ORIGINAL ARTICLE

COVID-19 infection and renal injury: where is the place for acute interstitial nephritis disease?

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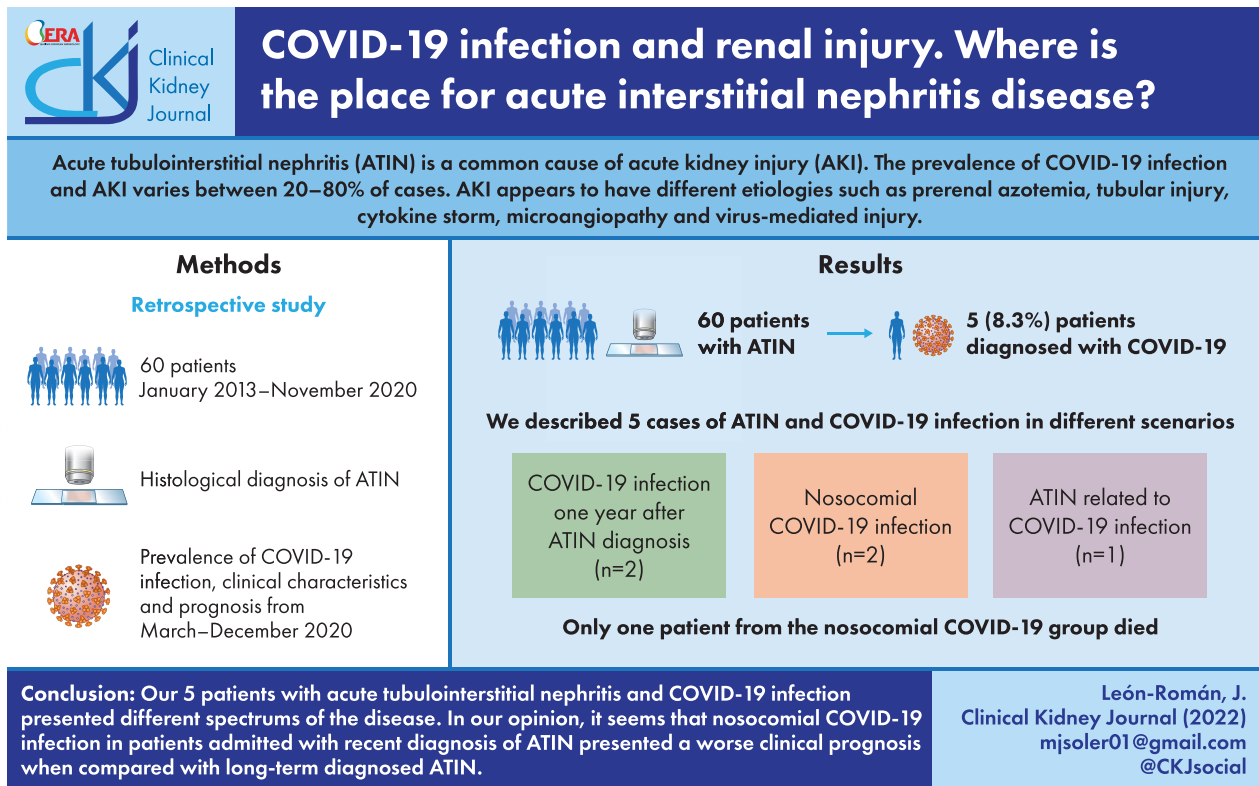Correspondence to: María José Soler; E-mail: m.soler@vhebron.net

ABSTRACT

Novel coronavirus disease infection (coronavirus disease 2019, COVID-19) was declared a global pandemic in March 2020 and since then has become a major public health problem. The prevalence of COVID-19 infection and acute kidney injury (AKI) is variable depending on several factors such as race/ethnicity and severity of illness. The pathophysiology of renal involvement in COVID-19 infection is not entirely clear, but it could be in part explained by the viral tropism in the kidney parenchyma. AKI in COVID-19 infection can be either by direct invasion of the virus or as a consequence of immunologic response. Diverse studies have focused on the effect of COVID-19 on glomerulonephritis (GN) patients or the 'novo' GN; however, the effect of COVID-19 in acute tubulointerstitial nephritis (ATIN) has been scarcely studied. In this article, we present five cases with different spectrums of COVID-19 infection and ATIN that may suggest that recent diagnosis of ATIN is accompanied by a worse clinical prognosis in comparison with long-term diagnosed ATIN.

GRAPHICAL ABSTRACT

COVID-19 infection and renal injury. Where is the place for acute interstitial nephritis disease?

Acute tubulointerstitial nephritis (ATIN) is a common cause of acute kidney injury (AKI). The prevalence of COVID-19 infection and AKI varies between 20–80% of cases. AKI appears to have different etiologies such as prerenal azotemia, tubular injury, cytokine storm, microangiopathy and virus-mediated injury.

Methods

Retrospective study

60 patients
January 2013–November 2020

Histological diagnosis of ATIN

Prevalence of COVID-19 infection, clinical characteristics and prognosis from March–December 2020

Results

60 patients with ATIN → 5 (8.3%) patients diagnosed with COVID-19

We described 5 cases of ATIN and COVID-19 infection in different scenarios

COVID-19 infection one year after ATIN diagnosis (n=2)

Nosocomial COVID-19 infection (n=2)

ATIN related to COVID-19 infection (n=1)

Only one patient from the nosocomial COVID-19 group died

Conclusion: Our 5 patients with acute tubulointerstitial nephritis and COVID-19 infection presented different spectrums of the disease. In our opinion, it seems that nosocomial COVID-19 infection in patients admitted with recent diagnosis of ATIN presented a worse clinical prognosis when compared with long-term diagnosed ATIN.

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INTRODUCTION

Novel coronavirus disease infection (coronavirus disease 2019, COVID-19) was declared a global pandemic in March 2020 and since then has become a major public health problem to both out- and inpatients [1]. COVID-19 infection presents from its asymptomatic form to pneumonia associated with multiple organ failure and death. The prevalence of COVID-19 infection and acute kidney injury (AKI) varies between 20 and 80% of cases, and this may be in part ascribed to the clinical characteristics of patients and their geographical location [2, 3].

Several publications have focused on the pathogenesis of kidney injury in the setting of COVID-19 [2]. AKI appears to have different aetiologies such as prerenal azotemia, tubular injury, cytokine storm, microangiopathy and virus-mediated injury [4] (Figure 1). The pathophysiology of renal involvement in COVID-19 infection is not entirely clear, but it seems that kidney injury could result from direct damage to the parenchyma, sepsis, thrombotic phenomena and treatment complications [1, 2, 4]. In addition, other authors consider that kidney disease is more likely related to the systemic and proinflammatory effect of sepsis instead of direct damage from viral-like particles in the kidney parenchyma [5]. Taking this into consideration, in our opinion, the mechanisms of AKI secondary to COVID-19 are mainly multifactorial, involving both direct and indirect viral damage. Histologically, COVID-19 infection develops a wide spectrum of glomerular and tubular diseases, with acute tubular necrosis being the most frequent kidney lesion, and focal and segmental collapsing glomerulonephritis (GN) the most common glomerulopathy [6, 7]. Whereas some authors have identified viral-like particles by electron microscopy or by *in situ* hybridization of RNA severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the kidney with unknown clinical significance, other authors have not been able to identify SARS-CoV-2 viral particles in COVID-19 patients with associated kidney injury [7, 8, 9].

Acute tubulointerstitial nephritis (ATIN) is a common cause of AKI and presents with inflammatory infiltrates and oedema in histological samples. Pharmacological exposure is the most frequent aetiology; however, bacterial and viral infections are also important, accounting for 5–10% of cases [10]. High clinical suspicion is needed to diagnose ATIN since the initial phase of ATIN does not typically manifest with oliguric AKI and haematuria. A proper and fast diagnosis of ATIN is required because the disease is reversible when early corticosteroid treatment is started [2, 10]. ATIN patients started kidney function recovery within a few weeks and complete improvement of baseline kidney function after 5–8 weeks of steroid treatment. Maintenance of steroid treatment should be shortened to 2–3 months, avoiding the secondary effects related to steroids [11].

Currently, there is limited scientific literature on COVID-19 and ATIN in terms of its clinical course and short- and long-term prognosis. In this article, we present five cases of COVID-19 infection and ATIN, and review current evidence on AKI and COVID-19 infection.
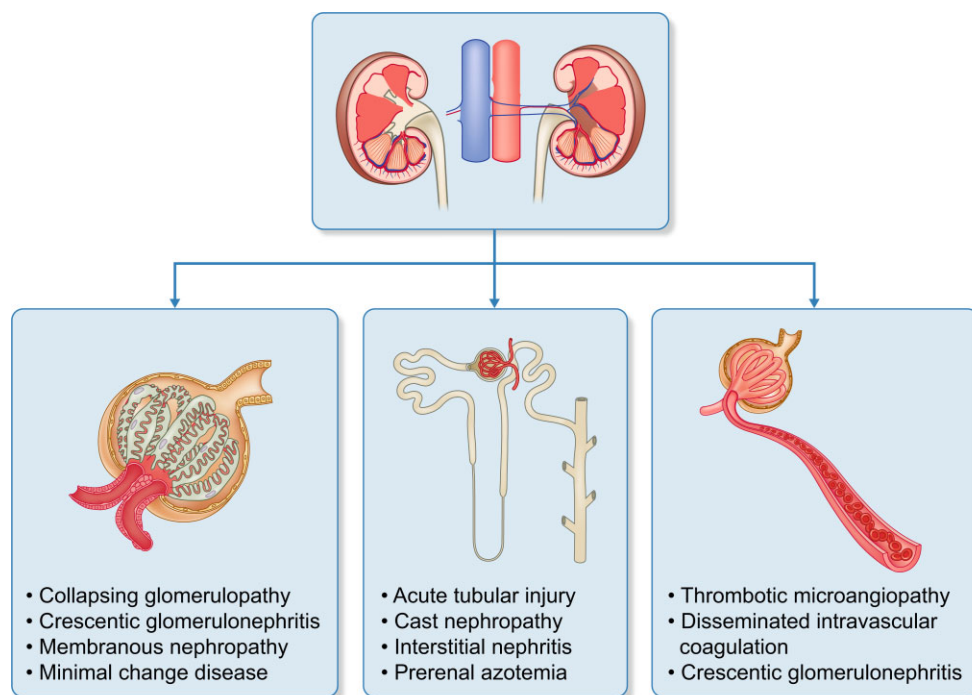
FIGURE 1: Spectrum of kidney damage in COVID-19 infection. The kidney damage lesions in the different compartments namely glomeruli, tubuli and renal vasculature associated with COVID-19 infection are shown in this picture. Interestingly, COVID-19 infection in the kidney has been associated with several diseases such as focal and segmental glomerulosclerosis, acute interstitial injury and thrombotic microangiopathy.

MATERIALS AND METHODS

We performed a retrospective study of medical records of 60 patients with histological diagnosis of ATIN from January 2013 to November 2020. In these patients, we studied the prevalence of COVID-19 infection, clinical characteristics and prognosis from March to December 2020. In addition, we reviewed the published literature in PubMed up to 19 July 2021. The search strategy included the terms 'acute tubulointerstitial nephritis,' 'acute kidney injury and COVID,' 'COVID-19,' 'coronavirus' and 'SARS-CoV2' without language or type of article restrictions.

RESULTS

Of 60 patients with ATIN, 5 (8.3%) patients were diagnosed with COVID-19 (Table 1]. The characteristics of the five patients are detailed below.

First case

An 85-year-old woman with a history of scalp melanoma BRAF wild-type gene mutation with pulmonary metastasis that was successfully treated with nivolumab and LAG-3 antibody, who developed ATIN secondary to immunobiological agents in 2018. She was diagnosed with mild COVID-19 in April 2020 with a positive swab test performed in a hospice as screening without indication for hospital admission. Her renal function was stable and maintained after 3 and 6 months of follow-up.

Second case

A 64-year-old man without prior renal impairment presented with acute shortness of breath and fever. He was admitted and diagnosed with COVID-19 infection. Twenty-four hours after admission, he developed severe COVID-19 pneumonia and AKI Akin stage 3 with proteinuria/creatinine ratio of 1.7 g/g (albumin/creatinine 0.13 g/g) without haematuria that required orotracheal intubation and continuous veno-venous haemodiafiltration. During his admission, antibiotic therapy with ceftriaxone, nebulized tobramycin and linezolid was started due to pneumonia secondary to methicillin-resistant *Staphylococcus aureus* (MRSA). Kidney biopsy was performed and ATIN probably associated with COVID-19 infection was diagnosed. Steroid treatment was initiated with methylprednisolone pulses for 3 days followed by maintenance steroid therapy (mg/kg) with complete recovery of renal function and improvement of proteinuria at 3 months of follow-up (see Figure 2).

Third case

An 82-year-old woman with a past medical history of hypertension, diabetes mellitus and mixed anxiety-depressive disorder was admitted with AKI Akin stage 3 due to ATIN secondary to ciprofloxacin. After 8 days of her admission, she developed hospital-acquired pneumonia associated with severe COVID-19 infection. The patient died 20 days after the COVID-19 diagnosis despite ventilatory support delivered by warmed and humidified oxygen at high flows through nasal cannula at 90%, 60 L/min, high-dose steroids therapy, remdesivir and tocilizumab.

Fourth case

A 75-year-old man with a past medical history of metastatic lung adenocarcinoma successfully treated with

Table 1. Clinical characteristics of our five patients with COVID-19 infection and ATIN

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	85	64	82	75	86
Gender	Female	Male	Female	Male	Male
ATIN cause	Nivolumab AntiLAG3	COVID-19 infection	Ciprofloxacin	MEK/Braf inhibitors	Proton-binding inhibitors
ATIN treatment: steroids (pulses)	Yes (Yes)	Yes (Yes)	Yes (Yes)	Yes (Yes)	Yes (Yes)
Cumulative dose of prednisone (mg/kg)	82.4	48.4	5.7	61.8	61.8
Date of positive COVID-19 swab test	23 April 2020	23 September 2020	10 October 2020	24 April 2020	11 December 2020
Time from ATIN to COVID-19 diagnosis from ATIN to COVID-19 diagnosis (months)	19	0	0	13	0
Basal serum creatinine (mg/dL)	1.6	0.9	0.8	1.7	1.6
Serum creatinine (mg/dL) in COVID-19 diagnosis	Unknown	0.9	0.9	2.4	4.9
Serum creatinine (mg/dL) 7 days after COVID-19 infection	Unknown	2.4	0.5	2.4	3.7
Serum creatinine (mg/dL) 3 months after COVID-19 infection	1.4	0.8	Unknown	1.8	1.7
Death (date) related to COVID-19 infection	NA	NA	30/10/2020	NA	NA

Abbreviations: ATIN, allergic tubulointerstitial nephritis; NA, not applicable.
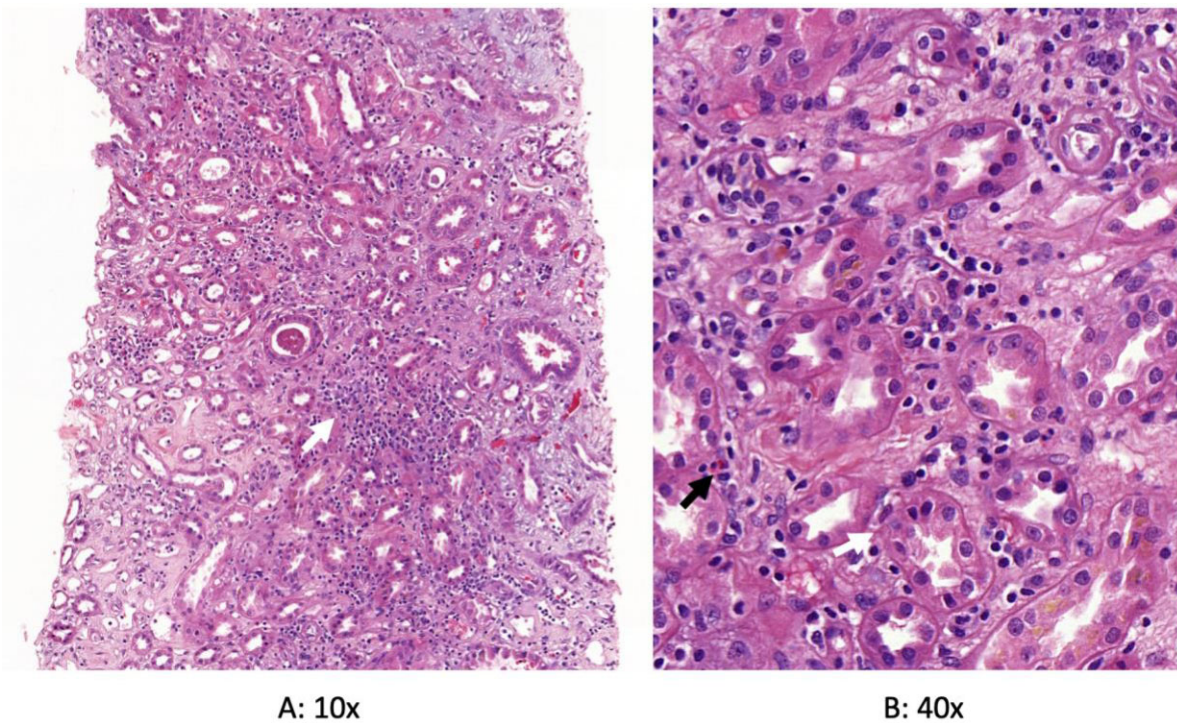
FIGURE 2: Histopathology of the kidney biopsy performed in the second case. Acute tubulointerstitial nephritis and acute tubular damage are shown in haematoxylin eosin staining. (**A**) White arrow shows interstitial inflammatory infiltrates in low power light micrograph. (**B**) White and black arrows show tubulitis and eosinophils, respectively. SARS-CoV-2 immunohistochemistry was negative.

dabrafenib/trametinib complicated with AKI Akin stage 3 secondary to ATIN in 2018. He was admitted in March 2020 with mild COVID-19 pneumonia. A deterioration in kidney function was observed and oxygen support with low flows oxygen (2 L/min) was needed. Dexamethasone and hydroxychloroquine were administered for 5 days with complete recovery of basal renal and pulmonary function. The patient was discharged one week after the admission.

Fifth case

An 86-year-old man with a past medical history of hypertension, diabetes mellitus, atrial fibrillation and chronic kidney disease stage 3b A3 was admitted with deterioration of kidney function due to ATIN secondary to proton-binding inhibitors on December 2020. Eight days after his admission, he developed a nosocomial COVID-19 infection without oxygen requirement or respiratory involvement. After 2 weeks of steroids initiation, kidney function improved and reached basal serum creatinine levels at 3 months.

DISCUSSION

In this article, we described five cases of ATIN and COVID-19 infection in different scenarios: (i) COVID-19 infection diagnosed 1 year after ATIN diagnosis ($n = 2$), (ii) recently diagnosed ATIN patients who presented nosocomial COVID-19 infection ($n = 2$) and (iii) ATIN related to COVID-19 infection ($n = 1$). We defined nosocomial COVID-19 infection in patients with a positive nasopharyngeal swab test and/or development of pneumonia more than 5 days after admission in accordance with the Swissnoso guidelines [12]. Only one patient from the nosocomial COVID-19 group died 20 days after nosocomial infection despite empirical treatment with corticosteroids, remdesivir and tocilizumab. These results may suggest that nosocomial COVID-19 in recently ATIN diagnosed patients may have worse clinical prognosis when compared with longtime ATIN diagnosis. Perhaps this can be explained by the high immunosuppression therapy at the moment of COVID-19 infection. However, further studies are needed to confirm this hypothesis.

During the pandemic, many patients with severe COVID-19 infection presented AKI requiring renal replacement therapy and extracorporeal membrane oxygenation (ECMO) secondary to multiorgan failure. Kidney biopsy in many patients could not be performed due to high hemorrhagic risk; therefore, the real prevalence of ATIN may be underestimated.

ATIN is a common and reversible cause of AKI that sometimes may be underdiagnosed due to the fact that most of the patients present only a mild alteration in kidney function and urinalysis [13]. The following causes of ATIN have been described: (i) use of immunobiological therapies for cancer, (ii) use of antibiotics, (iii) proton-pump inhibitors and (iv) COVID-19 damage. To our knowledge, few cases of ATIN and COVID-19 disease have been published. Recently, May *et al.* in an international collaborative study where a total of 284 biopsies from COVID-19 patients were evaluated, including 240 native biopsies and 44 allografts, identified 4 (1.7%) patients with histological diagnosis of acute interstitial nephritis in COVID-19 patients [14]. Szajek *et al.* also described a 62-year-old Caucasian man with cough, fever, myalgia and chills who was admitted for severe acute respiratory distress syndrome and multiorgan failure secondary to COVID-19 infection and AKI with renal replacement therapy [15]. Kidney biopsy was performed and revealed granulomatous tubulointerstitial nephritis thus steroids treatment was initiated with partial recovery of kidney function at 2 months of follow-up. In concordance, our patient with ATIN-related COVID-19 presented a good prognosis with complete kidney function recovery.

There has been a wide spectrum of histological findings in COVID-19 infection. Viral involvement of kidney parenchyma has been shown by Westhoff *et al.* [16], who presented a 69-year-old male with pancreas–kidney transplantation 13 years ago admitted with COVID-19 pneumonia, and impaired pancreas and kidney allograft function. Tubular damage and an interstitial mononuclear cell infiltrate were present in the kidney biopsy. Reverse transcriptase polymerase chain reaction detected positive SARS-CoV-2 RNA in tubular cells and interstitial parenchyma [16, 17]. Another study that analysed kidney biopsies in 26 autopsies of patients with COVID-19 also identified direct evidence of the invasion of SARS-CoV-2 into kidney tissue with coronavirus-like particles in the tubular epithelium and podocytes. This was associated with upregulation of the angiotensin-converting enzyme (ACE) 2 receptor and positive SARS-CoV nucleoprotein antibody in tubules [18]. In contrast, in our patient with ATIN related-COVID-19, we were not able to detect viral SARS-CoV-2 particles by electron microscope.

Acute tubular injury has been identified as the main cause of AKI in patients with COVID-19 infection secondary to prolonged volume depletion and haemodynamic changes with renal hypoperfusion [19, 20]. The hyperinflammatory state with release of proinflammatory cytokines, especially interleukin-6, is also an exacerbating factor for poor prognosis at the renal tubule and lung since its high concentration is associated with greater respiratory distress [20]. Werion *et al.* described that COVID-19 infection showed prominent tubular injury with brush border loss, acute tubular necrosis, intraluminal debris and decrease in the expression of megalin; proximal tubule dysfunction was independent of comorbidities, adverse drugs reactions and viral load [21]. Hypouricemia with uricosuria has also been identified as a risk factor for severity and respiratory failure [21].

Collapsing glomerulopathy is the most common glomerular disease, especially in Afro-American people with high-risk genotypes of apolipoprotein L1 (APOL1) [22]. To date, 24 cases of AKI with nephrotic syndrome and COVID-19 infection associated with APOL1 have been described [20, 22]. The pathophysiology still remains uncertain, although it is believed that viral involvement resembles other infections such as HIV-associated nephropathy, Epstein–Barr virus, cytomegalovirus and Parvovirus B19 ascribed to cytokine storm release and podocyte involvement due to upregulated viral infection that results in an inflammatory 'second hit' [23, 24]. Furthermore, León-Román *et al.* described a case of non-collapsing focal and segmental glomerulosclerosis in a 56-year-old patient with nephrotic syndrome and mild COVID-19 infection in which treatment with corticosteroids was started and cyclosporine was added after 12 weeks due to persistent proteinuria [8].

The incidence of disseminated intravascular coagulation reaches 75% in patients with severe COVID-19 infection. In contrast, there are limited clinical cases with the development of thrombotic microangiopathy (TMA) in which cortical necrosis and glomerular microthrombosis are seen in the biopsy [20]. The development of coagulopathy in COVID-19 infection is not fully clarified despite the fact that many studies associate it with sepsis [25]. TMA secondary to COVID-19 infection is similar to systemic diseases such as systemic lupus erythematosus, antiphospholipid syndrome, typical and atypical haemolytic uremic syndrome and thrombotic thrombocytopenic purpura [26]. COVID-19 infection seems to involve complement and platelet activation without observing platelet consumption. One of the suggested mechanisms for complement activation has been the binding of the nucleocapsid protein to a protease of the lectin-dependent complement pathway [26].

To date, few cases of acute interstitial nephritis have been described as a result of SARS-CoV-2 viral damage and/or pharmacological treatment [20–27]. For this reason, the prognosis of COVID-19 in ATIN patients is unknown in accordance with the scarcity of literature data.

Our study has some limitations. First, the retrospective character of the study, and second the small sample size ($n = 5$) of ATIN patients with COVID-19 infection. However, we would like to highlight the importance that this study was performed in one of the centres with highest COVID-19 incidence in Spain and which is the reference centre for ECMO in Barcelona [28].

Our data expand the current knowledge of ATIN and COVID-19 in three different scenarios: (i) long-term ATIN patients that presented SARS-CoV-2 infection, (ii) recent ATIN diagnosis that developed nosocomial SARS-CoV-2 infection and (iii) ATIN diagnosed in patients with severe SARS-CoV-2 infection. In our study, the recent ATIN diagnosis patient that presented with nosocomial COVID-19 disease died. This may suggest a poor prognosis in recently diagnosed older patients undergoing intensive steroids treatment. However, further studies are needed to assess the effect of COVID-19 on newly diagnosed ATIN.

CONCLUSIONS

COVID-19 infection affects different sites of the kidney parenchyma (Figure 1). Our five patients with ATIN and COVID-19 infection presented different spectrums of the disease. In our opinion, it seems that nosocomial COVID-19 infection in patients admitted with recent diagnosis of ATIN presented a worse clinical prognosis when compared with long-term diagnosed ATIN. Further multicentric studies including a larger sample size would be of great interest.

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AUTHORS' CONTRIBUTIONS

J.L.R. and M.J.S. collaborated on the original idea and study design. I.A., A.V., N.R., N.T., C.G.C., R.B., S.B., and O.B. contributed to the inclusion of patients. J.L.R. and M.J.S. wrote the paper. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

M.J.S. reports conflicts of interest with fees from NovoNordisk, personal fees from Janssen, grants and non-financial support from Boehringer, non-financial support from Eli Lilly, personal fees from AstraZeneca, non-financial support from Esteve, personal fees from Fresenius, personal fees from Mundipharma, personal fees from Pfizer, personal fees from Bayer and personal fees from Vifor, outside the submitted work. M.J.S. is member of the *CKJ* editorial board. The results presented in this article have not been published previously in whole or part, except in abstract format.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

(See related article by Storrar et al. Have we missed AINything? Acute interstitial nephritis in SARS-CoV-2 infection and vaccination. *Clin Kidney J* (2022) 15: 1643–1652.)

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