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CASE REPORT

WILEY

Hyponatremia: A possible immuno-neuroendocrine interface with COVID-19 in a kidney transplant recipient

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Abstract

There is fast-emerging, cumulative clinical data on coronavirus disease 2019 (COVID-19) in kidney transplant recipients. Although respiratory tract symptoms are often the initial presentation among kidney transplant recipients who contract COVID-19, other clinical features which may indicate underlying SARS-CoV-2-related inflammation, such as gastrointestinal symptoms, are not uncommon. Hyponatremia can develop and may reflect underlying inflammation. Interferon-6 is an important pro-inflammatory cytokine involved in the pathogenesis of severe COVID-19 complications and may play a role in the inappropriately higher secretion of antidiuretic hormone leading to hyponatremia. This pathway is the so-called immuno-neuroendocrine interface. Hyponatremia in COVID-19 has been reported in a few case series of non-kidney transplant patients and only one reported kidney transplant recipient. However, the clinical course and prognostic value of hyponatremia in this population are not described in detail. We report a kidney transplant recipient who was infected with COVID-19 and exhibited severe hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion. Hyponatremia is one of the clinical presentations of COVID-19, although less common, and may occur more frequently in kidney transplant recipients. Thus, the possible underlying immuno-neuroendocrine relationship related to the inflammatory process of COVID-19 leading to hyponatremia and its prognostic value are reviewed.

KEYWORDS

coronavirus disease 2019, COVID-19, gastrointestinal symptoms, gut-lung axis, immuno-neuroendocrine interface, kidney transplantation

Abbreviations: ADH, antidiuretic hormone; AKI, acute kidney injury; COVID-19, coronavirus disease 2019; DDRT, deceased donor renal transplantation; DM, diabetes mellitus; EBV, Epstein-Barr virus; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IL, interleukin; ITP, immune thrombocytopenia; MPS, mycophenolate sodium; PTA, prior to admission; PTLD, post-transplant lymphoproliferative disease; rRT-PCR, real-time reverse-transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SNa, serum sodium.

1 | INTRODUCTION

There are several case reports, and case series, of coronavirus disease 2019 (COVID-19) in kidney transplant recipients. One reported kidney transplant recipient presented with hyponatremia, but the details regarding clinical presentation, clinical course, prognostic value, and mechanistic hypothesis of hyponatremia specifically in kidney transplant recipients with COVID-19 are lacking. Therefore, we report a kidney transplant recipient with COVID-19 presenting with severe hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH) and discuss the possible mechanisms of COVID-19-related hyponatremia in the kidney transplant population.

2 | CASE REPORT

Our patient is a 55-year-old Korean American woman with end-stage renal disease secondary to type 2 diabetes. She received a 0-A-B-DR-mismatched antigen deceased-donor renal transplantation with thymoglobulin induction in July 2019. Her initial presenting symptom of COVID-19 was fever. She was maintained on triple immune-suppressive therapy throughout admission, including tacrolimus, mycophenolate sodium (MPS), and prednisone. She did not require angiotensin pathway modulators.

Approximately 20 days prior to admission (PTA), her son had travelled to Texas. After returning home, to the same house as our patient, he developed fever, cough, fatigue, and weakness and went to a local hospital. Evaluation confirmed he had contracted severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. He was hospitalized for 3 days and recovered without the need for supplemental oxygen.

Six days prior to our patient's admission, her son was discharged home despite ongoing, albeit improving symptoms. Our patient, who resides with her son, was concerned about the risk of COVID-19 transmission, and called the transplant center for advice. She was at the time symptom free and instructed to leave her home and move in with her sister for two weeks.

Two days PTA on during a telephone follow up visit with the transplant center she reported increased fatigue. Her vital signs were unremarkable however, and her son's symptoms had completely resolved by this point.

On the day of admission, she had developed a cough, and dyspnea. She also reported a headache, decreased appetite, nausea, and fatigue. Her home temperature was 37.4°C, and admission was arranged for suspected for COVID-19.

Admission vital signs were a temperature of 36.3°C, heart rate of 87 beats/min, respiratory rate of 22/min, blood pressure of 147/76 mm Hg, and oxygen saturation was 99% on room air. She was noted to be in mild distress, with moist mucous membranes, and without peripheral edema. Her cardiovascular and respiratory system examinations were unremarkable.

Her initial laboratory results showed an acute hyponatremia with a serum sodium (SNa) down to 120 mmol/L. Her blood glucose was 134 mg/dL, urine sodium was 28 mmol/L, and serum and urine osmolality were 255 and 326 mOsm/kg, respectively. High sensitivity troponin-I was 8 ng/L (reference 0-15), and a 12-lead electrocardiogram was unremarkable. A chest x-ray revealed patchy consolidations in the right middle and lower lung zone, peribronchial cuffing, and mild pulmonary vascular congestion (Figure 1). Nasaopharyngeal swabs for SARS-CoV-2 by real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) assay was positive, but negative for respiratory syncytial virus, and influenza A & B viruses. She had transient lymphopenia on hospital day 2. Inflammatory markers were normal, including a lactate dehydrogenase of 171 U/L (reference 140-271) and c-reactive protein of 0.8 mg/dL (reference 0-1). Interleukin (IL)-6 was <5 pg/mL (reference ≤5 pg/mL) (Table 1).

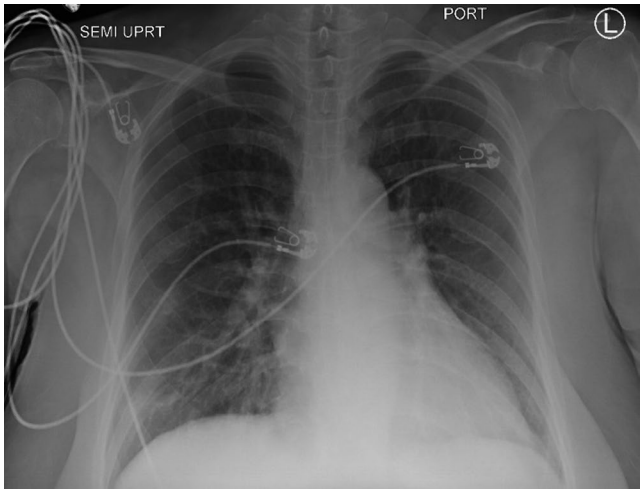


FIGURE 1 A chest x-ray frontal view on the day of admission reveals bibasilar atelectatic changes, with possible patchy consolidation in the right middle and lower lung zones. There is peribronchial cuffing. There is mild pulmonary vascular congestion

The tacrolimus dose was titrated to a 12-hour target trough level of 4-5 ng/mL, and MPS was discontinued. She was continued on oral prednisone 5 mg daily. Hydroxychloroquine was started at 400 mg every 12 hours for two doses, followed by 200 mg every 12 hours. She was given 0.9%NaCl at 100 mL/h for 10.5 hours without improvement in SNa. After discontinuation of the intravenous fluid, her SNa gradually increased up to 134 mmol/L over the following 48 hours (Figure 2). The serum creatinine remained stable at her baseline level of 0.7-0.9 mg/dL. Given her euvolemic status, lack of response to isotonic saline, and urine electrolytes, her hyponatremia was thought to be secondary to SIADH. Vital signs remained normal throughout the rest of her admission, and she did not require supplemental oxygen and was discharged home on hospital day 5.

3 | DISCUSSION

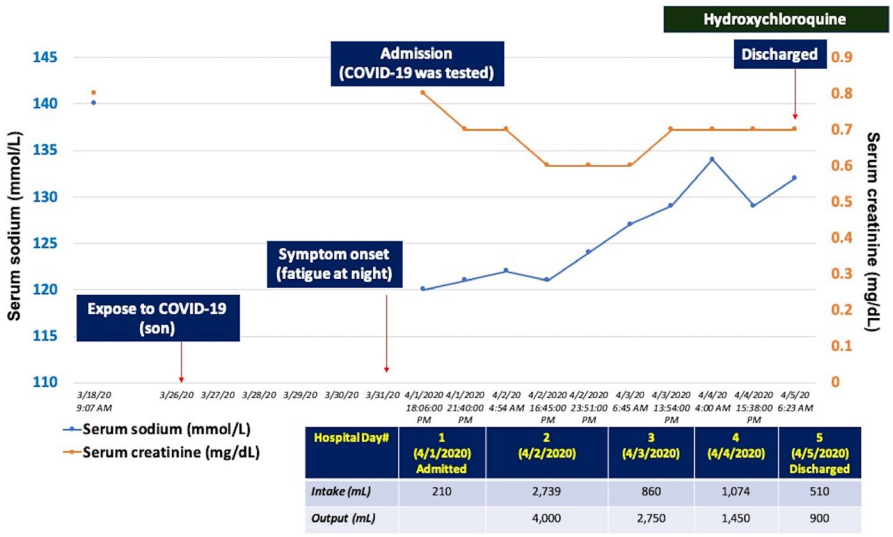
Our patient initially presented with non-specific and relatively common clinical manifestations of COVID-19. She however had significant

TABLE 1 Laboratory data during 5 days of hospitalization demonstrates transient lymphopenia on hospital day #2

	1 (4/1/2020) Admission	2 (4/2/2020)	3 (4/3/2020)	4 (4/4/2020)	5 (4/5/2020) Discharged
Hemoglobin (g/dL)	12.7	12	12.1	13.1	11.9
Hematocrit (%)	37.3	35.9	36.2	39.5	35.4
MCV (%)	92.1	93.2	92.7	93.7	92.6
WBC (x10^3 μL)	4.9	2.9	2.5	2.8	3.3
Neutrophil (x10^3 μL)	3.8	2.2	0.9	1.1	1.1
Band (x10^3 μL)	0	0	0	0	0
ANC (x10^3 μL)	3.8		0.9	1.1	1.1
Lymphocyte (x10^3 μL) *(Ref: 0.9-3.3)*	1	**0.5**	0.9	1.1	1.1
Monocyte (x10^3 μL)	0.1	0.2	0.5	0.4	0.4
Eosinophil (x10^3 μL)	0.0	0.0	0.1	0.1	0.1
Basophil (x10^3 μL)	0.0	0.0	0.0	0.0	0.0
Platelet (x10^3 μL)	140	118	133	150	168
Procalcitonin *(Ref: <0.1 ng/mL)*	<0.02				
CRP *(Ref: 0.0-1.0 mg/dL)*			0.8		
LDH *(Ref: 140-271 U/L)*			171		
IL-6 *(Ref: <5 pg/mL)*				<5	
12-h tacrolimus trough level (ng/mL)		7.6	7.9	6.2	5.6

Abbreviations: ANC, absolute neutrophil count; CRP, c-reactive protein; IL, interleukin; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; WBC, white blood cell.

Significant value is given in bold.



Hospital Day#	1 (4/1/2020) Admitted	2 (4/2/2020)	3 (4/3/2020)	4 (4/4/2020)	5 (4/5/2020) Discharged
Intake (mL)	210	2,739	860	1,074	510
Output (mL)		4,000	2,750	1,450	900

FIGURE 2 Clinical course, serum sodium, and serum creatinine from the date of COVID-19 exposure until hospital discharge

hyponatremia with an initial SNa of 120 mmol/L. The mean SNa of 1099 hospitalized, non-transplant, COVID-19 cases from China was 138 mmol/L (range 135-141 mmol/L)[1] and comparatively a larger case series from 5,700 hospitalized COVID-19 patients in the New York City area, including 55 solid organ transplant recipients, showed a slightly lower mean SNa of 136 mmol/L (range 133-138 mmol/L).[2]

There is one other reported kidney transplant recipient with COVID-19 who also had hyponatremia. This patient initially presented with fever and vomiting and was diagnosed with non-severe viral gastroenteritis. Five days later, he was then admitted with persistent fever and productive cough. He developed acute kidney injury (AKI) and hyponatremia with a SNa of 129 mmol/L. Interestingly, this patient had significant underlying immunological risks. This is his third kidney transplant, and he has a history of Epstein-Barr virus-associated post-transplant lymphoproliferative disease with his second kidney transplant and thus is status post splenectomy. At the time of publication, he remained intubated with worsening respiratory failure[3] (Table 2).

TABLE 2 A previously published kidney transplant recipients with confirmed COVID-19 presenting with hyponatremia and our current case

Patients	• Age • Gender (race) • Cause of organ failure	• Organ transplant (Donor) • Maintenance immunosuppression (Induction)	• Exposure risk for COVID-19 • Duration from transplant until COVID-19 diagnosis	• Initial symptoms • Courses • Duration from the symptom onset until admission • Duration from the symptom onset until COVID-19 diagnosis • Diagnosis for SARS-CoV-2	Significant laboratory data	Underlying diseases	Treatment	Outcomes
Guillen et al[3]	• 50 y/o • M • IgAN	• 3rd DDRT • FK, Evarolimus, Pred 5 mg daily (Thymoglobulin)	• No history of exposure to COVID-19 • ~3.5 y	• Fever, vomiting 24 h • 5 d later, persistent fever and productive cough, left eye conjunctivitis • 1 d • ~6 d • NP swab by rRT-PCR	• Lymphopenia • Normal CRP • SNa 129 mmol/L • ↑Procalcitonin • Negative for RSV, influenza A and B • CXR: Medium lobe consolidation on posteroanterior	• ITP s/p splenectomy • EBV- associated PTLD • HTN on losartan	• Empiric ceftriaxone and azithromycin • Lopinavir/ Ritonavir, empiric ceftaroline and meropenem • Interferon-β • HQ • Hold FK and evarolimus	• ICU admission. • Intubated • AKI with SCr 2.1 mg/dL and then 3 mg/dL and not discharged at the time of reporting case
Our patient	• 55 y/o • F (Korean) • DM	• 0-A-B-DR mis-matched Ag DDRT (45-y/o M donor) • FK, MPS, and Pred 5 mg daily (Thymoglobulin)	• Family member with positive COVID-19 • 0.68 y	• Fatigue • Then, subjective fever, cough, worsening dyspnea, headache, nausea, decreased po intake for 1 wk • 6 d • 6 d • NP swab by rRT-PCR confirmed COVID-19	• SNa 120 mmol/L • Transient lymphopenia • Procalcitonin <0.02 ng/mL • Normal LDH, CRP, IL-6 • Negative for RSV, influenza A & B • CXR: Patchy consolidation in the right middle and lower lung zones	• DM • HTN • HLD • Overweight • GERD • Hashimoto's thyroiditis	• Stop MPS • Lower FK target level • Started Amoxicillin and HQ	• No ICU admission • Serum Na gradually improved to 134 mmol/L • Discharged home on hospital Day 5 • LOS 4 d • Duration from the symptom onset until discharge 10 d

Abbreviations: Ag, antigen; AKI, acute kidney injury; COVID-19, coronavirus disease 2019; CRP, c-reactive protein; CXR, chest x-ray; DDRT, deceased donor renal transplantation; DM, diabetes mellitus; EBV, Epstein-Barr virus; F, female; FK, tacrolimus; GERD, gastroesophageal reflux disease; HLD, hyperlipidemia; HQ, hydroxychloroquine; HTN, hypertension; ICU, intensive care unit; IgAN, immunoglobulin A nephropathy; IL interleukin; ITP, immune thrombocytopenia; LOS, length of hospital stay; M, male; MPS, mycophenolic acid; NP, nasopharyngeal; Pred, prednisone; PTA, prior to admission; PTLD, post-transplant lymphoproliferative disease; rRT-PCR, real-time reverse-transcriptase–polymerase- chain-reaction; RSV, respiratory syncytial virus; SARS-CoV-2, severe Acute Respiratory Syndrome Coronavirus 2; SCr, serum creatinine; SNa, serum sodium; y/o, years old.

Apart from one previously reported kidney transplant patient, severe hyponatremia, likely from SIADH, associated with COVID-19 infection is unique to the presentation in our case.

Hyponatremia is the most common electrolyte disturbance in general clinical practice.[4] It is associated with underlying comorbidities such as infection, malignancy, cardiovascular and hepatic diseases, and acute respiratory distress syndrome.[5]

In the kidney transplant population, hyponatremia is associated with poor renal allograft and patient outcomes. A cohort of 1,786 kidney transplant recipients demonstrated that hyponatremia at 3 months post-transplant, defined as SNa < 135 mmol/L, is associated with an increased risk of renal allograft failure and all-cause mortality than those without hyponatremia. However, it was not associated with an increased risk of acute rejection.[6]

Hyponatremia is essentially a water disturbance. Normal SNa levels are tightly regulated by antidiuretic hormone (ADH), or vasopressin release, in response to osmotic or non-osmotic stimulation. Non-osmotic ADH release can result from appropriate or inappropriate stimulation. Common appropriate ADH stimulation includes low effective circulatory volumes, such as heart failure or cirrhosis, whereas inappropriate stimulation is a constellation of clinical features called SIADH[5] and commonly occurs in neurological or pulmonary diseases, like with our patient.

Hyponatremia has been associated with underlying inflammatory diseases, both infectious and non-infectious.[7] IL-6 is one of the most important proinflammatory cytokines released from inflammatory cells of innate immune response and is involved in the pathogenesis of the cytokine storm in COVID-19. It causes non-osmotic ADH stimulation, which may explain hyponatremia in COVID-19 patients via the immuno-neuroendocrine interface pathway.[8]

Elevated levels of IL-6 may be associated with an increased mortality rate in elderly individuals infected with COVID-9. One study demonstrated that during periods of inflammatory conditions aging rats had higher vassopressinergic neuron activity, which is associated with increased IL-6 mRNA.[9] Hyponatremia in COVID-19 patients, particularly in kidney transplant recipients, may be a prognostic marker of poor outcomes due to the increased levels of IL-6. However, there are a lack of studies examining the clinical outcomes of IL-6 in elderly hyponatremic COVID-19 patients with and without kidney transplantation.

Nevertheless, the prognostic value of hyponatremia in COVID-19 patients needs further examination. One previously reported kidney transplant recipient with hyponatremia (SNa 129 mmol/L) had a normal IL-6 level at the time of an initial admission. A repeated IL-6 level was notably increased but the patient was still intubated with progressive respiratory failure at the time of publication (12 days after found positive for SARS-CoV-2 by rRT-PCR by both nasopharyngeal and oropharyngeal swabs).[3] Our patient had a normal IL-6 level and favorable clinical outcome despite having severe hyponatremia at the time of admission. This suggests that hyponatremia was possibly a result of ADH stimulation from IL-6 released by inflammatory cells[7] due to COVID-19 infection. Additional studies are required to prove the relationship between IL-6, hyponatremia, and clinical outcomes in kidney transplant recipients.

An additional observation regarding the clinical presentation of our patient relates to one other reported kidney transplant case where gastrointestinal symptoms were one of the initial presenting symptoms, which may be related to immune alteration. Fever and respiratory symptoms are the most common presentations of COVID-19 in non-transplant patients.[1,10] Gastrointestinal symptoms preceding respiratory symptoms have been reported in a chronic dialysis patient.[11] Pan et al reported gastrointestinal symptoms including diarrhea, vomiting, or abdominal pain as the presenting symptom in up to 18% of confirmed COVID-19 cases enrolled in a cross-sectional, multicenter study in China. These patients had longer time from symptom onset to admission than those with respiratory symptoms of COVID-19.[12] Our patient and this other reported case did not have a delay in the admission or diagnosis of COVID-19 despite presenting with gastrointestinal symptoms. Concomitant fever and respiratory symptoms may be a reason these particular patients sought out medical attention sooner. There are several hypotheses which can explain concomitant gastrointestinal and respiratory symptoms. One is due to changing the interaction between the common mucosal immune system and bacterial flora within the gastrointestinal and respiratory systems, the so-called gut-lung axis.[13] It is known that within the first six months following liver transplant, gut microbiota are altered.[14] Additionally, there exists a tight relationship between microbiome and human immunity. In the setting of chronic immunosuppression, the changes in immune cells affected by this novel coronavirus may further interfere with the gut microbiome and result in predominant gastrointestinal symptoms, particularly in transplant recipients.[15]

The clinical manifestations of COVID-19 in kidney transplant recipients may or may not be typical; thus, a high index of suspicion, particularly in patients with COVID-19 exposure, warrant close monitoring and further investigation. Although a history of close contact with a confirmed COVID-19-infected person brought this diagnosis to the forefront for our patient, this case highlights a critical role of transplant providers to vigilantly monitor their patient's symptoms. This may require routine phone or other telehealth interactions in an effort to be compliant with recommendations for social distancing. Along with other transplant centers, we have integrated phone and telehealth visits to remain in close contact with our patients. Moreover, encouraging patients to be engaged and notify transplant providers of symptoms may lead to earlier diagnosis and therapy. Additionally, social history is a crucial element in preventing transmission of COVID-19 to transplant patients who are immunosuppressed.

In conclusion, hyponatremia may be one of the clinical features of COVID-19 in kidney transplant recipients, but may be underreported. The proposed mechanisms of hyponatremia as a result of proinflammatory cytokine IL-6 may lead to further studies to determine the prognostic value of hyponatremia in COVID-19 kidney transplant recipients. Gastrointestinal symptoms are common at presentation and may also provide a link to immune alteration. Given the potential life-threatening status of COVID-19 infection, the current armamentarium for fighting off the disease in critically

ill transplant patients may be dependent on altering the immunosuppressive medications and utilizing agents to counter the inflammatory cascade.

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CONFLICT OF INTERESTS

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AUTHORS CONTRIBUTION

ET participated in designing of topics and detail of manuscript, writing of the manuscript, and preparing figures and tables. UGR, AJF, and KKZ participated in the design of topics of manuscript and editing and reviewing of the manuscript. DKD, HI, and DCD participated in preparing, editing, and reviewing the manuscript.

DISCLOSURE

KKZ serves as a physician in a US Department of Veterans Affairs medical centers with or without compensation or are part- or full-time employees of a US Department of Veterans Affairs medical centers. Opinions expressed in this paper are those of the authors' and do not represent the official opinion of the US Department of Veterans Affairs.

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