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Relapses or de-novo IgA nephropathy following COVID-19 vaccination; a narrative review

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ABSTRACT

Immunoglobulin A (IgA) nephropathy is the most common type of glomerulonephritis worldwide characterized by excessive serum levels of glycosylated which triggers the generation of glycan-specific IgG and IgA autoantibodies. This pathological condition results in the formation of circulatory IgA immune complexes, which are essential for the development of glomerular inflammation, especially IgA nephropathy. The serum galactosylated IgA1, IgG, and IgA autoantibodies are suggested as the biomarkers of IgA nephropathy since IgA antibodies are early markers for disease activity too. Serum IgA antibodies emerged as the early COVID-19-specific antibody response about two days after initial symptoms of COVID-19 in comparison with IgG and IgM antibody concentrations, which appeared after five days. IgA nephropathy is frequently presented as microscopic or macroscopic hematuria and proteinuria with a male predominance. COVID-19 infection can include several organs aside from the lungs, such as kidneys through different mechanisms. It is demonstrated in most cases that short-lasting symptoms such as gross hematuria resolve either spontaneously or following a short course of steroids. This review summarized the reported cases of relapses or de-novo reported cases of relapses or de-novo IgA nephropathy and IgA vasculitis following COVID-19 vaccination.

Implication for health policy/practice/research/medical education:
Some case reports emphasize COVID-19 vaccination can aggravate pre-existing occult, un-diagnosed and known kidney diseases such as IgA nephropathy with significant clinical flares as kidney dysfunctions. Therefore, the recognition of autoimmune diseases flare following COVID-19 vaccination is important to improve our knowledge on the diagnosis and control of acute post-vaccination complications..

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Review

A brief overview on IgA nephropathy

The most prevalent glomerulonephritis in the world, immunoglobulin A (IgA) nephropathy is characterized by excessive immunological complexes of glycosylated immunoglobulin IgA1 in serum, which functions as a stimulant to produce glycan-specific IgG and IgA autoantibodies. These autoantibodies lead to the formation of circulating IgA immune complexes, which are necessary for the development of glomerular inflammation, especially IgA nephropathy. IgA nephropathy frequently manifests as microscopic or macroscopic hematuria and proteinuria with a higher prevalence in male gender (1). IgA nephropathy is diagnosed as a complex multifactorial disease that involves genetic preference and other effective

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agents such as infection, dietary and environmental factors as well as raised abnormal glycosylated IgA1 serum levels.

The serum galactosylated IgA1, IgG, and IgA autoantibodies are the biomarkers of IgA nephropathy (2), since IgA antibodies are essential and early markers of disease activity. IgA antibodies in serum are also detected in the early COVID-19-specific antibody response about two days after initial symptoms of COVID-19 in comparison with IgG and IgM antibody concentrations, which appeared after five days.

The presentation of IgA nephropathy is often with hematuria after a viral upper respiratory infection (3). IgA nephropathy-associated hematuria is prevalent in individuals older than 65 years and is improved once hematuria resolves.

The most common reported renal biopsy evidence with SARS-CoV-2 infection is tubulopathy, followed by glomerulopathies. Among COVID-19-induced glomerulopathies, IgA nephropathy is the most common, while it is important to distinguish acute tubular injury from glomerulopathy for the control and prognosis of diseases. The development of continuous urinary abnormalities in patients with COVID-19 should stimulate the necessity for renal biopsy to exclude the glomerulopathies. Laboratory examinations, such as urinalysis are not able to anticipate exactly the glomerulopathies as a reason for renal complications. Thus, early renal biopsy is important for exact diagnosis.

Search method

For this review, we searched PubMed/Medline, DOAJ (Directory of Open Access Journals), Embase, Web of Science, EBSCO, Scopus, and Google Scholar, using various keywords including; IgA nephropathy, COVID-19 vaccination, IgA vasculitis, immunoglobulin A nephropathy, COVID-19, hematuria, autoimmune disease and gross hematuria

Kidney and COVID-19 infection

COVID-19 infection involves other organs aside from lungs, such as kidneys through several different mechanisms such as direct infiltration or indirectly through activation of the complement system, infiltration of inflammatory cells, cytokine storm, drug toxicity, immune system dysfunction, micro-thrombi in the renal vasculature, and hemodynamic instability (4).

The angiotensin-converting enzyme 2 (ACE2) is detected as an entry receptor for binding to the SARS-CoV-2 spike protein. The importance of this receptor in COVID-19 infection is due to its presence in several body organs, particularly podocytes and proximal renal tubes. Therefore, COVID-19 patients may suffer from renal damage as ACE2 receptors are highly expressed in the renal system.

COVID-19 vaccination in IgA

IgA is considered as the primary and most prominent neutralizing antibody produced upon SARS-CoV-2 infection. IgA neutralizes viruses by preventing their adhesion to the epithelial cells.

COVID-19 vaccination induces anti-S IgG antibodies in addition to the IgG response and neutralizes its activity against the pandemic SARS-CoV-2. It has been assumed that the vaccine activates the production of anti-glycan antibodies, along with the pre-existing under-galactosylated IgA1 antibodies in some predisposed patients, which results in IgA nephropathy.

It is approved by Wisnewski et al (5) that COVID-19 messenger RNA-based (mRNA) vaccines efficiently activate spike antigen-specific IgG and IgA, which could result in an IgA nephropathy flare. The mRNA-based COVID-19 vaccine's response is characterized by increased spike specific type I interferon, tumor necrosis factor (TNF) producing T cells, Th1 and Th17 response (6,7). Accordingly, the flare of autoimmune diseases following COVID-19 vaccination should be kept in mind to prompt diagnosis and control of acute post-vaccination complications.

Cases of IgA nephropathy following COVID-19

A 56-year-old male was presented by severe back pain and gross hematuria about one month after his COVID-19 infection. The two separate diseases of IgA nephropathy which detected by renal biopsy and also epidural abscess diagnosed by spine magnetic resonance imaging (MRI) imaging were approved as coincidental. This case of IgA nephropathy was cured with methylprednisolone. Some reasons for these simultaneous events are prolonged lymphopenia, endothelial dysfunction, expression of ACE2 receptors in body organs, susceptibility to thrombosis and immune system dysregulation induced by COVID-19 infection (8).

A 65-year-old Chinese woman with a long-time history of hypertension, and more than one-year history of proteinuria revealed dark-colored urine, progressive proteinuria, and elevated serum creatinine level a day after recovery from SARS-CoV-2 infection. Renal biopsy revealed IgA nephropathy without any indication of COVID-19 infection. The patient improved following the administration of glucocorticoids for three days along with an angiotensin II receptor blocker (9).

It is reported by Amin et al, a case of a 33-year-old Pakistani male who developed weakness, headaches, and mild swelling of the feet, three weeks after the onset of COVID-19 infection. The patient showed proteinuria and deposition of IgA in the glomeruli and renal tubules

based on immunofluorescence images, which were consistent with IgA nephropathy following recovery from COVID-19 infection. This patient recovered with furosemide and enalapril administration (10).

Histological features after autopsy in 42 patients dying by COVID-19 infection and COVID-19–associated acute kidney injury (AKI), revealing only one patient developed IgA nephropathy in the setting of chronic liver disease (11).

A 30-year-old man without medical history appeared with de novo IgA vasculitis on renal biopsy and leukocytoclastic vasculitis on skin biopsy in association with COVID-19 infection. The patient's primary presentations were painful purpuric rash, arthralgia, and abdominal pain, which improved following prednisone treatment. Proteinuria was accordingly improved through treatment with losartan for six weeks (12).

A systematic review reported 13 cases relating to IgA vasculitis and IgA nephropathy related to COVID-19 infection and 4 cases of IgA nephropathy after COVID-19 vaccination. About 77% cases of COVID-19 infection-induced IgA vasculitis and IgA nephropathy were males. The most prevalent clinical appearances were rash and purpura in 85% of cases since gastrointestinal symptoms were detected in 62% of cases. It is increasing evidence for the effect of IgA on the immune response against COVID-19. It has been supposed, the cascade of events induced by mucosal infection such as SARS-CoV-2 involve the increase of interleukin-6 (IL-6) levels, abnormal glycosylation of IgA1 antibodies, production of immune complexes with IgG autoantibodies and accumulating in numerous tissues like skin, soft tissues, and kidneys (13).

COVID-19 vaccination and IgA nephropathy

Recently, a 54-year-old Caucasian female presented as an IgA nephropathy relapse, which was detected by IgA staining and mild tubular atrophy on renal biopsy across with the evidence of gross hematuria, strep throat infection, and obesity, hypertension, and also gastroesophageal reflux disease after the second dose of Moderna vaccine was reported. Gross hematuria developed two days after vaccination, which was associated with noteworthy AKI. Renal function was improved on day 10th and returned to normal after about three months from the onset prednisone (14).

Moreover, Martinez Valenzuela et al studied two cases of IgA nephropathy flare after COVID-19 vaccination and proposed the role of hyper-activation of the Th-1 pathway in IgA nephropathy flare by the vaccine (15).

Another case on this subject was an IgA vasculitis relapse less than one day in a 23-year-old man with an eight-month history of petechial rash demonstrated symptom of acute-onset hematuria after receiving second dose of the Pfizer-BioNTech COVID-19 vaccine. His rash and gross hematuria had completely resolved by prednisone treatment after 2 weeks (16).

Similarly, the is a case report of a Japanese 78-year-old woman with three years history of persistent urine occult blood, who recently developed fever, chills, shivering, marked thrombocytopenia, and gross hematuria nine days after her first dose of the Pfizer-BioNTech mRNA vaccine against COVID-19 infection. The acute worsening of IgA nephropathy, induced by auto-reactivity of IgA antibody in serum against COVID-19 was detected; since, there was not auto-reactivity of IgA in healthy individuals. This case emphasizes COVID-19 vaccination can aggravate pre-existing occult, un-diagnosed and known kidney diseases such as IgA nephropathy with significant clinical flares as kidney dysfunction (17).

Similarly, a 46-year-old Japanese woman with a four-year history of IgA nephropathy, presented with high-grade fever, myalgia, and macro-hematuria 12 hours post-second dose vaccination of vaccine, without any symptoms after the first dose of Pfizer vaccine. The fever and proteinuria were resolved during two weeks spontaneously, though micro-hematuria persevered (18).

The first case report in Korea was a 27-year-old female without known past medical history, presented brown-red urine and gross hematuria with sub-nephrotic proteinuria two days after the second dose of the Moderna SARS-CoV-2 vaccine. This case demonstrated *de novo* IgA nephropathy on renal biopsy after mRNA COVID-19 vaccine injection (19).

A recent case report related to a 26-year-old man with suspected IgA nephropathy in his past- history, presented fever, gross hematuria, worsening proteinuria and nearly twice rises in serum creatinine, a day following his second dose of Pfizer-BioNTech COVID-19 vaccination. Renal biopsy revealed histological findings suggestive of IgA nephropathy with acute renal tubular damage. Proteinuria was sufficiently controlled with losartan. One possible description for the IgA nephropathy after vaccination is the construction of antiglycan antibodies that cross-react with pre-existing under-galactosylated IgA1 which leads to IgA nephropathy (20).

There is little trial information on renal outcomes after IgA nephropathy flares associated with COVID-19 vaccination. A large cohort suggested inactivated COVID-19 vaccination is largely safe in patients with IgA nephropathy (21). In an observational cohort study, it is determined the renal outcomes in IgA nephropathy patients, following mRNA COVID-19 vaccination. Around 116 patients were included in the study with mean age of 50 years. It was concluded that alterations of proteinuria and glomerular filtration rate in these patients is mild since proteinuria in post-vaccination does

not significantly increase more than 0.5 g/d. Moreover, proteinuria ≥0.5 g/d was resolved without any new treatment to its baseline medications (22).

The recent case reports of IgA nephropathy flare-up after vaccination, showed macroscopic hematuria, following the second dose of SARS-CoV-2 vaccination in adults. In addition to adult patients, two pediatric patients with IgA nephropathy presented with macroscopic hematuria less than one day after Pfizer COVID-19 vaccination without COVID-19 infection history or allergy to any vaccinations. Two boys, 13-year-old with a history of type 1 diabetes mellitus and known IgA nephropathy in one and another 17-year-old healthy boy presented a new-onset gross hematuria, proteinuria, and AKI one day following the second dose of the vaccine. Thus, relapse and new-onset of IgA nephropathy respectively is demonstrated in these two pediatric patients (23).

Likewise, a healthy 12-year-old Jordanian boy showed mild interstitial edema, red cell casts with mild kidney tubular damage and flattening of renal epithelial cells without fibrosis or inflammation with macroscopic hematuria which detected less than one day after the first dose of Pfizer-BioNTech vaccine, approved the presence of IgA nephropathy on renal biopsy (24).

There was also a report of two patients who underwent their first kidney biopsy due to the development of gross hematuria two days following the second dose of the Moderna vaccine for COVID-19 including a 50-year-old white woman with history of 32 years of hypertension, obesity, and antiphospholipid syndrome and a 19-year-old white man with a 6-month history of micro-hematuria, without a family history of kidney disease (25). The rapid development of gross hematuria within several days after the second vaccination implicates a systemic cytokine-mediated flare, possibly via induction of heightened IgA1 anti-glycan immune responses.

Four additional cases of IgA nephropathy and/or IgA vasculitis are reported which were associated with Moderna SARS-CoV-2 mRNA vaccination. Patients one, and two are both women with normal kidney function who developed gross hematuria and mild proteinuria without a rise in serum creatinine less than two days after a second vaccine dose. In contrast, cases three and four are both men with chronic renal failure and mild proteinuria since patient three showed an active and chronic IgA nephropathy which was treated with an angiotensin-converting enzyme inhibitor. In addition, patient four showed IgA vasculitis and received a one-week course of prednisone, which improved rash and renal function (26).

Two Japanese brothers, 15-year-old and 18-year-old, mans with a 6-months and 3-year history of microscopic hematuria, one day and two days respectively, following injection of the second dose of the Pfizer-BioNTech SARS-CoV-2 vaccine were referred to hospital due to macroscopic hematuria. Macroscopic hematuria is recovered in both cases spontaneously across several days. Pathological evidence of renal biopsy specimens in both two cases was consistent with IgA nephropathy.

Regarding the cases diagnosed as IgA nephropathy following the second dose of SARS-CoV-2 vaccination, it is possible that the mRNA vaccination causes the production of abnormally glycosylated IgA1 via Toll-like receptor (TLR) signaling and is related to at least partially to exacerbation of immunoglobulin A nephropathy (27).

Recently, it is reported a 41-year-old woman presented headache, generalized myalgia, and new-onset macroscopic hematuria one day after the second dose of the Pfizer-BioNTech COVID-19 vaccine. Histopathology showed IgA nephropathy on renal biopsy with fibro cellular and fibrous crescents, non-nephrotic proteinuria, hypertension, and elevated serum creatinine after the second dose of vaccine, while the patient had no prior history of macroscopic hematuria and any proteinuria on urine analysis even during pregnancy. Thus, all findings suggested unmasking preexisting unknown IgA nephropathy after the vaccination (28).

A survey based on the web in Japan evaluated the association between gross hematuria and COVID-19 vaccination in 27 patients after injection of COVID-19 vaccination. Among them, 19 (70.4%) patients had the diagnosis of IgA nephropathy. Only one case displayed a slightly increased serum creatinine concentration since none of the cases developed significant kidney dysfunction.

Importantly, the reported gross hematuria was only after receiving an mRNA vaccination including the Pfizer-BioNTech and the Moderna vaccines with purified mRNA lipid nanoparticle-encapsulated platform. This novel RNA platform induces T cell responses that produce several pro-inflammatory cytokines such as IL-1, IL-6, type I interferon and TNF alpha. These cytokines can flare previous glomerular disease or induce de novo glomerulonephritis, particularly IgA nephropathy (29).

In a more recent case series, Lim et al, report the pathology results of new-onset renal dysfunction following COVID-19 vaccination as confirmed by renal biopsy. The study contained five patients where baseline kidney function was normal in all of them. Biopsy showed IgA nephropathy reporting with painless gross hematuria painless, proteinuria and symptom of dark reddish urine without family history of kidney diseases, in one of them, one day after receiving the second dose Moderna vaccine (30).

It is summarized reported cases relapses or de-novo IgA nephropathy and IgA vasculitis following COVID-19 vaccination in Table 1. It is observed often cases of flare-up or de novo IgA nephropathy showing gross hematuria,

following mRNA COVID-19 vaccination (23,26,28). It is demonstrated in mostly these studies that short-lasting symptoms such as gross hematuria resolving either spontaneously or following a short course of steroids. More studies however are needed to evaluate the accuracy of this content for all cases of COVID-19 vaccination-induced IgA nephropathy and evaluate mechanisms associated with them.

Conclusion

Thus, recognition of the probability of autoimmune diseases flare after COVID-19 vaccination is important to help in the diagnosis and control of acute post-vaccination complications. IgA nephropathy is associated with hematuria in most of the cases and is improved when hematuria resolves. It is demonstrated in most of these studies that short-lasting symptoms such as gross hematuria resolving either spontaneously or following a short course of steroids. More studies are required to evaluate the accuracy of this content for all cases of COVID-19 vaccination-induced IgA nephropathy and evaluate different mechanisms associated with them.

Table 1. Reported cases relapses or de-novo IgA nephropathy and IgA vasculitis following COVID-19 vaccination

Age	Gender	Manufacture vaccine	Dose of vaccine or infection	Presentation	Distance between vaccine and disease onset (days)	Disease	References
56	Male	-	Infection	Severe back pain and gross hematuria	1 month	IgA nephropathy and spinal epidural abscess	8
65	Female	-	Infection	Dark-colored urine, worsening proteinuria and rise of eGFR	a day after recovery	IgA nephropathy	9
33	Male	-	Infection	Weakness, headaches, and mild swelling of the feet	21 days	IgA nephropathy	10
30	Male	-	Infection	Painful purpuric rash, arthralgia, and abdominal pain	≥10 days	IgA vasculitis	12
54	Female	Moderna	Second	Gross hematuria	2 days	IgA nephropathy	14
36	Female	Moderna	Second	Fever, malaise and gross hematuria	≤1 day	IgA nephropathy	15
50	Male	Pfizer	First	Gross hematuria	≤1 day	IgA nephropathy	15
23	Male	Pfizer	Second	Acute hematuria	≤1 day	IgA vasculitis	16
78	Female	Pfizer	First	Fever, chills, shivering, marked thrombocytopenia, and gross hematuria	9 days	IgA nephropathy	17
46	Female	Pfizer	Second	Fever, myalgia and gross haematuria	≤1 day	IgA nephropathy	18
27	Female	Moderna	Second	Subnephrotic proteinuria and gross hematuria	2 day	De-novo IgA nephropathy	19
26	Male	Pfizer	Second	Proteinuria, rise in serum creatinine and gross hematuria	1 day	IgA nephropathy with acute tubular injury	20
13	Boy	Pfizer	Second	Gross hematuria	≤1 day	IgA nephropathy	23
17	Boy	Pfizer	Second	Gross hematuria	≤1 day	De-novo IgA nephropathy	23
12	Boy	Pfizer	First	Edema, red cell casts with mild tubular injury, gross hematuria	≤1 day	IgA nephropathy	24
50	Female	Moderna	Second	Gross hematuria	2 days	IgA nephropathy	25
22	Female	Moderna	Second	Gross hematuria and mild proteinuria	2 days	IgA nephropathy	26
39	Female	Moderna	Second	Gross hematuria and mild proteinuria	2 days	IgA nephropathy	26
50	Male	Moderna	Second	Gross hematuria	1 day	IgA nephropathy	26
67	Male	Moderna	First	Gross hematuria	30 days	IgA vasculitis	26
15	Male	Pfizer	Second	Gross hematuria	1 day	IgA nephropathy	27
18	Male	Pfizer	Second	Gross hematuria	2 days	IgA nephropathy	27
41	Female	Pfizer	Second	Headache, generalized myalgia, gross hematuria	1 day	IgA nephropathy	28
42	Female	Moderna	Second	Gross hematuria, proteinuria and dark reddish urine	1 day	De-novo IgA nephropathy	30

Some case reports emphasize COVID-19 vaccination can aggravate pre-existing occult, un-diagnosed and known kidney diseases such as IgA nephropathy with significant clinical flares as kidney dysfunctions.

Authors' contribution

Conceptualization: MH, SS and MK.
Validation: MH, MK, HRJ, PP, SA and SS.
Investigation: MH, SA, PP and HRJ.
Resources: MH, SS and MK.
Data curation: MH, SS, MK, PP and SA.
Writing—original draft preparation: MH, SS.
Writing—reviewing and editing: PP, SA and MK.
Visualization: MH.
Supervision: MH, MK, SS and HRJ.
Project Management: SS.

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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