COVID-19 in a pregnant kidney transplant recipient - what we need to know: A case report

Roberta Angelico, Maria Luisa Framarino-dei-Malatesta, Giuseppe Iaria

Abstract

BACKGROUND

In the era of the coronavirus disease 2019 (COVID-19) pandemic, kidney transplant recipients are more susceptible to severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection, developing severe morbidity and graft impairment. Pregnant women are also more likely to develop severe COVID-19 disease, causing pregnancy complications such as preterm births and acute kidney injury.

CASE SUMMARY

Herein, we report the case of a pregnant woman with a third kidney transplantation who developed COVID-19 disease. The reduction of immunosuppressive drugs and strict monitoring of trough blood levels were needed to avoid severe SARS-CoV-2-related complications, and permitted to continue a healthy pregnancy and maintain good graft function. In such a complex scenario, the comitance of COVID-19-related morbidity, the risk of acute rejection in the hyper-immune recipient, graft dysfunction and pregnancy complications make the management of immunosuppression a very difficult task and clinicians must be aware.

CONCLUSION

Tailoring the immunosuppressive regimen is a key factor affecting both the graft outcome and pregnancy safety.

Key Words: Kidney transplantation; Pregnancy; SARS-CoV-2 infection; COVID-19 disease; Immunosuppression; Complications; Case report
INTRODUCTION

Kidney transplant (KT) recipients are susceptible to coronavirus disease 2019 (COVID-19), with an associated 18%-39% intensive care admission rate and 13%-39% mortality[1]. Pregnant women are more likely to develop severe COVID-19, causing pregnancy complications such as preterm births and acute kidney injury[2,3].

CASE PRESENTATION

Chief complaints
In October 2020, a 37-year-old woman at 20 wk of gestation, who had received a third KT 2 years ago, presented with fever, cough, and anosmia.

History of present illness
The patient presented with fever, cough, and anosmia.

History of past illness
Her past medical history consisted of end-stage chronic kidney disease due to focal and segmental glomerulosclerosis, requiring three sequential KTs due to chronic rejections with a panel reactive antibody titer of 100%.

Personal and family history
The patient’s personal and family histories were unremarkable.

Physical examination
At presentation, the severe acute respiratory syndrome coronavirus (SARS-CoV-2) polymerase chain reaction (PCR) test was positive.

Laboratory examinations
Biochemical tests showed 7.640/μL white blood cells, C-reactive protein of 10.1 mg/L and creatinine of 1.18 mg/dL (baseline at pregnancy: 1.1 mg/dL). The immunosuppression (IS) regimen consisted of steroids (5 mg/d), once-daily tacrolimus (extended-released Envarsus, target level: 7-8 μmol/L) and azathioprine (1 mg/kg/d), the latter started 1 year previously, replacing mycophenolate acid as she declared the intent to become pregnant.

Imaging examinations
Chest X-ray was negative for pneumonia.

FINAL DIAGNOSIS

SARS-CoV-2 infection in a KT pregnant lady.
TREATMENT

At diagnosis of SARS-CoV-2 infection, azathioprine was suspended, while steroids and tacrolimus were maintained at unchanged doses. During the infection, the patient developed moderate respiratory symptoms and close clinical monitoring was performed, showing persistent stable graft function, steady tacrolimus blood levels and regular fetal growth. One month later, the patient achieved a complete clinical recovery. The SARS-CoV-2 swab became negative after 40 d. At 39 wk of gestation, she had an uneventful delivery of a healthy male infant (weight: 3.2 kg; Apgar score: 9/10) by caesarean section.

OUTCOME AND FOLLOW-UP

At the time of delivery, the placenta and the newborn were not tested for SARS-CoV-2. The patient’s renal graft function remained stable throughout the post-delivery period, and after 17 mo of follow-up the creatinine was 1.09 mg/dL (Table 1). During pregnancy, anti-human leukocyte antigen donor-specific antibody (DSA) screening was performed and these antibodies were not detected. In particular, no evidence of post-COVID-19 DSA was identified. Graft biopsy was not done. At the last follow-up, both the mother and the child were in good clinical condition.

DISCUSSION

The reduction of the immune response due to both IS drugs and pregnant status render pregnant KT recipients vulnerable to viral infections such as SARS-CoV-2[1,2]. In our case, this was further enhanced by her non-vaccinated status, since at that time the vaccine for SARS-CoV-2 was not available yet. Therefore, the concomitance of COVID-19-related morbidity, the risk of acute rejection in hyperimmune re-KT, graft dysfunction and pregnancy complications make the management of IS a very difficult task.

In KT recipients, recommendations suggest the modification of IS drugs according to the severity of COVID-19, ranging from no modification in asymptomatic patients, anti metabolite withdrawal in mild/moderate symptomatic disease, to complete drug discontinuation in severely ill patients requiring mechanical respiratory support[4,5]. In this case, we decided to withdraw azathioprine, which inhibits purine synthesis, aiming to avoid the depletion of T- and B-cells during the SARS-CoV-2 infection. Tacrolimus and steroids at low-doses remained the only IS drugs, without increasing their blood target levels. The extended-release formula of tacrolimus Envarsus, which provides effective and stable blood concentration with less toxic levels compared to other Tacrolimus formulæ[6], permitted the safe control of rejection risk and the avoidance of severe COVID-19. Thus, a recent report suggested that a mammalian target of rapamycin inhibitor may have potential antiviral benefits in SARS-CoV-2 infection [7].

In this case, strict monitoring of DSA was performed before and after COVID-19, since the IS regimen had been reduced. Despite the significant decrease of the IS and the high risk of rejection due to the hyperimmune status of third-KT recipients, our patient did not develop new DSA or rejection episodes. These data confirm a recent report investigating the alloreactive immune response during and after SARS-CoV-2 infection in KT recipients, which showed that the incidence of acute rejection is about 1.3% (all in hospitalized patients) and the occurrence of post-COVID-19 DSA is 4% overall, ranging from 0% to 8% in non-hospitalized and hospitalized patients, respectively[8]. Despite the immunosuppressed status of a third KT pregnant lady, our patient was very lucky because she was in this group of patients who do not develop severe COVID-19 disease. Since the stable kidney function and the pregnant status, we did not perform a graft biopsy in order to avoid possible biopsy-related complications. Additionally, venous thromboembolism prophylaxis was not administrated as no evidence was present, but its utility should be explored in pregnant COVID-19 KT recipients.

Pregnancy in KT recipients may be associated with a high-risk of maternal complications and decreased graft function, which could further deteriorate in the presence of COVID-19[9]. In fact, the occurrence of acute kidney injury in infected pregnant KT recipients could be due to the SARS-CoV-2 infection or to other pregnancy-related causes, which need to be differentiated[10]. In immunosuppressed transplant recipients as well as pregnant women, SARS-CoV-2 showed the potently to replicate into the kidney causing renal disfunction[11,12]. Lastly, despite the fact that the risk of acquiring SARS-CoV-2 infection during pregnancy seems to be similar to that of non-pregnant patients, severe maternal COVID-19 is associated with acute kidney injury and preterm birth.

The risk of congenital infection with SARS-CoV-2 to the newborn is still unknown[2,13]. In our case, the placenta and the baby were not tested for SARS-CoV-2 PCR, therefore unfortunately we do not have these interesting data. Moreover, despite KT pregnant recipients are more susceptible to chronic infection such as cytomegalovirus (CMV) infection, we didn’t detect any CMV infection during pregnancy. This is the first report focusing on IS management in SARS-CoV-2-positive pregnant KT recipients.
## Table 1 Patients’ characteristics

| Variables at presentation | Values |
|---------------------------|--------|
| **Demographics**          |        |
| Age, yr                   | 37     |
| Sex                       | Female |
| Race                      | White  |
| Number of KT              | 3      |
| Primary nephropathy       | Focal and segmental glomerulosclerosis |
| Causes of previous KT losses | Chronic rejection |
| Time from last KT         | 24 mo  |
| Comorbidities             | Arterial hypertension |
| Pregnancy                 |        |
| Gestation age, wk         | 20     |
| Fetal grow                | Regular |
| Symptoms/signs            |        |
| Fever, T > 37.5 °C        | Yes    |
| Dyspnea                   | Yes    |
| Anosmia                   | Yes    |
| Myalgias                  | Yes    |
| SARS-CoV-2 status         |        |
| SARS-CoV-2 swab test positive | Yes (positivity for 40 d) |
| SARS-CoV-2 vaccination    | No     |
| **Biochemical tests**     |        |
| At infection diagnosis    |        |
| Creatinine, mg/dL         | 1.18   |
| WBC as \( \times 10^3/\text{mmc} \) | 7.640 |
| Lymphocytes, cells/\text{mmc} | 1.590 |
| PTL as \( \times 10^3/\text{mmc} \) | 202   |
| C-reactive protein, mg/L  | 10.1   |
| Procalcitonin, ng/mL      | 0.52   |
| Peak during infection     |        |
| Creatinine, mg/dL         | 1.3    |
| WBC as \( \times 10^3/\text{mmc} \) | 12.700|
| Lymphocytes, cells/\text{mmc} | 3.400 |
| PTL as \( \times 10^3/\text{mmc} \) | 250   |
| C-reactive protein, mg/L  | 20.2   |
| Procalcitonin, ng/mL      | 2.01   |
| **Immunosuppression regimen** |        |
| Tacrolimus                | Continued at unchanged doses (target levels: 7-8 \( \mu \)mol/L) |
| Azathioprine              | Withdrawal |
| Steroids                  | Continued at unchanged doses (5 mg/d) |
| Outcomes                  |        |
| Recovery from COVID-19 disease, mo | 1     |
De novo DSA after SARS-CoV-2 infection  No
Rejection episode No
Delivery
Time of delivery, wk 39
Newborn status Healthy, no complication
Time of follow-up after infection, mo 17
Renal function at last follow-up
Creatinine, mg/dL 1.09

COVID-19: Coronavirus disease 2019; DSA: Donor-specific antibody; KT: Kidney transplant; PTL: Primary testicular lymphoma; SARS-CoV-2: Severe acute respiratory syndrome coronavirus; WBC: White blood cell.

CONCLUSION
We suggest that all efforts should be made to avoid severe maternal COVID-19 disease through tailored adjustment of the IS regimen and close monitoring of calcineurin inhibitor trough-blood levels, graft function and fetal parameters. Currently, mRNA vaccines against SARS-CoV-2 are recommended both in KT recipients and pregnant women, and may help in preventing severe COVID-19 disease[14,15]. However, KT patients have been shown to frequently be poor responders to the vaccines, thus remaining at high risk of developing severe COVID-19[16], especially in pregnancy. In fact, recent data suggest that only selected KT recipients seem to respond to the third booster dose of SARS-CoV-2 vaccine (assessed by anti-receptor binding domain immunoglobulin G titers and/or positive interferon-gamma-releasing assay)[17]. Moreover, in pregnancy, the boosting effect of a third vaccine dose is suggested to have a potential benefit only in those who completed the two-dose vaccine series in early pregnancy or prior to conception[16]. We feel that, although no data are yet available on the efficacy of the vaccine in preventing COVID-19 disease in pregnant KT recipients, a complete vaccine cycle against SARS-CoV-2 with three doses should preferably be performed before pregnancy. In addition, clinicians should be ready to tailor IS drugs when a member of this rare population is infected by SARS-CoV-2.

FOOTNOTES
Author contributions: Angelico R contributed to the study conception and design, writing; Framarino-dei-Malatesta ML was involved in the acquisition of clinical data, analysis, and interpretation; Iaria G contributed to the study conception; and all authors were involved in critical revision.

Informed consent statement: Informed consent was obtained from the patient for publication of their information.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Italy

ORCID number: Roberta Angelico 0000-0002-3439-7750; Maria Luisa Framarino-dei-Malatesta 0000-0001-7824-7511; Giuseppe Iaria 0000-0002-3429-6407.

S-Editor: Wang JJ
L-Editor: Filipodia
P-Editor: Wang JJ
Angelico R et al. SARS-CoV-2 infection in pregnant KT recipient

REFERENCES

1. Azzi Y, Bartash R, Scalea J, Loarte-Campos P, Akalin E. COVID-19 and Solid Organ Transplantation: A Review Article. Transplantation 2021; 105: 37-55 [PMID: 33148977 DOI: 10.1097/TP.0000000000003523]

2. Dushraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, Choolani M, Mattar C, Su LL. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol 2020; 222: 521-531 [PMID: 32217113 DOI: 10.1016/j.ajog.2020.03.021]

3. Misra SS, Ahirwar AK, Sakarde A, Kaim K, Ahirwar P, Jahid M, Sorte SR, Lukhande SL, Kaur AP, Kumawat R. COVID-19 infection in pregnancy: a review of existing knowledge. Horm Mol Biol Clin Invest 2022; [PMID: 35172416 DOI: 10.1515/hmbci-2021-0081]

4. Angelico R, Blasi F, Manzia TM, Toti L, Tisone G, Cacciola R. The Management of Immunosuppression in Kidney Transplant Recipients with COVID-19 Disease: A Systematic and Detailed Review of the Literature. Medicina (Kaunas) 2021; 57 [PMID: 33946462 DOI: 10.3390/medicina57050435]

5. Manzia TM, Angelico R, Toti L, Pisani G, Vita G, Romano F, Pirozzi BM, Vinci D, Cacciola R, Iaria G, Tisone G. The haemetic dilemma of patients waiting for kidney transplantation during the COVID-19 pandemic: To accept or not to accept (an organ offer)? Transpl Infect Dis 2021; 23: e13560 [PMID: 33393172 DOI: 10.1111/tid.13560]

6. Budde K, Bunnapradist S, Grinyo JM, Ciechansowski K, Denny JE, Silva HT, Rostaing L; Envarsus study group. Novel once-daily extended-release tacrolimus (LCPT) versus twice-daily tacrolimus in de novo kidney transplants: one-year results of Phase III, double-blind, randomized trial. Am J Transplant 2014; 14: 2796-2806 [PMID: 25278376 DOI: 10.1111/ajt.12959]

7. Granata S, Carrati P, Stallone G, Zaza G. mTOR-Inhibition and COVID-19 in Kidney Transplant Recipients: Focus on Pulmonary Fibrosis. Front Pharmacol 2021; 12: 710543 [PMID: 34497515 DOI: 10.3389/fphar.2021.710543]

8. Masset C, Gauthier-Vargas G, Cantarovich D, Ville S, Dantal J, Delbos F, Walencic A, Kerleau C, Hourmant M, Garandeau C, Meurette A, Giral M, Benotmane I, Caillard S, Blancho G. Occurrence of De novo Donor-Specific Antibodies After COVID-19 in Kidney Transplant Recipients Is Low Despite Immunosuppression Modulation. Kidney Int Rep 2022; 7: 983-992 [PMID: 35155948 DOI: 10.1016/j.eKid.2022.01.1072]

9. Gleeson S, Noori M, Lightstone L, Webster P. Lesson for the clinical nephrologist: Kidney transplant, COVID-19 and pregnancy. J Nephrol 2021; 34: 369-371 [PMID: 33180315 DOI: 10.1007/s40620-020-00897-9]

10. Bajpai D, Shah S. COVID-19 Pandemic and Pregnancy in Kidney Disease. Adv Chronic Kidney Dis 2020; 27: 397-403 [PMID: 33380505 DOI: 10.1053/j.accd.2020.08.005]

11. Tarris G, de Rougemont A, Estienceny MA, Journet J, Lariotte AC, Aubignat D, Rebibou JM, De La Vega MF, Legendre M, Belliot G, Martin L. Chronic kidney disease linked to SARS-CoV-2 infection: a case report. BMC Nephrol 2021; 22: 278 [PMID: 34376184 DOI: 10.1186/s12882-021-02490-

12. Kemp SA, Collier DA, Datir RP, Ferreira IATM, Gayed S, Jahun A, Hosmillo F, Lumb IU, Roberts DJ, Chandra A, Temperton N; CITIID-NIH BioResource COVID-19 Collaboration; COVID-19 Genomics UK (COG-UK) Consortium, Sharrocks K, Blane E, Modis Y, Leigh KE, Briggs JAG, van Gils MJ, Smith KGC, Bradley JR, Smith C, Dofinger R, Ceron-Gutierrez L, Barcenas-Morales G, Pollock DD, Goldstein RA, Smielewksa A, Skittirall JP, Goulouri T, Goodfellow IG, Gkrania-Klotsas E, Ilingworth CJR, McCoy LE, Gupta RK. SARS-CoV-2 evolution during treatment of chronic infection. Nature 2021; 592: 277-282 [PMID: 33545711 DOI: 10.1038/s41586-021-02391-9]

13. Vanni G, Materazzo M, Santori F, Pellicc驷oro M, Costesta M, Orsaria P, Cattadori F, Pistolese CA, Perretta T, Chiocchi M, Meucci R, Lamachiccia F, Assogna M, Caspi J, Granai AV, De Majo A, ChiaraVallotti A, DAngelillo MR, Barbara R, Ingalinellia S, Morando L, Dalli S, Portarena I, Altomare V, Tazzioli G, Buonomo OC. The Effect of Coronavirus (COVID-19) on Breast Cancer Teamwork: A Multicentric Survey. In Vivo 2020; 34: 1685-1694 [PMID: 32503830 DOI: 10.21873/invivo.11962]

14. Buchwinkler L, Solagna CA, Messner J, Pirklbauer M, Rudnicky M, Mayer G, Kerschbaum J. Antibody Response to mRNA Vaccines against SARS-CoV-2 with Chronic Kidney Disease, Hemodialysis, and after Kidney Transplantation. J Clin Med 2021; 11 [PMID: 35011888 DOI: 10.3390/jcm11010148]

15. Rottenstreich A, Zabirg V, Otknine-Djian E, Vorontsov O, Zigron R, Kleinest G, Wolf DG, Porta S. The Effect of Gestational Age at BNT162b2 mRNA Vaccination on Maternal and Neonatal Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Antibody Levels. Clin Infect Dis 2022; 75: e603-e610 [PMID: 35171998 DOI: 10.1093/cid/ciac135]

16. Ducloux D, Bannoulid J, Chabannes M, Colladant M, Munshi A, Roubiou C, Seibel J, Tschak T, Yannaraki M, Crepin T, Courvau C. Current vaccine strategies against SARS-CoV-2 only poorly protect kidney transplant recipients. J Infect 2022; 84: e34-e35 [PMID: 35074507 DOI: 10.1016/j.jinf.2022.01.020]

17. Charmetant X, Espli M, Barba T, Ozvize A, Morelon E, Mathieu C, Thaunat O. Predictive factors of a viral neutralizing humoral response after a third dose of COVID-19 mRNA vaccine. Am J Transplant 2022; 22: 1442-1450 [PMID: 35114060 DOI: 10.1111/ajt.16990]
