COVID-19 REINFECTION IN A PATIENT WITH END-STAGE RENAL DISEASE ON CHRONIC HEMODIALYSIS: IS IT POSSIBLE OR IS IT INACCURACY OF TESTING?

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Patients with end-stage renal disease (ESRD) on hemodialysis (HD) are at a high risk of acquiring SARS-CoV-2 and of developing severe COVID-19 and death. The possibility of being reinfected with this virus is poorly understood. To date, there are a small number of reports of reinfections in COVID-19 patients, especially in HD patients, with only four cases described so far. The aim was to show the possibility of reinfection and developing severe acute respiratory syndrome in HD patients. We describe a 69-year-old ESRD patient who had been on HD treatment for three years, with diabetes mellitus and a history of ischemic cardiomyopathy. The patient was tested for SARS-CoV-2 by a nasopharyngeal polymerase chain reaction (PCR) test because of a positive cluster at his dialysis unit and initially diagnosed with COVID-19 in July 2020. In this period, he had mild symptoms for a few days and remained asymptomatic afterwards. Four months later, he presented to the hospital with fatigue, high fever and shortness of breath, and was COVID-19 positive again. This case points to the possibility of reinfection, lack of immune response after an asymptomatic or mild infection, or even the possibility of the first false-positive PCR test. Future longitudinal studies are needed to evaluate the potential reinfections, recurrence, and duration of antibody detection.

Key words: chronic kidney disease, hemodialysis, COVID-19 reinfection

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INTRODUCTION

In December 31, 2019, the World Health Organization (WHO) China country office notified of the cases of pneumonia of unknown etiology detected in Wuhan city, Hubei province, with subsequent detection of a new strain of coronavirus on January 7, 2020. The virus was subsequently named by the WHO as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by it as COVID-19. COVID-19 has evolved into a global pandemic as declared by the WHO on March 11, 2020 (1), and caused over 15 million infections and half a million deaths worldwide (2).

Patients with chronic kidney disease (CKD) and those on renal replacement therapies are potentially susceptible to developing COVID-19 infection, given the concentration of the risk factors and comorbidities (3). Patients on chronic hemodialysis (HD) have a high risk of both infection and severe disease because of their fragility and unavoidable health care-related contacts. The diagnosis may be challenging; false-negatives are frequent, and persistence of positivity may be prolonged (4).

CASE REPORT

We report on a 69-year-old-man on chronic HD due to diabetes nephropathy, with a history of ischemic cardiomyopathy and implanted bypass due to a three-vessel coronary heart disease.

He was screened because of a positive cluster in his dialysis unit. He was found positive for SARS-CoV-2 by a nasopharyngeal polymerase chain reaction (PCR) test on July 22, 2020. The patient was isolated and ambulatory dialyzed in a special COVID unit. Except for fatigue, the patient did not report any other symptoms for several days. On the first physical examination, he was afebrile and hemodynamically stable (blood pressure 120/70 and heart rate 89 beats/minute) with oxygen saturation of 98%. Auscultatory finding on the lungs was normal. Complete blood count revealed normal findings, with the exception of thrombocytopenia, which had been present before (Le $6.1x10^9$, Er $4.59x10^{12}$, Hgb 144 g/l, Plt $91x10^9$) and normal values of C-reactive protein (CRP; 5 mg/mL). His chest x-ray showed a congestive state, which could not completely rule out incipient infiltrative changes and he was administered antibiotic therapy with azithromycin 500 mg for six days. He continued with HD every other day and was regularly monitored by a nephrologist. During this period, the patient was feeling well and was clinically stable. He tested negative on August 3, 2020 and his isolation measures were discontinued.

On November 11, 2020, the patient's daughter called his dialysis unit to inform that her father was febrile and felt fatigue with occasional vomiting. The patient had a PCR test, which came back positive. On physical examination, he was febrile and dyspneic with oxygen saturation of 93%, and bilateral basal crackles were heard on the lungs. The blood count was similar to the previous one but increased CRP levels were noticed (>120 mg/mL). Now his chest x-ray showed congestive changes and bilateral infiltration. He continued his ambulatory HD treatment in the COVID positive unit and there he received antibiotic treatment with cephazolin 2 g intravenously (i.v.), but he still felt unwell. On day 9 of illness, after HD he worsened, could not breathe, and had severe dyspnea with oxygen saturation of 75% and limb cyanosis. He was urgently transported to the COVID Disease Isolation Center. Upon arrival, his clinical state worsened with a very low oxygen saturation of 42% and he was immediately placed on oxygenation. His blood count and CRP were the same with azotemia (urea 29.2 mmol/L, creatinine 899 μmol/L), electrolyte imbalance (Na 128 mmol/L, K 5.7 mmol/l, Cl 101 mmol/L), very high values of D-dimer (36.5 mg/L) and immeasurable fibrinogen. Native computed tomography scan (CT) of the thoracic organs showed extensive ground glass opacities (GGO) and gentle consolidation of the peripheral and basal parts of the lungs. He was administered dexamethasone 6 mg i.v., ceftriaxone 2 g i.v., doxycycline cps 2x100 mg *per os* daily, and low molecular weight heparin 40 mg twice a day, in addition to the patient's chronic therapy. The patient was also on CVVHD treatment according to the protocol and under oxygenation up to 6 L/min. When the PCR test came negative a few days later, he was transferred to the Nephrology Department, where his laboratory findings were similar to those mentioned above, with high LDH level (1098 U/L) and a decrease in CRP (94.4 -57.7 mg/L), D-dimer (8.05 mg/L) and fibrinogen (2.1 g/L) values. Control CT showed significant regression of the previously observed changes. Serologic testing showed an IgG level of 91.4600 AU/mL and IgM of 14.7200 AU/mL.

With the given therapy and regular HD treatment, the patient gradually recovered but still was weak, hypotensive, and cardiopulmonary compensated. Upon discharge, he continued HD in his unit, but his overall condition worsened compared to the condition before the infection, when he was a clinically stable patient.

DISCUSSION

To the best of our knowledge, only four cases of COVID-19 reinfection in HD patients have been reported. Mendoza *et al.* (5) presented a case of a clinically manifest infection that followed two months after detecting low IgG antibody with a negative PCR test. Krishna *et al.* (6) described two patients with suspected recurrent COVID-19 infection, each with documented clearance of virus between the episodes. In these two patients, the time elapsed between the negative reverse-transcription PCR test result for SARS CoV-2 and symptomatic reinfection was 31 and 55 days, respectively. Both of these patients were tested after a contact with a positive person and had no symptoms; then, one patient had severe symptoms and required hospitalization, whereas the other had mild symptoms and was treated as outpatient (6).

In addition, Torreggiani *et al.* (4) report on a patient who was screened because of a positive cluster in his nursing home and tested PCR positive; 22 days after testing negative, he developed fever and bilateral pneumonia. In this case, besides reinfection, the authors highly suspected the occurrence of virus reactivation and inaccuracy of testing (4).

In our case, we could not rule out the possibility of the initial false-positive test either. It was quite unlikely because the patient lived in a city that recorded a large number of infected inhabitants and also had a suspicious contact in his HD unit.

The PCR tests for SARS-CoV-2 detection are considered as the gold standard but are not perfect, especially in clinical practice because false tests can have fatal consequences (7). Technical problems including con-

tamination during the sampling and cross-reactions with other viruses or genetic material may be responsible for false-positive results. When interpreting the results, it is important to consider the patient epidemiologic history and previous COVID-19 disease. When there is a low probability based on all these data, a positive result should be interpreted with caution and another test should be performed (8).

In our case, additional test was not performed after the first positive PCR test because our patient had a positive epidemiologic survey.

Reinfections with other human coronaviruses can occur, while reinfection with SARS-CoV-2 in humans is rare and unknown (9). Selvaraj *et al*. presented a number of 34 reinfections recorded worldwide until November 2020 (10). Most people infected with SARS-CoV-2 have detectable antibodies for 10-14 days of symptom onset, while antibody titer is low or even impossible to detect in patients with a mild clinical picture (11). There is little information about the strength and length of protection provided by this immune response against future infections (10). One Chinese study showed 40% of asymptomatic cases and 12.9% of symptomatic patients who became seronegative in the early convalescent phase (8 weeks after infection) (12). Whether these findings of the presence of SARS-CoV-2 antibodies in patients with CKD is similar to the general population is still unknown (13).

In our case, no serologic testing was performed after the first positive test, which is a limitation of our report, and we do not know whether the patient developed antibodies after the initial infection or became seronegative after a certain period. After the second infection, serologic testing showed a high amount of both IgG and IgM antibodies. This goes in favor to the fact that infections with mild symptoms have lower antibodies and is more likely to get reinfected (10). But, opposite to our case where reinfection presented with severe symptoms, most infections with respiratory viruses occur with milder symptoms due to a stronger immune system response that can occur when reinfection occurs with a different strain of the same virus (14).

This case presents the possibility of reinfection, lack of immune response after mild symptoms, or even an initial false-positive test. Based on the previously reported cases of reinfection, it is indicative that the immunity developed after COVID-19 infection cannot provide lifetime protection. There is also a paradox between the decrease in antibody titer that occurs over time and the low incidence of reinfections, which points to complex immune mechanisms. In order to better understand those mechanisms, longitudinal studies in the future are needed, as well as a uniform diagnostic approach to the patient, which will allow better comparison of patients from different hospitals and countries.

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SAŽETAK

PONOVNA INFEKCIJA COVID-19 U BOLESNIKA SA ZAVRŠNIM STADIJEM KRONIČNE BOLESTI BUBREGA NA KRONIČNOJ HEMODIJALIZI: JE LI TO MOGUĆE ILI SE RADI O DIJAGNOSTIČKOM PROPUSTU?

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Bolesnici s terminalnom bubrežnom bolešću koji su na hemodijalizi (HD) pod visokim su rizikom od zaraze virusom SARS-CoV-2 i od razvijanja teške kliničke slike bolesti COVID-19. Mogućnost ponovne zaraze ovim virusom još je uvijek većinom nepoznata. Do danas je opisan manji broj COVID-19 reinfekcija, pogotovo kod bolesnika na HD gdje su dosad opisana samo četiri slučaja. Prikazujemo mogućnost reinfekcije virusom SARS-CoV-2 i razvoja teškog akutnog respiracijskog sindroma kod bolesnika na HD. *Prikaz bolesnika:* Bolesnik u dobi od 69 godina je na kroničnom programu HD tri godine zbog bubrežnog zatajenja tijekom dijabetičke nefropatije s anamnezom ishemijske kardiomiopatije te dvostrukim CABG zbog trožilne koronarne bolesti. U srpnju 2020. godine bolesnik je testiran pozitivno metodom PCR na SARS-CoV-2 zbog kontakta s pozitivnim bolesnikom u zajedničkom prijevozu na dijalizu. U tom je razdoblju imao blage simptome, umor nekoliko dana, nakon čega je postao asimptomatičan. Nakon četiri mjeseca javlja se u bolnicu s visokom tjelesnom temperaturom, teškom zaduhom i lošim općim stanjem te je opet COVID-19 pozitivan. *Zaključak:* Ovaj slučaj ukazuje na mogućnost reinfekcije, slabog imunosnog odgovora nakon asimptomske ili blage infekcije ili čak prvog lažno pozitivnog PCR testa. Da bi se evaluirao potencijalni mehanizam reinfekcija, eventualnih recidiva i trajanje imunosnog odgovora potrebne su buduće longitudinalne studije.

Ključne riječi: kronična bubrežna bolest, hemodijaliza, reinfekcija COVID-19