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Case Report

A case of crescentic glomerulonephritis with exacerbation of pre-existing IgA nephropathy after COVID-19

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ABSTRACT

Background. Relapses or new-onset IgA nephropathy (IgAN) have been documented in patients after vaccination against SARS-CoV-2; however, only one adult patient has been reported in whom pre-existing IgAN worsened during coronavirus disease 2019 (COVID-19).

Case. We present the first pediatric case with biopsy-proven IgAN and genetically confirmed Alport syndrome, who developed end-stage kidney disease after an exacerbation of IgAN associated with COVID-19. The patient's basal serum creatinine was 0.7-0.9 mg/dL before infection. He had not been vaccinated against COVID-19. He was admitted to the hospital with edema, hypertension, an elevated serum creatinine of 4.7 mg/dL, and massive proteinuria. Three months before admission, he had been admitted to another hospital with COVID -19 and an elevated serum creatinine (1.9 mg/dL), but no biopsy had been performed at that time. The kidney biopsy revealed IgAN with 50% fibrocellular crescents with sclerosed glomeruli, tubular atrophy, and interstitial fibrosis. His serum creatinine did not decrease even after five administrations of pulse steroids, and hemodialysis was initiated.

Conclusion. In conclusion, COVID -19 may pose a high risk for exacerbation of pre-existing glomerular disease. It is therefore necessary to closely monitor the kidney function of patients with underlying glomerulonephritis during and after COVID-19 and consider an early biopsy if serum creatinine does not return to baseline levels. In addition, this case report highlights the clinical importance of the co-occurence of IgAN and Alport syndrome.

Key words: Alport syndrome, children, crescentic glomerulonephritis, COVID-19, IgA nephropathy.

Since the first description of coronavirus disease 2019 (COVID-19) in December 2019, it has been well known that kidney involvement is the second leading cause of morbidity and mortality in patients with COVID-19.[1] There are numerous mechanisms that may contribute to kidney injury in patients with COVID-19, including virus-mediated damage, cytokine storm, activation of the Angiotensin II pathway, complement activation, hypercoagulation, and thrombotic microangiopathy.[2-4] Kidney involvement manifests as both glomerular and tubular diseases and varies from acute kidney injury to glomerulonephritis.[4] IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis (GN) and is usually triggered by infections.[5-7] Several cases of IgAN have been reported following administration of the SARS-CoV-2 vaccine[8,9], but there is only one documented instance of an adult patient experiencing an exacerbation of pre-existing IgAN during COVID-19 infection.[10]

To date, a few cases have been reported in which IgAN and Alport syndrome (AS) occurred together.[11-13] Familial cases of IgAN suggest

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that this may not be a coincidence.[11] The case presented here was previously published in the context of biopsy-proven IgAN and genetically confirmed autosomal dominant AS[14,15], but experienced a severe exacerbation of IgAN after COVID-19.

In the present report, we have attempted to highlight the following aspects: 1) presentation of the first pediatric case with an exacerbation of IgAN following COVID-19, which rapidly progressed to end-stage kidney disease (ESKD), 2) highlight the co-occurrence of IgAN and AS with the clinical significance of this association, and 3) emphasize the importance of timely kidney biopsy in such cases of management.

Case report

A 16-year-old boy, who was diagnosed with IgAN and AS at the age of 8 years, was hospitalized with complaints of an increase in serum creatinine. He was born to consanguineous parents, and his parents were first degree cousins. Within his family history, three members had hematuria, one had hematuria and proteinuria, and his father had chronic kidney disease (CKD). Furthermore, hematuria was identified in two additional family members (paternal uncle and cousin) and proteinuria was detected in two other relatives (paternal cousins). As previously reported in detail[14,15], he had concomitant glomerular pathologies, IgAN and AS. The light microscopy and immunofluorescence findings of the kidney biopsy were consistent with those of IgAN, but electron microscopy revealed a partially thinner and thickened glomerular basement membrane with a basket-weave appearance, suggesting AS. Targeted next-generation sequencing revealed a homozygous frameshift mutation in the COL4A4 gene; c.2438delG (p.Gly813AspfsTer56). In addition, he had sensorineural hearing loss and anterior lenticonus. He was subsequently treated with the maximum dose of ramipril; his basal serum creatinine was 0.7-0.9 mg/dL, and his urine protein was 1.5 g/day. He had not been vaccinated against COVID-19.

Three months prior to the current admission, he had a history of COVID-19 and had been hospitalized in another hospital with fever and elevated serum creatinine (1.9 mg/dL). During COVID-19 hospitalization, angiotensin-converting enzyme inhibitor had been discontinued, no additional treatment had been given, and no biopsy had been performed. On admission to our hospital, physical examination revealed edema and hypertension (blood pressure 140/90 mmHg, >95th percentile). No oliguria or macroscopic hematuria was noted. Laboratory examination revealed a serum urea of 142 mg/dL, a creatinine of 4.7 mg/dL, an albumin of 2.9 g/dL, and a 24-hour urinary protein excretion of 6 g. Other laboratory tests showed hyperkalemia, hyperphosphatemia and increased parathormone levels. Complete blood count was normal, serum complement levels were within the normal range. Antinuclear antibodies, anti-dsDNA antibodies, and anti-neutrophil cytoplasmic antibodies were all negative (Table I). Ultrasonography revealed bilaterally increased echogenicity of the kidney parenchyma with normal size of both kidneys.

Because of the increase in serum creatinine, a kidney biopsy was performed, which revealed IgAN (2+ granular mesangial staining for IgA) with 50% fibrocellular crescents (6 of 12 glomeruli). In addition, of the total 12 glomeruli, 5 glomeruli were globally sclerosed, and one showed segmental sclerosis, tubular atrophy and interstitial fibrosis, interstitial nonspecific mononuclear cell infiltration (Fig. 1). Arterioles showed hyaline sclerosis and hyperplastic changes. Unfortunately, we were unable to perform an immunohistochemical examination for SARS-CoV-2. The ultrastructural analysis of renal tissue did not reveal any evidence of the presence of SARS-CoV-2. Five doses of pulse methylprednisolone (1g per dose) were administered for the treatment of crescentic GN. Despite this intervention, there was no improvement in the serum creatinine levels. Consequently, hemodialysis was initiated, and the decision was made to discontinue immunosuppressive treatment due to the

Table I. Laboratory findings of the patient before, during, and after COVID-19 infection.

	Before COVID-19	During COVID-19	After COVID-19
TLC (cells/μL)	2300	2200	1700
TNC (cells/μL)	8900	2600	9600
Urea (mg/dL)	93	94	142
Creatinine, mg/dL	0.9	1.9	4.7
eGFR (ml/min/1.73m²)	80	38	10
Serum albumin (gr/dL)	3.6	3.1	2.9
C-reactive protein (< 5 mg/dL)	<0.5	0.28	0.94
C3 (0.9-1.8 g/L)			0.97
C4 (0.1-0.4 g/L)			0.21
ANA			Negative
Anti-dsDNA (IgG) (<12 IU/mL)			2.1
PR3 ANCA (<12 IU/mL)			Negative
MPO ANCA (IgG) (< 12 IU/mL)			Negative
Urinary protein excretion (gr/day)	1.5	2.2	6

ANA: anti-nuclear antibody, anti-dsDNA: anti-double stranded DNA, C3: complement 3, C4: complement 4, MPO ANCA: anti-myeloperoxidase antineutrophil cytoplasmic antibody, PR3 ANCA: anti-proteinase 3 antineutrophil cytoplasmic antibody, TLC: total lymphocyte count, TNC: total neutrophil count

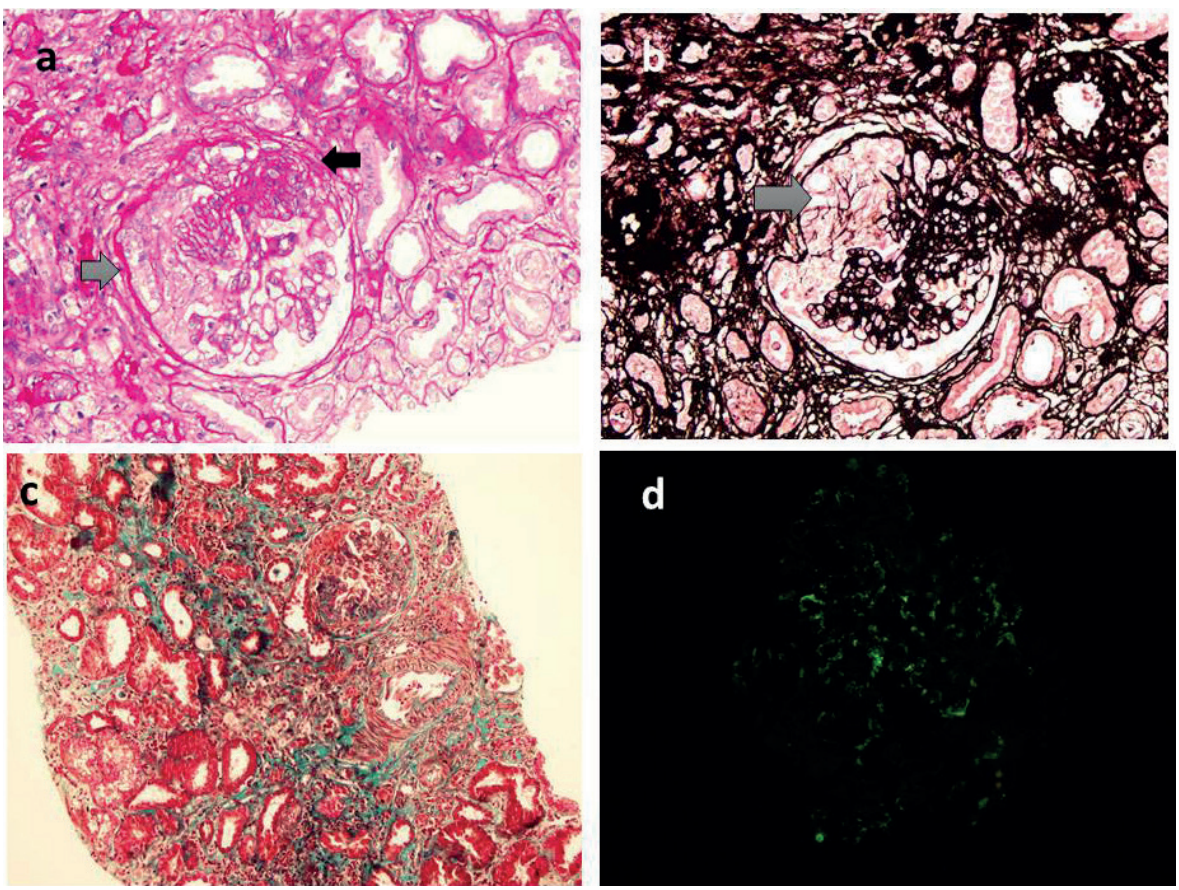

Fig. 1. Biopsy shows segmental sclerosis (black arrow) and fibrocellular crescent (gray arrows).
(a: PAS, periodic acid schiff; b: PAMS, periodic acid methenamine silver), focal tubular atrophy and interstitial fibrosis (c: MT, Masson's Trichrome) and mesangial IgA deposits by immunofluorescence (d: FITC, fluorescein isothiocyanate).

chronic findings in the biopsy specimen. Three months after the initiation of hemodialysis (HD), he remained on HD three times a week for four hours. The patient was still doing well on chronic HD and was on a waiting list due to no available living donor in the family.

An informed consent was received from the patient's family for the publication of this report.

Discussion

Although the development of new-onset or relapses of IgAN has been reported after COVID-19 vaccination, only one adult patient has been reported to have experienced an exacerbation of pre-existing IgAN during COVID-19.[10] Here, we presented the first pediatric case who rapidly progressed to ESKD with an exacerbation of pre-existing IgAN after COVID-19.

IgA nephropathy is the most common primary glomerular disease and viral infections may exacerbate IgAN. The increase in IL-6 production during mucosal infections stimulates poor glycosylation/galactosylation of IgA1. This leads to the formation of Gd-IgA1 and contributes to the development of IgA-related diseases, such as IgAN and IgA vasculitis nephritis (IgAVN).[16] It has been suggested that COVID-19 as a mucosal infection may also trigger IgAN and IgAVN through a similar mechanism.[9] Other cytokines that are elevated in COVID-19 can also lead to IgAN through the proliferation and maturation of these IgA1-producing B cells.[9] It has previously been reported that an excessive production of IgA1 monomers after influenza vaccination led to IgAN or the disease exacerbation[17]; therefore, it has been suggested that a similar process may occur after COVID-19 vaccination.[9] More cases have been reported of new-onset IgAN or exacerbation of pre-existing IgAN after SARS-CoV2 vaccination than cases of IgAN following a natural COVID-19 infection.[8]

Corticosteroid treatment is used in patients at high risk for the progression of IgAV or IgAN.[18] New-onset or relapse of IgAN has been reported following SARS-CoV-2 infection and vaccination, and all patients reported so far recovered spontaneously or with systemic steroids, and none have progressed to ESKD.[8,9] Our case had two distinct primary kidney diseases: biopsy-proven IgAN and molecularly proven AS (*COL4A4* homozygous), which we have previously reported[14,15], and had stage 2 CKD. This patient was admitted to our hospital three months after COVID-19. It was noted that the patient had acute kidney injury with an increase in serum creatinine during COVID-19 without fever, dehydration, or severe respiratory disease and no kidney biopsy was performed at the time. The kidney biopsy performed on admission to our hospital revealed a crescentic IgAN with chronic changes. Treatment with pulse steroids did not improve kidney function, and he progressed to ESKD requiring hemodialysis. It is difficult to say whether the outcome would have been different if the patient had been treated with corticosteroid earlier. This is because the patient had concomitant glomerular disease i.e. AS, that might have led to the rapid progression to ESKD. However, it seems more reasonable to assume that the deterioration in kidney function was mainly related to the exacerbation of IgAN.

Finally, some cases of co-occurrence of IgAN and AS have been reported.[12,13,19] In a large family with familial IgAN, a susceptibility locus for IgAN was detected at locus 2q36, which is in the neighborhood of the *COL4A3* and *COL4A4* genes (2q36.3)[11], suggesting that the co-occurrence of these distinct kidney pathologies in familial cases is not a coincidence. Alport syndrome and IgAN may have similar clinical and laboratory findings, but require different management strategies, including genetic counseling, treatment, and risk of recurrence after transplantation. Therefore, it is important to be aware of this coexistence. Our case demonstrated a severe exacerbation

of IgAN as a cresentic glomerulonephritis following COVID-19. This indicates that the IgA deposition in the kidneys was not an incidental finding. Therefore, this case also demonstrates that a kidney biopsy will be required in a patient with the co-occurrence of AS and IgAN if any clinical or laboratory finding that deviates from the natural course of AS.

In summary, we report an adolescent who was diagnosed with both IgAN and AS and who progressed to ESKD treated with dialysis with a relapse of IgAN after COVID-19. It is important to note that COVID-19 may also pose a high risk for exacerbation of pre-existing glomerular disease, leading to worsening of the kidney disease. This underscores the potential impact of viral infections on kidney and disease progression and highlights the need for careful monitoring and treatment of patients with IgAN and AS, particularly in the context of viral infections. In addition, it highlights that IgAN and AS together can significantly affect disease progression, and that early biopsy should be performed if the kidney function deteriorates unexpectedly.

Ethical approval

Written informed consent has been obtained from the parents.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: NC; data collection: EKY, GM, SS, YÖ; interpretation of results: EKY, RG, NC; draft manuscript preparation: EKY; critically review of the manuscript: SS, AA, NC. All authors reviewed the manuscript and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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