COVID-19 in patients starting hemodialysis in the Alentejo region: case reports

L'epidemia Covid-19: diario di bordo di una emergenza

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ABSTRACT
COVID-19 has a wide spectrum of clinical presentation, ranging from asymptomatic or mild symptoms to severe multiorgan failure. In Portugal, the first cases affecting patients on a chronic hemodialysis program arose in the city of Oporto.
The authors report here two cases of COVID-19 infection in patients incident in renal replacement therapy in the Alentejo region and hypothesise that the high serum concentration of urea may decapitate the appearance of typical symptoms of the SARS-CoV-2 infection. The fact that the hemodialysis population can present active infection without fever may lead to a delayed diagnosis and consequently an increased risk of mortality.

PAROLE CHIAVE: COVID-19, hemodialysis, urea, case reports, Alentejo region

Introduction

Patients with end stage chronic kidney disease (ESKD) have a greater morbidity and mortality, mainly due to cardiovascular risk, underlying immunosuppression and advanced age with multiple comorbidities.

The disease caused by SARS-CoV-2 coronavirus emerged in the city of Wuhan in the Chinese province of Hubei in December 2019. In March 2020, the WHO declared coronavirus disease (COVID-19) a pandemic. The first case of infection in Portugal was on 1st March 2020. The first cases affecting patients on chronic hemodialysis (HD) arose in the city of Oporto. The Alentejo region was affected from late March.

COVID-19 has a wide spectrum of clinical presentation, ranging from asymptomatic to mild symptoms such as dry cough, high fever and difficulty breathing, to severe symptoms with multiorgan failure. However, despite the high risk of death for patients on hemodialysis, not all government policies advocate for their hospitalization.

The authors decided to highlight here the only two cases of COVID-19 infection in patients incident in renal replacement therapy in the Alentejo region, their clinical course and outcome.

Case report 1

The first patient was a 72-year-old man, with chronic bronchitis and chronic kidney disease stage 5 of unknown etiology, with a two-year-old arteriovenous fistula. The patient was admitted to our dialysis unit to start HD as he claimed to have light uremic symptoms. The first dialytic session, lasting 2 hours and with zero ultrafiltration, went well and the patient was discharged the same day. On the next day, he went to the emergency room with epistaxis. Screening for SARS-CoV-2 was positive and he was admitted to hospital.

Blood results showed elevated markers of inflammation: CRP 17.6mg/dL, ferritin 2130ng/mL, PCT 1.18ng/ml, LDH 445U/L, IL-6 84.62pg/mL (Table I). During his stay he became febrile, with respiratory distress and at day 5 after admission he had to be put on invasive mechanical ventilation and was transferred to the intensive care unit (ICU) where, on day 2, he developed multiorgan failure and died. He underwent 2 intermittent dialysis sessions.

Patient 1	Hospital Admission	ICU Admission	24h ICU	48h ICU (death)
Leucocytes x10^9 cells/L	7200	10300	13600	13300
CRP mg/dL	17,8	31		
PCT ng/mL	1,18	3,93	2,76	2,09
Ferritin ng/mL	2130	3240	3280	
LDH U/L	445	578	41403	41236
IL-6 pg/mL	84,62	214	596,1	4413
Cr mg/dL	7,11	4,21	2,96	1,38
Ur mg/dL	193	91	69	21

Table I: Blood test results for patient 1

Case report 2

The first patient was a 70-year-old woman with hypertension, type 2 diabetes mellitus on insulin therapy, congestive heart failure class II NYHA and chronic kidney disease stage 5, with an arteriovenous fistula built two years before. The patient resided in a Nursing Home affected by a

COVID-19 outbreak, where she got infected. She was admitted to the emergency room with dyspnea, hypoxemia and generalized muscle pain. Due to the worsening of her clinical status and uremic symptoms, she was started on hemodialysis 5 days later. After her first intermittent hemodialysis session she developed fever and raised markers of inflammation (Table II). After her third dialysis session, she became obnubilated, developed polypnea and went on invasive mechanical ventilation on day 7 after her hospital admission. One month later, she died on the ICU with multiorgan failure.

Patient 2	Hospital Admission	ICU Admission	24h ICU	48h ICU	Discharge (death)
Leucocytes x10^9 cells/L	4700	5400	7200	6600	11200
CRP mg/dL	2,3				
PCT ng/mL	0,46	0,95	1,15	1,49	2,31
Ferritin ng/mL	706	1570	1510	1610	1890
LDH U/L		502	422	402	431
IL-6 pg/mL	49	134.2	259,3	500,6	351,5
Cr mg/dL	12,54	3,67	4,62	1,37	0,5
Ur mg/dL	331	65	80	21	10

Table II: Blood test results for patient 2

Discussion and conclusions

The severity of the SARS-CoV-2 infection is associated with risk factors such as advanced age, male gender, diabetes *mellitus*, obesity, hypertension, lung disease and elevated serum creatinine levels [1]. In one study the authors showed that the presentation of the disease in patients undergoing dialytic treatment was similar to that of the general population. However, the prognosis was worse with 31% overall mortality and 75% mortality in patients undergoing invasive mechanical ventilation [2].

Given the increased number of SARS-CoV-2 infections in the general population, we expected that the disease would soon reach the hemodialysis population. Travelling to dialysis centres with shared ambulances and sharing the same treatment room create the ideal environment to increase the risk of transmission.

Most patients with COVID-19 do not have kidney damage. Nevertheless, those who develop acute kidney injury manifest the most severe phenotype of the disease, characterized by cytokine storm, overall respiratory failure and hypercoagulability [3]. Acute renal injury in patients with COVID-19 may result from: direct cytokine injury, myocardiopathy resulting in cardiorenal syndrome type 1, medullary renal hypoxia, increased vascular permeability, renal hypoperfusion, tubular toxicity, endotoxin injury in sepsis [4].Despite the high number of prevalent patients in HD in Portugal, the number of COVID-19 infections in these patients has so far been unexpectedly low. In part, this can be justified by the good hygienization practice implemented quickly in the intra- and extra-hospital dialysis units, by the generalized use of masks among personnel and patients, and by good patient education. The immunosuppressed status of those who did become infected seems to prevent the emergence of the cytokine storm that is a critical mediator for the clinical worsening. Another plausible explanation is the protective role of anticoagulation, since SARS-CoV-2 infection promotes thrombogenesis. Pisani et al. (2020) present heparin anticoagulation used in hemodialysis as a possible major contribution to a more indolent, limited, less severe clinical evolution in HD patients, either because of its role in preventing the entry of SARS-CoV-2 into host cells by interacting with the recombinant receptor-binding surface SARS-CoV-2 S1 RBD, or because of its anti-inflammatory properties [5].

The situation of the dialysis population in the Alentejo region can be seen to confirm the evidence already described. Until November, only five COVID-19 cases had been reported in patients on chronic HD. Most had fever and cough initially, 3 required additional oxygen support and even 1 patient with lung cancer needed invasive mechanical ventilation for only 5 days. All received only symptomatic treatment and recovered without sequelae. By contrast, the only 2 cases of patients incident on hemodialysis had the worst outcome.

The authors hypothesise that the high serum concentration of urea and other uremic toxins in stage 5 patients not on dialysis may decapitate the appearance of typical symptoms of SARS-CoV-2 infection, such as fever. Once the dialytic treatment is initiated, clearance of those molecules will lead to the reduction of this inhibitory effect and consequently to the elevation of the baseline temperature and onset of fever, if there is an active infection. Schreiner (1961) showed that uremic patients may be unable to develop a febrile immune system response to an infection. When urea levels are corrected through dialytic treatment, however, fever appears [6].

Other authors state that, when the serum urea level is higher than 100mg/dL, patients show a decrease in body temperature as a consequence of decreased metabolism caused by uremic substances [7]. The idea of “uremic hypothermia” dates back to the 18th century [8]. The role of the kidneys in thermoregulation is well documented in the literature: the kidneys contribute to more than 10% of body heat by high aerobic metabolism [9]. One study shows that 23% of patients with chronic renal disease stage 5 pre-dialysis are hypothermic [10].

With regards to the baseline temperature of patients on chronic hemodialysis, the evidence is contradictory. If, on the one hand, there are studies that report patients in renal replacement therapy having lower baseline temperature [11], on the other, the latest evidence shows that dialysed patients may exhibit a higher temperature during an infectious state than other patient populations [12]. In the study published by Weatherall et al. (2020), patients in HD were found to have a higher baseline temperature but the mechanism for this event was not clear [13]. Some authors speculate that chronic inflammation resulting from repeated exposure to dialysis and water contaminated with Gram-negative bacteria can lead to the release of endotoxins into the filter membranes, which in turn will lead to increased pro-inflammatory cytokine production [14]; this is not at all likely anymore, with the ultrapure water in use nowadays. Other authors argue that the increased metabolic rate and peripheral vasoconstriction during hemodialysis lead to increased body temperature [11]. The role of comorbidities may also influence body temperature, as diabetic patients have lower temperatures, probably due to autonomic dysfunction [15]. Despite these various studies, the physiological mechanism of uremic hypothermia has only partially been unveiled. Jones et al. suggested in 1985 that a decrease in hypothalamic response to the action of leukocytic pyrogen (LP) and a reduced capacity in heat generation through chills and vasoconstriction in response to LP could cause a lower body temperature in the presence of higher levels of serum urea; it also concluded that the production of LP in patients with chronic kidney disease is similar in patients without renal failure [16].

The cases reported here affected patients who started intermittent hemodialysis and were under continuous renal replacement therapy in the intensive care unit, on account of their critical clinical status and hemodynamic instability. It is still controversial wheather the most severe form of COVID-19 pneumonia is characterized by acute respiratory distress syndrome and high inflammatory markers like CRP, ferritin, PCT and cytokines: there are in fact many cases where patients get severe lung injury without the so-called “cytokine storm” [17].

SARS-CoV-2 is sufficiently aggressive to cause organizing pneumonia, which is a risk factor for secondary bacterial and fungal infections. However, believing that uremic toxins can have a

protective role against this hyperinflammatory phenotype, authors defend that end stage kidney disease patients should be managed with medical therapy (potassium and phosphate binders, liquid restriction), while delaying the start of hemodialysis. If this is not possible, then a lower clearance strategy should be employed to minimize the removal of uremic toxins with their protective effect.

The fact that patients with CKD stage 5 not on dialysis can present active infection without fever may lead to a delayed diagnosis and, consequently, to an increased risk of mortality. But in patients on maintenance hemodialysis COVID-19 has a different presentation. The data about patients on maintenance hemodialysis is contradictory, with papers showing that HD patients presented milder symptoms and were often asymptomatic, and other reports showing that the clinical presentation is similar to the general population. In fact, a recent report found that the mortality of patients on maintenance hemodialysis is higher, but the study has excluded asymptomatic HD patients. Furthermore, the number of patients on HD with fever was exactly the same as the number of patients in the control group and it would have been more interesting if the authors had included the different stages of CKD as a comorbidity in non-dialysis group [18].

The hemodialysis patient population has a chronic state of immunosuppression secondary to chronic kidney disease and a higher number of comorbidities, making it one of the most vulnerable populations in the current pandemic context.

The prognosis of incident and prevalent patients in HD still needs multivariate analysis and a long-term evaluation of the possible sequelae left in this population.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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