the skin, kidney, and the gut owing to significant depositions of IgA immune complexes in these organs (7). This disease may be provoked by various microorganisms (8). IgA nephritis has been increasingly described in relation with SARS-CoV-2 (9). In affected individuals, COVID-19 affects several organs arbitrated by the cascade of inflammatory mediators. IgA (immunoglobulin A) is one of the main parts of the inflammatory cascade which can result in endothelial inflammation and damage. Current research has emphasized the role of serum IgA in the hyperactivation of the immune system and initial seroconversion to IgA in SARS-CoV-2 individuals. This finding is regarded as the most reasonable description for the growth of case reports of IgA-related diseases (9).

Materials and Methods

In this mini-review, we searched Google Scholar, Scopus, PubMed, Embase, EBSCO and Web of Science, by the following keywords of COVID-19 vaccination, IgA nephritis, Schönlein-Henoch purpura nephritis, SARS-CoV-2 and glomerulonephritis. Search was conducted for relevant studies published from 2020 to 2022.

IgA vasculitis nephritis following COVID-19

Sandhu et al reported a case of a 22-year-old man who suffered from abdominal pain, fever and vomiting, and also a painful swelling of both ankles along with wrist joints. The patient additionally developed multiple red papules symmetrically in the lower body. The patient's RT-PCR (reverse transcription-polymerase chain reaction) was positive for COVID-19. He had no respiratory symptoms. Following proteinuria, a renal biopsy was conducted which demonstrated aspects of mesangial deposits of

IgA, in association with endocapillary hypercellularity, mesangial proliferation along with fibrinoid necrosis (7). In another case report by El Hasbani et al, a 16-year-old boy was described who developed palpable purpura on the buttocks and abdominal pain, along with hematochezia and also hemoptysis, two days following COVID-19 detection. The authors diagnosed IgA vasculitis with nephritis (IgAVN) by a raised in serum IgA, alongside an abnormal urine analysis by microscopic hematuria and proteinuria. Besides, this patient had 3651 mg/d proteinuria (10).

Another case was reported by Suso et al, who addressed a 78-year-old man with a normal renal function detected by absence of proteinuria and microhematuria and normal serum creatinine concentration assessed two months prior to hospitalization. This patient was admitted with bilateral pneumonia caused by COVID-19, detected a true a positive RT-PCR test for SARS-CoV-2. Three weeks after initial treatment, the patient was referred to the clinic due to the new symptoms of lower limb purpura and wrist arthritis. Cutaneous vasculitis was confirmed following skin biopsy of this patient. Additionally, proteinuria and urinary dysmorphic red blood cells were detected. Consequently, renal biopsy showed mesangial hypercellularity with expansion. Immunofluorescence detected IgA mesangial deposits, leading to a diagnosis of IgA vasculitis (11). Similarly, Borocco and colleagues studied a thirteen-year-old girl with COVID-19 related Henoch-Schönlein purpura. They presented with low-grade fever, purpuric skin rash and abdominal pain, subsequently leading to a diagnosis of e IgA (12). Another interesting case report describes a four-year-old boy's case from AlGhoozi and AlKhayyat (13). The boy presented with rash on the lower limbs, followed by edema in the ankles. The patient was clinically diagnosed as IgAV using the mandatory criteria for Schönlein-Henoch purpura (13).

A pediatric case describes a kid with gradual rash and abdominal pain who was detected to have IgAVN and SARS-CoV-2 infection. The patient had also hematochezia, purpuric lesions, increasingly elevated D-dimer and abnormal inflammatory biomarkers on laboratory assessment (14). Other case reports describe a three-year-old boy with a clinical diagnosis of IgAVN along with SARS-CoV-2 infection from Jacobi et al (15), and accordingly a case series of IgAVN succeeding SARS-CoV-2 infection by Oñate et al (16).

IgA vasculitis nephritis subsequent the SARS-CoV-2 vaccination

Obeid et al explained a 78-year-old woman with previous IgA vasculitis, who had been in remission for 2 years with no immunosuppressant medication, prior to injection of an

mRNA-1273 COVID-19 vaccine (Moderna). Seven days following vaccination, the patient's condition deteriorated with diarrhea and abdominal pain. The authors concluded this was a flare of IgA vasculitis nephritis post-vaccination (17). Hines et al reported a 40-year-old female with a past medical history of Hashimoto's thyroiditis who received a second dose of the Pfizer-BioNTech BNT16B2b2 mRNA vaccine. The patient presented with new onset purpuric lesions on the buttocks. The patient's symptoms started twenty days before presentation to the hospital. Immunoglobulins including IgA/G/M were found to be elevated. From the rash and the laboratory parameters, the authors diagnosed the patient with early-stage of IgA nephritis following Pfizer-BioNTech BNT16B2b2 mRNA vaccination (18).

More recently, Ito et al explained a case of cutaneous IgA vasculitis in a young male along with hematuria, pericarditis, and diarrhea after the 2nd COVID-19 mRNA vaccination. IgA vasculitis was confirmed by cutaneous biopsy. His purpura subsided and hematuria spontaneously disappeared in due course. They concluded that the hematuria was due to the glomerular vasculitis and active proliferative glomerular lesions following vaccine-induced IgAVN (19). Likewise, in a case described by Badier et al, a 72-year-old male, IgAV was diagnosed, fifteen days following the first injection of vaccination with Oxford-AstraZeneca vaccine (ChadOx1 nCoV-19 vaccine). Features of small capillary vasculitis and leukocytoclasia were found. To confirm the diagnosis immunofluorescence showed vascular wall IgA deposits (20). Maye et al stated a 23-year-old male admitted for the evaluation of acute-onset hematuria 24 hours following injection of the second dose of the COVID-19 vaccine (Pfizer-BioNTech). Eight months prior to the vaccine injection, the patient had been diagnosed with IgA vasculitis. The resultant diagnosis was that of an exacerbation of IgA nephritis (21). Nishimura et al also reported, two patients of IgA vasculitis nephritis following the first or second injection of the Pfizer-BioNTech BNT16B2b2 mRNA vaccine. Both patients were young males with arthritis and palpable purpura. Skin biopsies in both cases showed leukocytoclastic vasculitis. Moreover, the deposits of C3 and IgA were detected on immunofluorescence microscopy in one case (22). There is also a case report of an elderly healthy 94-year-old male with no history of COVID-19 infection, diagnosed with IgA disease who presented with palpable purpura from the waist down ten days following the 2^{ed} COVID-19 mRNA-1273 vaccination (23). Similarly, Valero et al reported two cases of previously controlled IgA vasculitis that presented kidney involvement and cutaneous flares of vasculitis following mild COVID-19, one of which was diagnosed with an acute ANCA vasculitis (24). The final

case reported by Sugita et al describes a 67-year-old female who developed IgAV and purpuric lesions following the second dose of the Pfizer-BioNTech COVID-19 vaccine. Endocapillary hypercellularity, mesangial proliferation with fibrinoid necrosis of capillary walls in the tufts, along with mesangial IgA deposition was seen in this case (25).

Discussion

We assume that a cytokine storm following COVID-19 could trigger an immunological dysregulation, which could be responsible for IgA vasculitis nephritis in some cases (11). Reactivation or first presentation of IgAN is not usually common; however, it is being increasingly described as a complication of COVID-19 vaccination (21). It is plausible that the COVID-19 mRNA vaccine provokes IgA vasculitis (22). In fact, COVID-19 mRNA vaccination may trigger several other autoinflammatory/autoimmune cascades (19). Recent studies have shown that Toll-like receptors have a role in the extension of IgAV. Following injection of a COVID-19 mRNA vaccine, the uptake of double-stranded RNA by-products will trigger Toll-like receptors, leading to a series of intracellular cascades starting an innate immunity-driven process of cell-mediated immunity and humoral-immunity (26-28). It has been suggested that the aberrant glycosylation (Gd-IgA1) may be capable of antigenically detecting compounds of various microbes and producing circulating complexes. The increased concentration of the circulating Gd-IgA1 may well play a role in the pathogenic process of IgA vasculitis nephritis (11). Several authors believe that Gd-IgA1 could be deposited via particular receptors in the mesangial region, followed by the proliferation of glomerular mesangial cells, which might result in kidney injury (29). Moreover, mucosal infections resulting in the upregulation of interleukin-6, directed towards the development of Gd-IgA1 by modifying the glycosylation pathway, may predispose to renal injury (29).

Conclusion

This mini-review of flares and new onset IgAV shows that a principal differential entity should be considered in cases with hematuria post-COVID-19 vaccination. It is expected that, following accumulation of further data on the post-vaccine nephropathy may lead to a deeper understanding of the mechanisms of vaccine-related immune provocation. We conclude that SARS-CoV-2 may be accompanied by triggering of vasculitis and could induce flares of previous autoimmune disease. Further work is therefore necessary especially following booster doses.

Authors' contribution

Conceptualization: LM, SN, RM, SAS.

Validation: LM, SN, RM.
 Research: LM, SN, RM, SAS.
 Resources: LM, SN, RM, SAS.
 Data Curation: LM, SN, RM, SAS.
 Writing—original draft preparation: All authors
 Writing—reviewing and editing: All authors
 Visualization: LM, SN, RM, SAS
 Supervision: LM, SN, RM, SAS
 Project management: LM, SN, RM, SAS
 Funding acquisition: LM, RM, SAS

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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