EDITORIAL COMMENT

Have we missed AINything? Acute interstitial nephritis in SARS-CoV-2 infection and vaccination

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ABSTRACT

Acute interstitial nephritis (AIN), defined by the presence of interstitial inflammation accompanied by tubulitis, is an often overlooked cause of acute kidney injury (AKI). It is now well established that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can cause a wide variety of kidney injuries, most commonly acute tubular injury and collapsing glomerulopathy. In comparison, AIN is rarely documented in association with SARS-CoV-2 both anecdotally and in larger series of autopsy or biopsy studies. In this issue of the Journal, León-Román describe five cases of AIN in patients with a history of coronavirus disease 2019 (COVID-19) and highlight AIN as a possibly under-reported or ignored facet of renal disease associated with SARS-CoV-2. They describe three scenarios in which AIN can be seen: (i) SARS-CoV-2 infection after diagnosis of AIN, (ii) AIN followed by SARS-CoV-2 infection in the same admission and (iii) Severe SARS-CoV-2 and AIN possibly associated with SARS-CoV-2 itself. Overall, AIN remains rare in SARS-CoV-2 and causality is difficult to ascertain. Interestingly, AIN is not only seen in association with the disease itself but also with SARS-CoV-2 vaccination. This scenario is equally rare and causality is no less difficult to prove. A history of preceding SARS-CoV-2 infection and vaccination should be actively sought when patients present with otherwise unexplained AIN.

Keywords: acute interstitial nephritis, severe acute respiratory syndrome coronavirus 2, vaccination

INTRODUCTION

Since the first descriptions of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19), nephrologists have discovered that several forms of renal disease may be linked to the virus [1]. Clinical reports on acute kidney injury (AKI) in patients with severe SARS-CoV-2 infection [2, 3] were rapidly followed by reports showing the virus in urine [4]. Viral presence in tubular cells [5] remains controversial but documented various glomerular lesions have been documented, most commonly collapsing glomerulopathy. More recently, SARS-CoV-2 vaccination has also received considerable attention with several reports describing new glomerular lesions after vaccination; these reports are noteworthy for the variety of glomerular pathology described, ranging from minimal change disease to IgA nephropathy and crescentic lesions with or without antineutrophil cytoplasmic antibodies (ANCA). It has not yet been established how SARS-CoV-2 vaccination can trigger so many different lesions, and causality remains difficult to ascertain. In comparison, acute interstitial nephritis (AIN) is rare both in the context of SARS-CoV-2 infection and vaccination. In this issue of the Journal León-Román et al. [6] highlight AIN as a poorly understood renal lesion in SARS-CoV-2 infection. In this editorial, we aim to put their findings into perspective. We discuss reports of AIN in patients with SARS-CoV-2 infection and
vaccination, speculate about underlying mechanisms and also emphasize important caveats and areas of uncertainty.

**AIN and SARS-CoV-2 infection**

In this issue of the Journal, León-Román et al. [6] highlight AIN as an interesting and probably often overlooked, aspect of renal disease associated with SARS-CoV-2 infection. They describe five additional cases of AIN associated with SARS-CoV-2 infection [6] in different settings. Two of these cases occurred in patients diagnosed with AIN several years previously. In both cases, the cause of the AIN was secondary to immunological therapy for metastatic cancer. These patients then subsequently contracted SARS-CoV-2 and required hospital admission. Both cases had a good outcome and their clinical course is what one expects in similar immuno-suppressed patients acquiring COVID-19 infection. In two cases [6], the initial presenting feature was acute kidney injury (AKI) secondary to AIN caused by medications with a known associated with AIN- namely ciprofloxacin and proton pump inhibitors (PPIs), respectively. Both patients developed SARS-CoV-2 infection in the hospital within days of their initial hospital admission. One patient unfortunately died, whilst the other made a good recovery. The final case, and probably the most interesting of the five, is a patient who presented with severe SARS-CoV-2, required intensive care admission and developed an AKI requiring continuous veno-venous haemofiltration. A kidney biopsy showed AIN that was felt to be due to COVID-19, although the patient also had exposure to ceftriaxone, tobramycin and linezolid. This patient was treated with steroids and had a good outcome.

Acute and chronic tubulointerstitial nephritis is one of the most common, but often overlooked, causes of AKI. Since patients with AKI frequently present with nonspecific clinical features, kidney biopsy plays an important role in establishing the diagnosis. Pathologic diagnosis of AIN is characterized by the presence of interstitial inflammation associated with tubulitis. When a cause of AIN can be determined, medications are the most common aetiology followed by autoimmune diseases (such as Sjogren’s syndrome, IgG4-related disease and sarcoidosis), infection and other rare entities such as Tubulointerstitial Nephritis and Uveitis (TINU) syndrome. Infectious aetiologies of AIN are relatively uncommon, but have been described in association with various bacterial, viral and fungal microorganisms including cases with granuloma formation [7].

Virus-associated AIN is most frequently seen in transplanted patients and is most often caused by BK polymavirus, JC polyomavirus, cytomegalovirus [8] and adenovirus [9]. When compared with other cases of AIN in which histology is often nonspecific, virus-associated AIN is unique, because kidney biopsy can often establish specific aetiology by demonstration of viral infection in the kidney using immunohistochemical stains. Consequently, direct infection of the kidney, together with the cytotoxic T-cell response directed against the viral compound, likely plays a role in the pathogenesis of some virus-associated AIN.

AKI is common amongst hospitalized patients with COVID-19 and a prevalence of up to 30% has been reported [10] although the exact figures remain disputed [11]. Although most do not undergo biopsy, COVID-19 is associated with a wide variety of kidney pathologies, most notably collapsing glomerulopathy in patients with high-risk APOL1 genotype and acute tubular injury in patients with severe COVID-19 [12–15]. However, only a few reports of AIN have been described in patients with COVID-19 [16–20].

The small number of cases of AIN following or during SARS-CoV-2 infection underscores the impression that AIN is an unusual complication. Furthermore, these reported cases highlight the difficulty and caution needed to establish COVID-19 as a possible cause or trigger of AIN from some other causes. For instance, a 12-year-old girl presented with a 3-week history of reduced appetite, weakness, weight loss and an AKI (creatinine 1.2 mg/dl) [20]. She was found to have SARS-CoV-2 IgG antibodies (titre 195 AU/mL, cut-off > 11.9 AU/mL) but tested negative for COVID-19 twice on routine swab testing, suggesting previous SARS-CoV-2 infection. She had tubular proteinuria. A kidney biopsy confirmed the presence of AIN with marked neutrophilic and lympho-plasma-cellular invasion of the interstitium. There were no immune deposits or virus-like particles seen on electron microscopy. She was treated with steroids and had complete resolution of kidney impairment [20]. In this case and in other reports, there was no convincing evidence of direct viral infection of the kidney parenchyma, in contrast to the typical cases of virus-associated AIN.

Therefore, even in this previously healthy patient without exposure to medications, whether this patient’s AIN is a direct result of SARS-CoV-2 infection or if the viral infection acted as a ‘second-hit’ to trigger AIN from other causes, such as TINU, one of the most common causes of AIN in the pediatric population, is not clear.

What does the report by León-Román et al. add to the literature? Their work reminds us to be mindful of AIN in patients with COVID-19 and highlights the existence of AIN and SARS-CoV-2 in different settings: (i) SARS-CoV-2 infection some years after initial diagnosis of AIN, (ii) AIN and SARS-CoV-2 infection in the same admission and (iii) severe SARS-CoV-2 and AIN possibly associated with SARS-CoV-2 itself. Furthermore, given the lack of convincing viral infection of the kidney in patients with AIN and COVID-19, their report highlights the need for nephrologists to be cautious when considering SARS-CoV-2 as a possible cause of AIN. In particular, nephrologists should carefully assess the timing of SARS-CoV-2 infection and onset of kidney injury, and exclude other causes of AIN before concluding that AIN is likely caused by SARS-CoV-2. In fact, as illustrated by León-Román et al. [6] in this issue, alternative causes for AIN are present in some cases, such as antibiotics administered for concurrent bacterial pneumonia or proton pump inhibitors (PPIs). Importantly, nephrologists should also be careful to exclude unusual causes of AIN in this setting, such as AIN caused by traditional or herbal medicines taken in an attempt to prevent SARS-CoV-2 [21].

It is also worth considering the possibility of whether any of the antiviral drugs used more recently in SARS-CoV-2 infection could potentially cause AIN, as other antivirals have been reported as possible triggers of AIN. Duque et al. described AIN associated with antiviral treatment for hepatitis C infection [22]. Famiciclovir has also been reported in conjunction with AIN [23]. Whether or not antivirals used in the treatment of COVID-19 are capable of causing AIN is currently unknown although a case of AIN associated with lopinavir/ritonavir has been reported in a different context [24]. The topic of nephrotoxicity of antiviral drugs, in general, is reviewed elsewhere [25].

There are several possible reasons for the paucity of cases of AIN reported in patients with COVID-19. One possibility is under-detection since most patients with AKI and COVID-19 do not undergo kidney biopsy. Alternatively, steroid therapy administered for COVID-19, especially in more severe diseases may result in recovery and under-reporting of AIN. Lastly, the paucity of AIN may be due to a lack of significant direct infection of kidney parenchyma, even among those with severe infection. This is in
contrast to BK virus infection where high viral load consistently correlates with the presence of AIN. However, the possibility of the immune response against filtered viral proteins causing AIN in rare predisposed patients cannot entirely be ruled out.

Irrespective of the discussion of causality, AIN is often regarded as an under-recognized and thus under-reported disease [26]. Given that prompt treatment with either steroids or removal of the causative drug is likely to drastically improve outcomes for patients with AIN, it is important for clinicians to keep an open mind as to the cause of AKI in patients with COVID-19, particularly those that are not responding to conventional management. Where possible, correctly identifying the cause of AKI in patients with COVID-19 is important because it has been shown that the rate of kidney function decline post-discharge is significantly greater (−11.3mL/min/1.73m² faster) in those patients with a diagnosis of COVID-19 compared with those without [27].

The small number of cases of AIN following or during SARS-CoV-2 infection underscores the impression that AIN is an unusual complication given the paucity of AIN in small and large series of biopsy and autopsy renal tissue obtained from SARS-CoV-2 patients. It is also possible that subtle presentations of AIN occur more frequently but that such cases recover spontaneously or do not undergo kidney biopsy. It is also worth remembering that subtle urinary abnormalities are surprisingly common in SARS-CoV-2 infection when compared with the incidence of AKI and to histological data. George et al. showed that SARS-CoV-2 spike protein is detectable in as many as 25% of patients and that many of them have albuminuria although the long-term implications of such findings remain unclear [28]. It is possible that mild and subtle cases of AIN are overlooked not least because quite a few of these patients are too unwell to undergo renal biopsy. Other patients may not undergo biopsy due to coagulopathy or because clinicians feel a biopsy is not warranted where meaningful immunosuppressive treatment would not be feasible anyway. Equally, one could speculate that steroid treatment is now so commonplace, especially across the more severe end of the spectrum of SARS-CoV-2 that some milder cases of AIN may recover and escape detection following steroid treatment.

Whilst reports of AIN as a cause for AKI in patients diagnosed with COVID-19 are few, there is a growing body of evidence to suggest that more subtle forms of tubulointerstitial injury are an important part of the pathophysiological response. In a study performed in France, 71 patients with COVID-19 were admitted to intensive care over a month-long period [29]. Of the 71 patients, 57 developed AKI and of these 10 required renal replacement therapy (RRT). Proteinuria was assessed with both protein:creatinine ratio (pPCR) and albumin:creatinine ratio (uACR). The median uPCR was significantly raised at 82 mg/mmol whereas the median uACR was normal at 0.23 mg/mmol. This discrepancy suggests a predominant tubulointerstitial injury which could indicate acute tubular injury or interstitial nephritis, or both. Interestingly, there was a low incidence of glycosuria pointing away from renal Fanconi syndrome. Another study has demonstrated that SARS-CoV-2 causes a proximal tubular dysfunction characterized by low molecular weight proteinuria, hyperphosphataemia, hypouricaemia and neutral aminoaciduria [30].

Finally, one might wonder whether AIN is ever associated with SARS-CoV-2 infection in transplant patients. Westhoff et al. report the interesting case of a kidney-pancreas transplant recipient with AIN and SARS-CoV-2 RNA in tubular cells [31]. Overall, AIN is believed to be rare in renal transplant recipients (and likely difficult to distinguish from T-cell mediated rejection) presumably due to the effect of the maintenance immunosuppressive medication [32].

**FIGURE 1: Renal biopsy showing AIN in conjunction with SARS-CoV-2 vaccination. Haematoxylin-Eosin (HE) stain, x 200. There is interstitial oedema with mixed inflammatory infiltrate composed of lymphocytes, plasma cells, scattered eosinophils and neutrophils. From [41], with permission.**

### AIN and COVID vaccination

A broad variety of glomerular lesions have been reported in conjunction with SARS-CoV-2 vaccination [33, 34]. Contemporary series report minimal change disease, IgA nephropathy, crescentic glomerulonephritis and collapsing glomerulopathy [13]. It is difficult to understand how a single trigger i.e. SARS-CoV-2 vaccination (although through different vaccines) could cause such a variety of lesions. It is conceivable that these vaccines act as a ‘second hit’ on a background of genetic vulnerability. Similar models of pathogenesis are being discussed for other glomerular diseases such as IgA nephropathy [35]. In comparison, AIN following SARS-CoV-2 vaccination is rare [36]. Prior to the pandemic, AIN had already been described in conjunction with other vaccines [37] such as influenza [38].

In June 2021, de la Flor described the first case of AIN in conjunction with the Pfizer-BioNTech COVID-19 vaccine [39]. Soon after Czerlau et al. reported on a case series of five patients with AIN associated with SARS-CoV-2 mRNA vaccination [40]. Interestingly, one of their patients had a pre-existent glomerular disease and the authors emphasized that patients with pre-existent kidney diseases can be affected as well [40]. Early evaluation for AIN and consideration of renal biopsy is, therefore, warranted in such patients i.e. if renal function worsens after vaccination with mRNA-based SARS-CoV-2 vaccines [40]. They also speculated about the pathogenic role of lipid or polyethylene glycol lipid component of the vaccine [40].

Our first case of AIN associated with preceding SARS-CoV-2 vaccination [41] was a man in his mid-forties who presented with AKI requiring renal replacement therapy (RRT) only weeks after his second SARS-CoV-2 vaccination (AstraZeneca). Somewhat unexpectedly, kidney biopsy showed florid AIN (Fig. 1) for which there was no other obvious alternative explanation, although we acknowledged the possibility that we had missed clues in the history despite comprehensive assessment [41]. He recovered renal function with steroid treatment.

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**Image Reference:**

FIGURE 1: Renal biopsy showing AIN in conjunction with SARS-CoV-2 vaccination. Haematoxylin-Eosin (HE) stain, x 200. There is interstitial oedema with mixed inflammatory infiltrate composed of lymphocytes, plasma cells, scattered eosinophils and neutrophils. From [41], with permission.
| Author/Country of case report | Age (yrs) | Sex | Time to pre-presentation from day of vaccination | Significant co-morbidities | New onset or relapse | Vaccine brand | Vaccine dose | Baseline Creatinine (μmol/L) | Presentation Creatinine (μmol/L) | Kidney Biopsy | Treatment | Outcome |
|------------------------------|-----------|-----|-------------------------------------------------|---------------------------|---------------------|---------------|--------------|-----------------------------|-----------------------------|--------------|----------|---------|
| Choi J H et al./South Korea [45] | 17        | M   | 3 days                                           |                           | New-onset           | Pfizer        | Second       | Not known                   | 265                         | Interstitial infiltrates mainly mononuclear. Focal and moderate interstitial fibrosis and tubular atrophy in 20% of cortex. Negative IF. Findings consistent with AIN. Tubules showed severe necrosis with heavy infiltration of neutrophils, eosinophils and mononuclear cells in the interstitium. Slight foot process effacement. | Supportive care | Discharged after 1 week |
| Choi J H et al./South Korea [45] | 12        | M   | 3 weeks                                          |                           | New-onset           | Pfizer        | Second       | Not known                   | 199                         | Oral steroids on day 10 of hospitalization | Recovery of renal function |
| Czerlau et al./Switzerland [40] | 55        | M   | 4 days                                           | Hypertension, prostate cancer treated with prostatectomy | New-onset           | Pfizer        | Second       | 76.5                        | 355                         | Lymphocytes, plasma cells, macrophages, eosinophilic granulo-cytes and some neutrophilic granulo-cytes, tubulitis and interstitial oedema. | Steroid treatment—dose and length of treatment not specified | Serum creatinine following treatment is 88 μmol/L |
| Czerlau et al./Switzerland [40] | 54        | M   | 3 days                                           | Myocardial infarction    | New-onset           | Moderna       | Second       | Not known                   | 268                         | Lymphocytes, plasma cells, macrophages, and eosinophilic granulocytes, two granulomas, tubulitis + tubular destruction. Glomerular lesions in keeping with FSGS | Steroid treatment—dose and length of treatment not specified | Serum creatinine following treatment is 235 μmol/L |
| Czerlau et al./Switzerland [40] | 58        | M   | ‘A few days’                                     | FSGS refractory to treatment, with multiple relapses | New-onset           | Moderna       | Second       | 167                         | 355                         | Lymphocytes, plasma cells, macrophages, with tubulitis and interstitial oedema | Steroid treatment—dose and length of treatment not specified | Serum creatinine following treatment is 210 μmol/L |
| Author/Country of case report | Age (yrs) | Sex | Time to presentation from day of vaccination | Significant co-morbidities | New onset or relapse | Vaccine brand | Vaccine dose | Baseline Creatinine (μmol/L) | Presentation Creatinine (μmol/L) | Kidney Biopsy | Treatment | Outcome |
|-------------------------------|----------|-----|---------------------------------------------|---------------------------|---------------------|----------------|-------------|--------------------------|-----------------------------|----------------|-----------|---------|
| **Czerlau et al./Switzerland [40]** | 38 | F | 1 month | Ulcerative colitis—received ustekinumab previously for treatment | New-onset | Moderna | Second | 76 | 86 | Lymphocytes, plasma cells, macrophages, sporadic eosinophilic granulocytes and neutrophil granulo-cytes with tubulitis + interstitial oedema. EM shows mesangial IgA deposition. | Steroid treatment—dose and length of treatment not specified | Serum creatinine following treatment is 72 μmol/L |
| **Czerlau et al./Switzerland [40]** | 35 | F | Exact time not specified | Rheumatoid arthritis—on certolizumab treatment since 2016 | New-onset | Pfizer | Second | 49 | 100 | Lymphocytes, plasma cells, macrophages, sporadic eosinophilic granulocytes and neutrophil granulocytes with tubulitis + interstitial oedema. EM shows mesangial IgA deposition. | Steroid treatment—dose and length of treatment not specified | Serum creatinine following treatment is 90 μmol/L |
| **De la Flor et al./Spain [39]** | 78 | M | 3 weeks | Hypertension, type 2 diabetes mellitus | New-onset | Pfizer | First | 150 | 475 | Features of AIN along with glomerular sclerosis and other chronic changes Tubulo-interstitial inflammatory infiltration containing eosinophils and lymphocytes and interstitial oedema. | IV MP followed by oral steroids | Remained dialysis-dependent |
| **Dheir H et al./Turkey [50]** | 44 | F | 48 hours | | New-onset | Pfizer | First | Not known | 186 | Features of AIN along with glomerular sclerosis and other chronic changes Tubulo-interstitial inflammatory infiltration containing eosinophils and lymphocytes and interstitial oedema. | Haemodialysis. Oral steroids 1 mg/kg | Complete recovery of renal function |
| **Fenoglio R et al./Italy [51]** | F | 78 | 52 days | Not stated | New-onset | Pfizer | First | Not stated | Not stated | Severe interstitial infiltration by mononuclear cells and polymorphonuclear leucocytes | Dialysis. Oral steroids | Dialysis discontinuation after 2 months |
| **Fenoglio R et al./Italy [51]** | F | 57 | 82 days | Not stated | New-onset | Pfizer | Second | Not stated | Not stated | Severe interstitial infiltration by mono-nuclear cells and polymorphonuclear leukocytes. | Oral steroids | |
| Author/Country of case report | Age (yrs) | Sex | Time to presentation from day of vaccination | Significant co-morbidities | New onset or relapse | Vaccine brand | Vaccine dose | Baseline Creatinine (μmol/L) | Presentation Creatinine (μmol/L) | Kidney Biopsy | Treatment | Outcome |
|-----------------------------|-----------|-----|---------------------------------------------|---------------------------|----------------------|-------------------|--------------|--------------------------|-------------------------------|--------------|----------|---------|
| Fenoglio R et al./Italy [51] | F 65 | 24 days | Not stated | New-onset | Oxford-AstraZeneca | Second | Not stated | | Severe interstitial infiltration by mononuclear cells and polymorphonuclear leucocytes | | Dialysis Oral steroids |
| Jongvilaikasem P and Rianthavorn P/Thailand [52] | 14 M | 5 days | New onset | Pfizer | First | Not known | 177 | Normal glomeruli with foot process effacement on EM. Tubular injury and interstitial infiltrate | | IV MP followed by oral steroids. Haemodialysis for 3 weeks |
| Liew et al./United Kingdom [41] | 53 M | 3 days | Hypertension | New-onset | Oxford-AstraZeneca | Second | Not known | 1034 | Morphologically normal glomeruli with interstitial oedema and infiltrate of lymphocytes, plasma cells and neutrophils with tubulitis | | Oral steroid treatment |
| Mira F S et al./Portugal [53] | 45 F | 8 days | Total thyroidectomy secondary to multinodular goitre | New-onset | Pfizer | Second | 75 | 1626 | Mild interstitial infiltrate with oedema and acute tubular necrosis. 20% IFTA | | Haemodialysis. MTP 500 mg daily for 3 days, followed by 50 mg prednisolone RRT on intensive care unit. Oral steroids 250 mg for 3 days then reduced to 80 mg daily. Oral steroids 50 mg per day. | Improvement of renal function. Dialysis-independent following discharge |
| Rieckmann S et al./Germany [54] | 63 M | 3 weeks | New-onset | Pfizer | First | Normal range (not specified) | 1679 | Acute tubular necrosis, interstitial oedema and lymphoplasmacellular interstitial infiltration with few eosinophil granulocytes | | | |
| Rieckmann S et al./Germany [54] | 18 M | 6 weeks | New-onset | Pfizer | Second | Not known | 150 | | | | | Complete recovery of renal function within 2 weeks.
Table 1. Continued

| Author/Country of case report | Age (yrs) | Sex | Time to presentation from day of vaccination | Significant co-morbidities | New onset or relapse | Vaccine brand | Vaccine dose | Baseline Creatinine (μmol/L) | Presentation Creatinine (μmol/L) | Kidney Biopsy | Treatment | Outcome |
|------------------------------|-----------|-----|---------------------------------------------|---------------------------|----------------------|---------------|--------------|-----------------------------|-------------------------------|---------------|-----------|---------|
| Rieckmann S et al./Germany [54] | 25        | F   | 3 weeks                                     |                           | New-onset            | Pfizer        | Third        | Not known                   | 1034                          |              | Oral steroids | Recovery of renal function within days. |
| Unver et al./Turkey [55] | 67        | F   | 3 weeks                                     | Type 2 diabetes mellitus. Recent new-onset minimal change disease following first dose of CoronaVac | New-onset            | CoronaVac     | Second       | Not known (serum creatinine was 53μmol/L) | 371                          | Degeneration of proximal tubular cells and interstitial inflammation. Proteinaceous material was detected in many tubule lumens. | Pulsed IV MP followed by oral steroids. Patient was then commenced on cyclosporine treatment | Ongoing treatment. Proteinuria of 3g/day still apparent from last follow-up |
| Wu et al./United Kingdom [36] | 69        | F   | 5 days                                      | Rheumatoid arthritis, Sjögren's syndrome, hypertension, hypothyroidism and anxiety | New-onset            | Oxford-AstraZeneca | First        | 85                          | 245                          | Florid interstitial infiltrate with prominent eosinophils, with no glomerular abnormalities and no chronic interstitial damage | Commenced on oral steroids. Discontinuation of regular medications such as ramipril, lansoprazole, methotrexate and paracetamol. | Improved serum creatinine to 130 μmol/L and resolved peripheral eosinophilia |
| Wu et al./United Kingdom [36] | 60        | F   | 2 weeks                                     | Hypertension             | New-onset            | Oxford-AstraZeneca | Second       | 59                          | 754                          | Widespread interstitial infiltrates in keeping with AIN | Single dose IV pulsed MP followed by oral steroids. | Full clinical recovery. Serum creatinine was 216 μmol/L in last follow-up review |

AIN, acute interstitial nephritis; EM, electron microscopy; FSGS, focal segmental glomerulosclerosis; IF, immunofluorescence; IFTA, interstitial fibrosis and tubular atrophy; M, male; MCD, minimal change disease; MP, methylprednisolone; IgA, immunoglobulin A; IV, intravenous.
As of late 2021, we reviewed 10 cases of AIN following SARS-CoV-2 vaccination which had been described in the literature [36] including one case with granulomatous lesions [17]. Since then, an additional case similar to our own first case was reported [42]. Lim et al. recently added two more cases, both with partial recovery after steroid treatment [43]. It is interesting to note that a case of relapse of IgG4-related interstitial disease following SARS-CoV-2 vaccination has also been reported [44]. More cases continue to emerge [45–47] although the overall number remains small, given how common SARS-CoV-2 vaccination is in the general population. Table 1 shows all cases of AIN in conjunction with SARS-CoV-2 vaccination as of the time of writing. So far as we can see, there does not seem to be a preponderance of any particular vaccine although mRNA-based vaccines seem to cause more allergic reactions overall [48].

Most cases reported so far recover to some degree with steroid treatment but it is important to appreciate that AIN associated with SARS-CoV-2 vaccination is not always benign. The case described by De la Flor et al. remained dialysis-dependent despite biopsy and steroid treatment [39].

All cases described in the literature have to be viewed with a degree of caution when it comes to causality. As part of the assessment, strong temporal association, lack of chronic lesions, absence of concomitant diseases and medication linked to AIN should all be considered [44]. It is quite possible that patients were too ill to remember alternative causes of AIN, such as the use of non-steroidal anti-inflammatory drugs (NSAIDs) or PPIs prior to the onset of kidney disease. Alternatively, they may have forgotten to mention the use of over-the-counter medication or they may be too embarrassed to report this. It is also the case that SARS-CoV-2 vaccination is such a common event in the general population that it is difficult to find any patient presenting with new-onset renal disease who has not had some form of SARS-CoV-2 vaccination in the recent past. We have ourselves encountered the occasional patient with pre-existing kidney disease who experienced worsening kidney function in conjunction with SARS-CoV-2 vaccination but where a biopsy was considered inappropriate or too risky and causality, therefore, remains difficult to assess. Again, it is difficult to completely exclude that these patients could have used NSAIDs or felt unwell overall with some degree of dehydration after vaccination. We emphasize the role of detailed history taking, as well as the fact, that all patients with otherwise unexplained AIN should be asked about prior SARS-CoV-2 vaccination.

CONCLUSION

We now have a much greater understanding of the types of renal injury caused by both SARS-CoV-2 infection, and also vaccination, than we did at the onset of the pandemic. AIN, however, has received much less attention than glomerular disease and many questions remain unanswered. The link between SARS-CoV-2 infection and vaccination and AIN remains incompletely understood. In patients with AIN in conjunction with SARS-CoV-2 infection, there is a lack of robust evidence that the virus is incorporated into kidney tissue when techniques such as immunohistochemistry and in-situ hybridization are used. This is in contrast to other viral-associated AIN such as the BK virus. Secondly, AIN is rarely seen in biopsy and autopsy series of patients with SARS-CoV-2 infection. Finally, it is noted that there are potentially other causes for AIN in many of the reported cases of AIN in the context of SARS-CoV-2 infection (such as antibiotics, PPIs or NSAIDs) and, to a lesser degree, in patients where AIN occurs after SARS-CoV-2 vaccination. Causality is, therefore, difficult to prove in many, if not most, cases. It is also worth keeping a sense of perspective: as of April 2022, the WHO reports a total of 509,531,232 cases of COVID-19 worldwide with 114,387,708,383 vaccine doses administered [49]. In the general population, preceding SARS-CoV-2 infection and vaccination are common in any patient’s history. On the other hand, it seems possible that AIN is under-diagnosed, under-reported or both, in conjunction with COVID-19 and COVID vaccination. This could apply where clinicians assume that both the disease and vaccination are so ubiquitous that taking a detailed vaccination and COVID history isn’t worth their while. We should use the work by León-Román [6] as a useful reminder that there may be more to renal disease associated with SARS-CoV-2 infection and vaccination than just glomerular disease. To ensure we are not missing AIN anything, we recommend vigilance and careful history taking, particularly in patients presenting with otherwise unexplained AIN.

CONFLICT OF INTEREST STATEMENT

A.W. is member of the CKJ editorial board.

(See related article by León-Román et al. COVID-19 infection and renal injury: where is the place for acute interstitial nephritis disease? Clin Kidney J (2022) 15: 1698–1704.)

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