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COVID-19 is a complex disease with wide spectrum of clinical patterns and an emerging problem for nephrologist

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In December 2019, an outbreak of coronavirus disease (COVID-19) due to the novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus began in China and spread rapidly worldwide. After China, Italy is the country with the highest number of cases so far. There are only limited data on COVID-19 in patients affected by chronic kidney disease. Herein, we report the outcomes of two patients with COVID-19 pneumonia who required renal replacement therapy. It is unknown whether hemodialysis patients represent a distinct group of patients with certain characteristics that may make them susceptible to infection or severe disease. In this letter, we describe our clinical experience with COVID-19 patients.

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In late December of 2019 throughout Wuhan, in the Hubei province of China, there started to appear several reports of a severe acute respiratory syndrome, pneumonia, that has been later recognised as an illness caused by the new coronavirus, SARS-CoV2 (severe acute respiratory syndrome coronavirus 2). At present we know this pathology as COVID-19 (coronavirus disease). COVID-19 has spread rapidly throughout Wuhan (Hubei province) to other provinces in China and around the world (1). Coronaviruses are a group of pathogens that co-infect humans and other vertebrates. These viruses affect the respiratory, gastrointestinal, and central nervous systems, as well as livers, of humans, birds, bats, and many other wild animals (2). The spectrum of symptomatic infection ranges from mild to critical. Most of the infections are not severe, but, even though 81% are mild (no or mild pneumonia), 14% manifest themselves through a severe disease (with dyspnea, hypoxia, or >50% lung involvement on imaging within 24 to 48 hours) and 5% develop a critical disease (e.g.: with respiratory failure, shock, or multiorgan dysfunction) (3). Severe illness can occur in otherwise healthy individuals of any age, but it predominantly occurs (tends to take place) in adults with an advanced age or underlying medical comorbidities

(cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, cancer and chronic kidney disease) (4). COVID-19 causes kidney involvement in about 3-9% of the patients, mostly presenting itself with acute kidney injury. Otherwise, COVID-19 is a major problem for dialysis facilities and for the nephrologist, because there is a higher incidence of severe and critical disease in patients with kidney disease (5).

After China, Italy is the country which has developed the major impact from the pandemic of SARS-CoV2, as it has the highest number of deaths so far (18,849 confirmed cases according to the 'Dipartimento della Protezione Civile' as of April 10) and is the third country with most confirmed infections in the world. Northern Italy, where the current prevalence of confirmed cases has surpassed in some areas 2 per 1000 people, presents some differences when it comes to the case-fatality rate compared to other countries (6). In the Lombardy region the disease seems to have a much higher mortality rate than the one that was reported in China, which led the Brescia Renal COVID Task Force to investigate with a retrospective and prospective cohort study all of the different factors, which are potentially responsible for this ominous outcome (7).

There are only limited data on COVID-19 in patients

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with chronic kidney disease. Herein, we report the different outcomes of two patients who underwent renal replacement therapy with COVID-19 pneumonia, who have been admitted to the Belcolle hospital in Viterbo (Italy) between March 22nd and April 11th, 2020. Table 1 summarizes clinical feature, history, laboratory data and

management strategies of the patients.

The most common symptoms the patients had were diarrhea, followed by fever, fatigue, dyspnea, and abdominal pain. None of them had rhinorrhea, sore throat, myalgia or other upper respiratory tract infection symptoms.

Table 1. Patients characteristics at admission and during our observation

Clinical characteristics	Patient #1	Patient #2
Age (y)	83	70
Gender	M	M
Race	White/Caucasian	White/Caucasian
Contact history with infected person	No	Yes
Other family members affected	Yes	No
History		
Primary nephropathy	ADPKD	None
Flu vaccination	Yes	No
Lung disease	No	No
Heart disease	Yes	No
Hypertension	Yes	Yes
Cancer	No	No
Obesity	No	No
Chronic kidney disease	Yes, dialysis dependent (4 y)	No
Symptoms		
Fever (T >37.5 °C)	Yes	Yes
Dyspnea	Yes	Yes
Diarrhea	Yes	Yes
Myalgias	No	No
AKI	No (HD patient)	Yes
Chest X-ray	Bilateral ground glass	Bilateral ground glass
Positive swab test	Yes	Yes
Biochemistry		
s-Cr (mg/dL); d0, d3, d7	9.56; 10.64	0.72; 6.85 ; 3.01
PLT (x10 ³ /mmc)	178	181
WBC (x10 ³ /mmc)	6.53	11.9
Lymphocytes (cells/mmc) d0, d3, d7	1120; 1010	610; 1040; 930
Hb (g/dL)	12.6	12.8
D-dim (mg/L)		35.78
AST (IU/mL)	18	67
ALT (IU/mL)	18	102
LDH (IU/mL)	316	613
CPK (IU/mL)	187	180
CRP (mg/L) d0, d3, d7	118.7	347.8; 401.1; 138.3
Procalcitonin (ng/mL) d0, d3, d7	0.95	0.44; 41.23; 2.92
Antiviral/antibiotics		
Antibiotics	Yes	Yes
Hydroxychloroquine	Yes	Yes
Lopinavir/ritonavir	Yes	Yes
Remdesivir	No	No
Tocilizumab	No	No
Outcomes		
NIV	Yes	Yes
ICU	No	Yes
CRRT	No	Yes
Death	Yes (3 days after admission)	No

NIV, non-invasive ventilation; CRRT, continuous renal replacement therapy.

The first one was an 83-year-old male (patient #1) and the other one a 70-year-old male (patient #2). Patient #1 was dialysis dependent for an end-stage renal disease due to ADPKD (autosomal dominant polycystic kidney disease), while patient #2 had no history of renal disease. Symptoms began to appear the first day before their hospitalization for both patients. Both presented themselves with fever (38-39°C) and dyspnea at admission. The chest radiography that was performed as soon as they entered showed the typical radiological findings of COVID-19 pneumonia, with extensive bilateral ground-glass opacities in both. Specific treatment was started before the arrival of the nasopharyngeal swab test results (PCR, confirming SARS-CoV-2 infection on day 3 and 2 after symptoms' onset). Both patients received hydroxychloroquine (200 mg twice daily) in addition to lopinavir+ritonavir. Patient #1 was on Angiotensin-converting enzyme inhibitor (ACE-I) therapy, while patient #2 was not in therapy with a renin-angiotensin-aldosterone system (RAAS) inhibitor. Both patients required non-invasive ventilation. On day 2 after admission, patient #1 underwent dialysis treatment; the following day he was well and was therefore moved to the COVID-19 ward in order to continue with the anti-viral therapy. The morning of the 3rd day the nurses found him dead in his bed; a sudden death likely occurred.

Patient #2 manifested an abrupt worsening of his respiratory conditions over a period of 24 to 38 hours, and was therefore transferred to the ICU, as he required mechanic ventilation. His renal function rapidly worsened associated with a reduction of urine output and the next day, and he started CVVHDF (continuous veno-venous hemodiafiltration).

The reasons behind kidney failure during COVID-19 are still unclear, even if the major hypothesis sees the cause in the direct tubular damage induced by the virus infection (8). The renal histopathological of post-mortem analysis showed a direct parenchymal infection of tubular epithelial cells and podocytes, with a marked acute tubular injury (ATI) and an erythrocyte aggregation, which occurs in the severe COVID-19 lethal cases. (9). At the time of writing (day 14 after initial symptoms), the patient is alert and stable on non-invasive ventilation positive airway pressure (PaO₂/FiO₂ 114, respiratory rate 22 rpm, arterial blood pressure 150/90 mm Hg, heart rate 105 rpm). Serum creatinine has returned to baseline levels (1 mg/dL) and liver function test are normal. Dialysis was discontinued and his renal function recovered on the seventh day after starting CRRT (Continuous renal replacement therapy).

It has been confirmed that T-cell immunity plays a key role in the recovery from the SARS-CoV2 infection. As the uremia status is associated with extensive impairment of lymphocyte and granulocyte function, an abnormal immune system may alter their response to the SARS-

CoV2 infection (10). This is of particular concern, given the densely populated and busy nature of dialysis facilities, which may be creating a high risk of exposure. However, in our dialysis center, the virus does not seem to have spread widely. Further observations will be needed in order to reach a deeper understanding of the full spectrum of clinical features, and to fully comprehend which is the optimal diagnostic and treatment to be approached, when it comes to cases of COVID-19 disease in hemodialysis patients.

Authors' contribution

DM and SF wrote the paper. FM and SC were the clinicians of the patients. All the authors review the manuscript and approve it for publication.

Conflicts of interest

The authors declare no conflicting interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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