

nearly 46,000 patients indicates that upper respiratory and flu-like symptoms predominate with less common complaints including headache, dizziness, abdominal pain, anosmia, diarrhea, nausea, and vomiting.² In this paper, we present the first report of COVID-19 related SIADH presenting as new onset seizures in the absence of fever or overt respiratory symptoms.

SIADH in the setting of pneumonia has been extensively studied and reported. Several potential mechanisms have been postulated including extensive cytokine release, hypoxemia, nausea and stress.³ Additionally, inflammation (IL-6 in particular) itself has been reported to directly impair osmoregulation leading to hyponatremia.⁴

Increasingly evidence indicates a propensity for hyperinflammation and cytokine release with COVID-19 infections.⁵ This has manifested as Acute respiratory distress syndrome, myocarditis and overt cytokine storm which are becoming increasingly well recognized associations.

We hypothesize that milder forms of hypercytokinemia and hyper-inflammation could result in a number of less dramatic atypical presentations including SIADH. Elderly populations are particularly susceptible due to impaired free water excretion and late recognition of symptoms. A high index of suspicion and awareness of this association is essential to mitigate SIADH related complications as cases of COVID-19 continue to rise.

REFERENCES

1. Fink S. Worst-case estimates for US coronavirus deaths. *New York Times*. 2020;13. <https://www.nytimes.com/2020/03/13/us/coronavirus-deaths-estimate.html> [accessed 15.03.20].

2. Wu Y, Jiang S, Lou T, Xu J, Zhang Y, Chen H, et al. A meta-analysis of clinical characteristics and mortality COVID-19 pneumonia; 2020, <http://dx.doi.org/10.21203/rs.3.rs-18723/v1>.
3. Edmonds ZV. Hyponatremia in pneumonia. *J Hosp Med*. 2012;7(S4), <http://dx.doi.org/10.1002/jhm.1933>.
4. Swart RM, Swart RM, Hoom EJ, Betjes MG, Zietse R. Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation. *NEP*. 2011;118:45–51.
5. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033–4, [http://dx.doi.org/10.1016/s0140-6736\(20\)30628-0](http://dx.doi.org/10.1016/s0140-6736(20)30628-0).

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Intravenous immunoglobulins: A therapeutic alternative to consider in kidney transplant patients with COVID-19[☆]

Inmunoglobulinas por vía intravenosa: una alternativa terapéutica a tener en cuenta en el paciente trasplantado renal con COVID-19

Dear Editor,

Infection with the coronavirus SARS-CoV-2, causing COVID-19, originated in Wuhan, China, in December 2019.¹ This infection quickly propagated around the world, affecting numerous countries, and was declared a pandemic by the World Health Organization on 11 March 2020.

Subgroups at risk of developing severe forms of the disease have been identified, including kidney transplant patients, who have a greater incidence of infection and admission, as well as a greater need for admission in intensive care units.² Immunosuppressant treatment is one of the reasons for this population's vulnerability.

The management of immunosuppressant treatment in a context of SARS-CoV-2 infection is unclear.^{3,4} In addition, the

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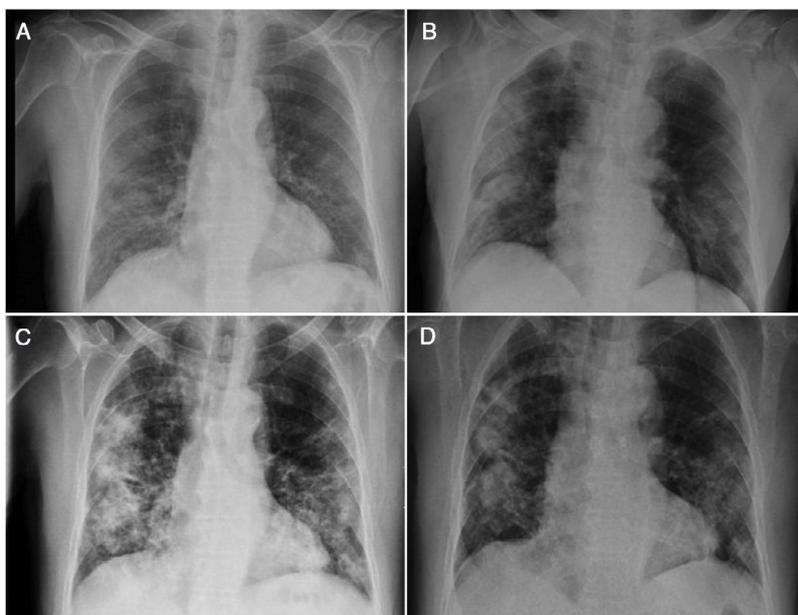


Fig. 1 – Chest X-ray showing the patient's radiological course during his first admission (A–B) and his second admission (C–D).

Table 1 – Summary table of the treatments administered during the patient's first and second admissions.

Treatment	Drug	Dose	Route of administration	Dosing regimen	Start (day since admission)	Duration (days)
Targeted COVID-19	Hydroxychloroquine ^a	400 mg/200 mg	Oral	Initial loading dose. Every 12 h	1	9
	Lopinavir/ritonavir ^a	400 mg/100 mg	Oral	Every 12 h	2	1
	Azithromycin	500 mg/250 mg	Oral	Initial loading dose. Every 24 h	3	7
	Immunoglobulins ^b	0.4 g/kg	Intravenous	Every 24 h	1	5
Support treatment	Ceftazidime	2 g	Intravenous	Every 12 h	2	8
	Methylprednisolone ^a	250 mg, 80 mg, 40 mg	Intravenous	Single initial dose with subsequent down-titration regimen Every 24 h	7	4
	Meropenem ^b	2 g	Intravenous	Every 12 h	1	7
	Linezolid ^b	600 mg	Intravenous	Every 12 h	1	7

^a First admission.

^b Second admission.

safety and interaction profile of certain drugs used to treat the infection limits their use. Within this treatment group, intravenous non-specific human immunoglobulins (IV Ig) may have a good profile, making them an interesting alternative treatment.⁵

We report the case of a 72-year-old man with hypertension and dyslipidaemia who underwent kidney transplantation in 2012. He was on immunosuppressant treatment with tacrolimus and everolimus and had a baseline creatinine level of 1.43 mg/dl. The patient visited the emergency department where he reported experiencing general malaise and headache for the previous three days. He had normal blood pressure levels, an axillary temperature of 37 °C and an oxygen saturation (O₂ sat) of 92% breathing room air. A

chest X-ray showed bilateral pulmonary interstitial infiltrates (Fig. 1A). Laboratory testing revealed kidney failure (creatinine 2.52 mg/dl and urea 77 mg/dl) and higher levels of tacrolimus (15.1 ng/ml) compared to his most recent visit. Polymerase chain reaction (PCR) testing of the patient's nasopharyngeal discharge was positive for SARS-CoV-2. A decision was made to admit him and start treatment with hydroxychloroquine, azithromycin and lopinavir/ritonavir along with ceftazidime and glucocorticoids (Table 1). The immunosuppressant treatment the patient was on was suspended.

Following five days of admission, during which the patient responded favourably (laboratory testing showed that his inflammatory parameters decreased and his kidney function returned to normal), he presented an increase in tacrolimus

levels (29.31 ng/ml), which returned to normal after four days. Another X-ray was taken and ruled out progression (Fig. 1B). A decision was made to discharge him from hospital and restart his prior immunosuppressant treatment at his usual doses.

Seven days later, the patient returned to the emergency department and reported experiencing fever in recent days, with gradually increasing dyspnoea accompanied by mic-turition syndrome. A new chest X-ray showed worsening compared to the patient's prior chest X-ray (Fig. 1C). Laboratory testing showed leukocytosis (16,400/ μ l) with lymphopenia (600/ μ l) and elevated acute-phase reactants (C-reactive protein [CRP] 7.6 mg/dl, D-dimer 886 μ g/l and procalcitonin 3.88 ng/ml). Treatment was started with IV Ig plus linezolid and meropenem. The patient was admitted (Table 1) and his prior immunosuppressant treatment was resuspended.

Five days of treatment with IV Ig were completed. The patient did not present any adverse reactions and did show marked clinical improvement; his dyspnoea disappeared and he showed improvement on X-ray (Fig. 1D). This allowed him to be discharged from hospital early, on day six.

The case reported reflects the complexity of treating SARS-CoV-2 infection in a kidney transplant patient, as the patient's treatment was found to be limited by drug interactions. In this case, the interaction between tacrolimus and lopinavir/ritonavir was assumed to be the main reason for the patient's elevated tacrolimus levels, though the concomitant decline in kidney function may have contributed.⁶ Management of immunosuppressant treatment in transplant patients with COVID-19 is debated. Although some published reports are available, the repercussions of maintaining usual immunosuppressant doses in the context of this infection are unknown.^{3,4,7}

Moreover, SARS-CoV-2 infection still lacks effective treatment. The limited benefits of lopinavir/ritonavir seen in recent studies cast doubt on their usefulness, especially in patients who are more susceptible to their toxic effects.⁸

Another group of drugs that have been gaining reputation in the control of severe forms of infection are biologic drugs. However, their use is restricted in previously immunosuppressed patients. In this regard, treatment with IV Ig is gaining importance and represents an appealing option due to their safety profile and their potential efficacy achieved by means of modulation of inflammatory response. While evidence supporting their use is limited, recently published cases point to a possible benefit in severe forms of COVID-19.⁹ Their use has also been associated with a good clinical outcome in kidney transplant patients.¹⁰ The case reported constitutes the first in Spain supporting the use of IV Ig in kidney transplant patients with severe forms of COVID-19.

REFERENCES

1. Wang H, Wang Z, Dong Y, Chang R, Xu C, Yu X, et al. Phase-adjusted estimation of the number of coronavirus disease 2019 cases in Wuhan, China. *Cell Discov.* 2020;6, <http://dx.doi.org/10.1038/s41421-020-0148-0>.

2. Sánchez-Álvarez JE, Pérez Fontán M, Jiménez Martín C, Blasco Pelicano M, Cabezas Reina CJ, Sevillano Prieto ÁM, et al. Situación de la infección por SARS-CoV-2 en pacientes en tratamiento renal sustitutivo Informe del Registro COVID-19 de la Sociedad Española de Nefrología (SEN). *Nefrología.* 2020, <http://dx.doi.org/10.1016/j.nefro.2020.04.002>.
3. López V, Vázquez T, Alonso-Titos J, Cabello M, Alonso A, Beneyto I, et al. Recommendations on management of the SARS-CoV-2 coronavirus pandemic (COVID-19) in kidney transplant patients. *Nefrología.* 2020, <http://dx.doi.org/10.1016/j.nefro.2020.03.017>.
4. Banerjee D, Popoola J, Shah S, Ster IC, Quan V, Phanish M. COVID-19 infection in kidney transplant recipients. *Kidney Int.* 2020, <http://dx.doi.org/10.1016/j.kint.2020.03.018>.
5. Committee for Medicinal Products for Human Use (CHMP). Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg). Eur Med Agency; 2007. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-core-smpc-human-normal-immunoglobulin-intravenous-administration-ivig-rev-5_en.pdf
6. Schonder KS, Shullo MA, Okusanya O. Tacrolimus and lopinavir/ritonavir interaction in liver transplantation. *Ann Pharmacother.* 2003, <http://dx.doi.org/10.1345/aph.1D076>.
7. Lopez-Oliva M, Gonzalez E, Miranda R, Jimenez C. Management of kidney transplant immunosuppression in positive coronavirus infection requiring hospital admission. *J Chem Inf Model.* 2013, <http://dx.doi.org/10.1017/CBO9781107415324.004>. Available from: https://www.era-edta.org/en/wp-content/uploads/2020/03/Management_of_kidney_transplant_immunosuppression_LaPaz.pdf
8. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med.* 2020, <http://dx.doi.org/10.1056/NEJMoa2001282>.
9. Cao W, Liu X, Bai T, Fan H, Hong K, Song H, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. *Open Forum Infect Dis.* 2020, <http://dx.doi.org/10.1093/ofid/ofaa102>.
10. Zhu L, Xu X, Ma K, Yang J, Guan H, Chen S, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. *Am J Transplant.* 2020, <http://dx.doi.org/10.1111/ajt.15869>.

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