CASE SERIES

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# ACUTE KIDNEY INJURY AND ACUTE RENAL FAILURE IN CORONAVIRAL INFECTION

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***Abstract.*** *In December 2019 a newly described single-stranded coronavirus, later named SARS-CoV-2, started its expansion around the world and subsequently caused a global pandemic, affecting the lives of millions of people worldwide. SARS-CoV-2 can bind multiple receptors on different cells and thus invade many target organs, including the respiratory and gastrointestinal mucous membranes, lungs, central nervous system, heart, etc. This virus can affect the kidney tissue both directly and as a consequence of other organ involvement or of the treatment administered, causing acute kidney injury and leaving long term squeals that worsen the prognosis. We describe three patients with acute kidney injury and subsequent acute renal failure at the background of coronaviral infection.*

***Key words:*** *coronarirus, acute renal failure, acute kidney injury, minimal-change nephropathy, tubule-interstitial nephritis, renal biopsy*

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## INTRODUCTION

In December 2019 a newly described single-stranded coronavirus started his expansion around the world and subsequently caused a global pandemic, affecting the lives of millions of people worldwide. The virus was named SARS-CoV-2. It is known to be spread by tiny droplets of biological fluids, including mouth and nose secretions. The standard methods for detection are the polymerase chain reactions and antigenic test on respiratory samples from nasal and nasopharyngeal swab.

SARS-CoV-2 can bind multiple receptors on different cells and thus invade many target organs, including the respiratory and gastrointestinal mucous membranes, lungs, central nervous system, heart, etc. This virus can affect the kidney tissue both directly and as a consequence of other organ involvement or of the treatment administered, causing acute kidney injury and leaving long term squeals that worsen the prognosis [1, 2, 3].

According to the literature, the incidence of acute kidney injury (AKI, defined as increase in urine protein excretion and/or urine protein/creatinine ratio, and/or increase in serum creatinine levels, and/or decrease in creatinine clearance levels) and acute renal failure (ARF) ranges from 0.5% to 80.3% [1, 2, 3, 4], with

the highest incidence being described in critically ill patients [4]. The development of AKI in SARS-CoV-2 patients is considered a risk factor for severe disease course and a negative prognostic factor for patients' survival [1, 2]. The main risk factors for the development of AKI and poor functional recovery of the kidney are considered to be the severity of pneumonia and the development of acute respiratory distress syndrome (ARDS) [5, 6].

The main pathogenic mechanisms underlying the AKI and ARF in SARS-COV-2 infection are direct (viral replication in renal tissue with tubular, endothelial and podocyte damage) and/or indirect (renal hypoperfusion, drug toxicity or allergies, contrast-induced nephropathy, immune response to the virus with subsequent type 2 (antibody-mediated), type 3 (immune-complex mediated) or type 4 (T-cell-mediated) reactions to renal cells and structure, flair of pre-existing immune disease, etc.).

We describe three patients with acute kidney injury and subsequent acute renal failure at the background of coronaviral infection.

## CLINICAL CASES PRESENTATION

### *Case 1*

A 34-year-old male patient was admitted to the Clinic of Nephrology in April 2021 for acute renal failure (serum creatinine of 390 mcmol/l, urea 18.2 mmol/l) with macroscopic hematuria, nephrotic range proteinuria (6 g/l) and low platelet count (91 G/l) with increased lactate dehydrogenase levels (480 U/l). Five days before the admission the patient had high fever and cough, flank pain, dark urine. PCR for COVID was negative, chest X-ray showed no pathological changes. At the admission the patient was in impaired general condition, pain in abdominal flanks with positive renal succession and edema on the legs. The initial clinical-laboratory investigations revealed negative rapid antigenic test for SARS-CoV-2, serum creatinine of 400 mcmol/l, urea 16.5 mmol/l, uric acid 445, d-dimer 1.17 mcg/ml, CRP 67 mg/l, ferritin 1379 mcg/l. Urine investigations revealed erythrocyturia, leukocyturia and proteinuria of 0.63 g/l. HBs antigen and anti-HCV antibodies were negative, anti-DNA, ANA and ANCA were negative, C3 and C4 were within the normal limits. On day 5 of the hospital stay the rapid SARS-CoV-2 test (nasal swab) came back positive. Abdominal ultrasound revealed enlarged kidney and parenchymal size with increased parenchymal echogenicity.

Chest X-ray revealed interstitial opacities in the right lower lung field (Figure 2).

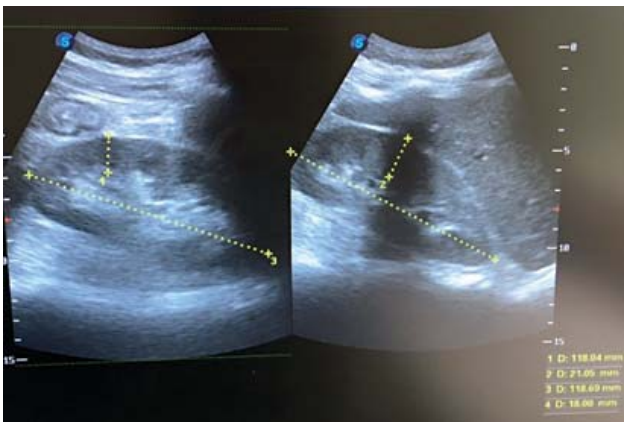


**Fig. 1.** Enlarged kidneys with wide and hyperechogenic parenchyma with slearly visible renal pyramids



**Fig. 2.** Chest X-ray of patient 1 – interstitial opacities in the right lower lung field

The patient was started on ceftriaxone, intravenous methylprednisolone 80 mg followed by 40 mg a day, famotidine, infusions and diuretics, subcutaneous fraxiparine. Rapid decrease in serum creatinine, urea and uric acid was observed, and improvement in CRP, d-dimer and ferritin levels was observed, erythrocyturia and proteinuria subsided. Platelet count and lactate dehydrogenase returned to normal limits.

Renal biopsy was performed in order to elucidate the renal pathological changes and revealed minimal-change nephropathy with negative immunofluorescence (Figure 3).

On the seventh day of treatment, new rapid antigen test was performed that came back positive and the described treatment was continued with azithromycine, corticosteroids, famotidine and fraxiparine for 7 more days. After that the patient's PRC test came back negative, renal function, urine, CRP, d-dimer, ferritine were within the normal limits. The oral corticosteroids were tapered within three months and

the patient remained asymptomatic with normal renal function.

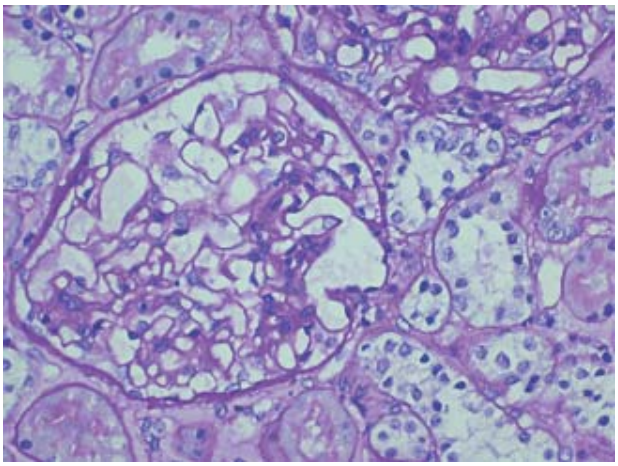


**Fig. 3.** Renal biopsy of patient 1: minimal-change nephropathy (hematoxylin-eosin, magnification x100)

### *Case 2*

A 32-year-old male patient was admitted to the Clinic of Nephrology in May 2021 for acute renal failure with oligoanuria, macroscopic hematuria and serum creatinine of 670 mcmol/l after 7 days treatment with 4-quinolone for pneumonia. The initial PCR test for SARS-CoV-2 was negative. The X-ray investigation revealed bilateral interstitial pneumonia. At the admission the patient was in impaired general condition, had low grade fever (37.2°C), and edema on the legs. The clinical-laboratory investigations revealed normal whole blood and differential count, increased ESR 55 mm/l h. and CRP 36.6; high serum creatinine 691 mcmol/l and high urea 43 mmol/l, high uric acid 1221 mcmol/l, increased d-dimer 1.86 mcg/ml, erythrocyturia and proteinuria of 0.29 g/l. All other biochemical and hemostasiological investigations were within the normal limits. HBs antigen and anti-HCV antibodies were negative, anti-DNA antibodies were low-positive (37.1 U/ml with normal values below 24 U/ml), ANA and ANCA were negative, C3 and C4 were within the normal limits. Abdominal ultrasound revealed hepato-splenomegaly without signs of portal hypertension, increased kidney and parenchymal size (128 mm and 25 mm resp.) (Figure 4) and increased RI 0.77-0.78 (segmental renal artery).

The chest X-ray revealed bilateral interstitial pneumonia (Figure 5).

The patient was started on ceftriaxone, intravenous infusions and alkalization, fraxiparine 0.6 ml, intravenous famitidine and intravenous corticosteroid (methylprednisolone 250 mg i.v. in three consecutive days, followed by 80 mg i.v. for two days and 40 mg i.v. afterwards), intravenous diuretics, oral allopurinol. Rapid restoration of diuresis was observed with decrease in serum creatinine within 7 days and on day 8 serum creatinine was 95 mcmol/l, urea 24 mmol/l, uric acid 272 mcmol/l, ESR, CRP and d-dimer levels gradually fell back to normal levels.

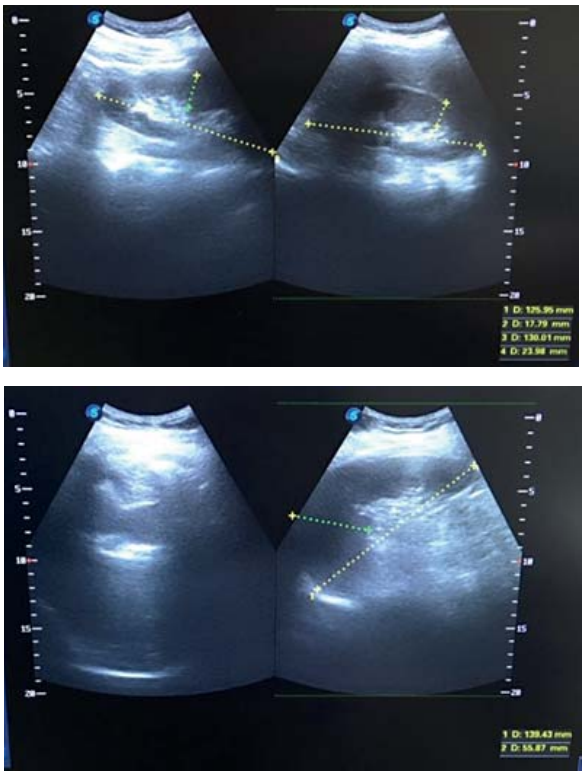


**Fig. 4**. Abdominal ultrasound of patient 2 – enlarged kidneys with widened parenchymal zone (**A**), enlarged spleen (**B**)

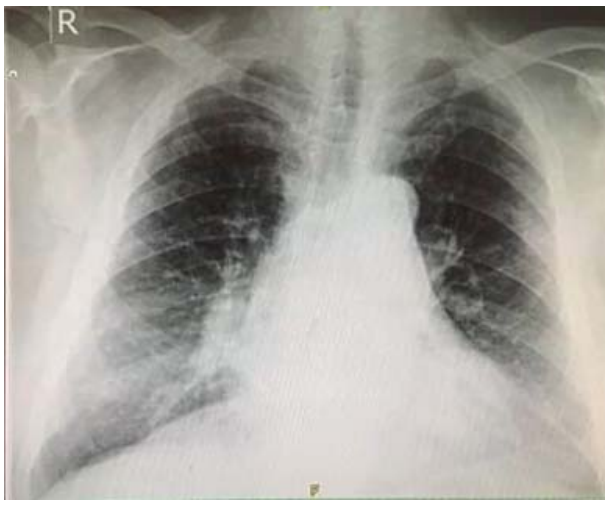


**Fig. 5.** Chest X-ray of patient 2 – bilateral interstitial pneumonia

Twenty days after the initial presentation of lung infection IgM and IgG anti-COVID antibodies were positive and the rapid antigenic test remained negative, and the condition was interpreted as COVID infection.

Renal biopsy (Figure 6) was performed in order to evaluate the renal changes and revealed normal glomerular structures, small fields of degenerative tubular changes with reduction and obscurity of the "brush-border" of the apical part of the tubular epithelial cells and balloon degeneration. The interstitium revealed mild mononuclear infiltration. The visible vessels showed no pathological changes. The immunofluorescent investigation showed mild mesangial deposition of IgM (+/-), moderate deposition of C3 within the vascular walls and mild to moderate deposition of fibrinogen (+/++) in the interstitium. The findings were interpreted as acute tubular injury.

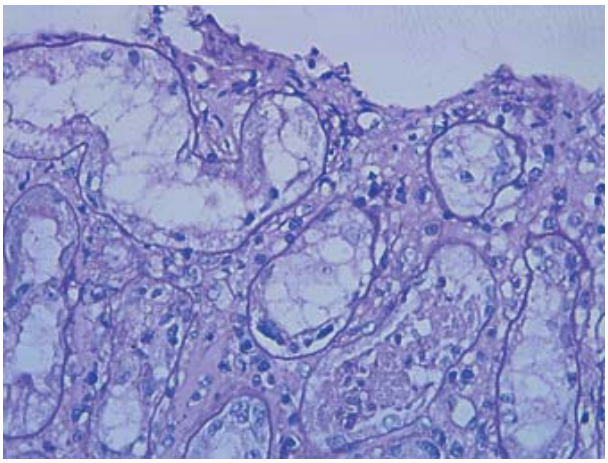


**Fig. 6.** Renal biopsy of patient 2: degenerative changes in the tubular epithelial cells, detritic material within the tubular lumina and mononuclear infiltration in the interstitium (hematoxilin-eosin, magnification x 400)

Corticosteroid treatment was gradually tapered within three months and the patient remains asymptomatic with normal renal function. Anti-DNA levels gradually decreased to normal levels.

***Case 3***

A 44-year-old male patient was admitted to the Clinic of Nephrology for acute renal failure (serum creatinine 399 mcmol/l) after marked dehydration due to fever and diarrhea for 7 days and treatment with antipyrrhetics and antibiotics (doxycyclin and cephalosporins). The patient reported arhtralgiae for the past 3 days before the admission. The initial COVID rapid antigen test was negative but two days after the first test the patient performed, a second test that came back positive.

At the admission the patient was in impaired general condition. The clinical-laboratory investigations revealed negative rapid antigen COVID test, increased ESR 68 mm/l h. and CRP 49, leukocytosis 11.7 G/l with high eosinophil count 0.53 G/l, high serum creatinine 313 mcmol/l and urea 20.6 mmol/l, high uric acid 810 mcmol/l. HBs antigen, anti-HCV antibodies, ANA, DNA, ANCA were negative, C3 and C4 were within the normal limits. Urine investigations were normal, proteinuria was 0.11 g/l.

Abdominal ultrasound (Figure 7) revealed diffuse renal parenchymal disease with increased kidney and parenchymal size, increased parenchymal echogenicity and contrasting hypoechogenic pyramids. The RI on segmental arteries was 0.75-0.77.

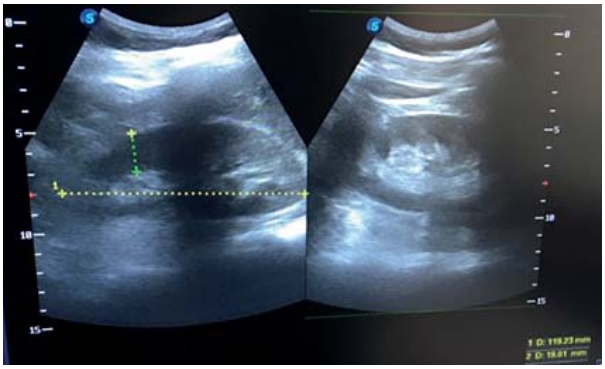


**Fig. 7.** Abdominal ultrasound of patient 3 – large kidneys with increased parenchymal echogenicity and contrasting hypoechogenic pyramids

The chest X-ray investigation was within the normal limits.

The patient was started on corticosteroids (methylprednisolone 40 mg intravenously for 3 days, followed by 20 mg intravenously), intravenous famotidine, alkalization. His condition improved rapidly after rehydration, normal diuresis was restored and creatinine, urea and uric acid serum levels decreased to the normal, eosinophil count decreased.

Renal biopsy (Figure 8) was performed and revealed no glomerular changes but showed acute tubulointerstitial nephritis. Immunofluorescence was negative.

Corticosteroid dose was gradually tapered down and the patient remained asymptomatic with normal renal function.

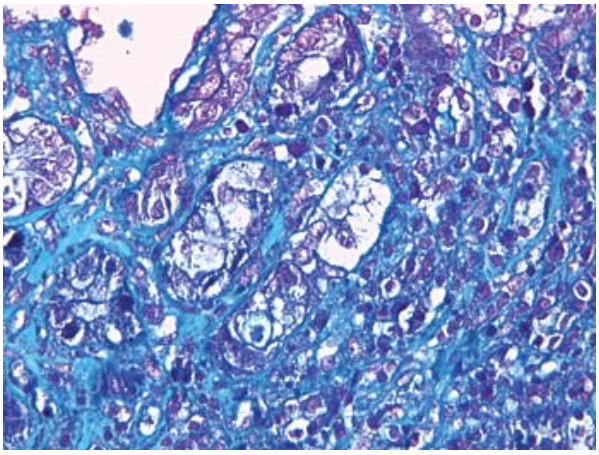


**Fig. 8.** Renal biopsy findings of patient 3: acute tubulointerstitial nephritis – interstitial edema, mononuclear infiltration of the interstitial spaces, degenerative and atrophic changes of the tubular cells (Masson Trichrom staining, magnification x 400)

## DISCUSSION

Coronaviruses are long-known pathogens in humans, causing multiple respiratory symptoms. Several mechanisms of kidney damage have been reported in SARS-CoV-2 patients, including [1, 7]:

Direct effect of the virus on the kidney via activation of the angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor. ACE2 is widely expressed in the renal tissue – both on podocytes and proximal tubular cells, and therefore these two types of cells can be damaged directly by the virus. Moreover, the activation of ACE2 may lead to initiation of the angiotensin II expression with subsequent vasoconstriction and renal ischemia.

Immune-mediated kidney injury – direct (destruction of the infected cells, tissue damage by antigen-antibody complexes – type II and III hypersensitivity reactions) or indirect (cytokine release with subsequent renal hypoperfusion and rhabdomyolysis-induced renal damage).

Endothelial damage and formation of microtrombi with renal ischemia and/or the development of glomerular microthrombi, resembling the pathogenesis of hemolytic-uremic syndrome.

Overactivation of the complement cascade with increase membrane-attack complex activity (C3b-9) and subsequent endothelial injury with the development of atypical hemolytic-uremic syndrome.

Drug-induced renal injury – toxic and allergic drug reactions.

Hemodynamic changes with renal ischemia/hypoperfusion due to dehydration, sepsis, increase synthesis of IL-6 and/or the intake of large amounts of temperature-lowering agents both leading to renal medullar vasoconstriction and tubular ischemic damage; hyperuricemia, etc.

All three patients in our small series presented with acute renal injury in the course of coronaviral infection. The first patient had histological data for minimal change nephropathy and laboratory data suggesting both nephrotic-range proteinuria and atypical hemolytic uremic syndrome (acute renal failure, increased lactate dehydrogenase and low platelet count) – i.e., both podocyte and endothelial damage by the virus. The second and the third patient both had acute kidney injury associated with renal tubular damage, probably due to two different mechanisms: acute tubular injury by the virus and hyperuricemia in dehydration and tissue damage due to pneumonia in patient 2 and dehydration in combination with hyperuricemia and allergic drug reaction with arthralgiae and eosinophilia in patient 3. In all patients abdominal ultrasound revealed diffuse parenchymal renal disease with increased parenchymal ehogenicity and contrasting hypoechogenic pyramids. Renal biopsy had crucial role for the proper diagnosis and treatment.

In all patients the timely and proper initiation of corticosteroid and supportive treatment lead to rapid resolution of kidney damage.

In conclusion, acute kidney injury is a serious complication of SARS-CoV-2 infection, and it can develop via different pathogenic mechanisms. The timely diagnosis, including biopsy evaluation, has crucial role for the proper treatment and beneficial outcome and preservation of renal function.

***Disclosure Summary:*** *The authors have nothing to disclose.*

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