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Early riser specific immune cell response by delayed-type hypersensitivity in a kidney transplant patient vaccinated against COVID-19

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SUMMARY

We present a female kidney transplant patient under conventional immunosuppression therapy. Her humoral immunity study (anti-spike-specific antibodies) was negative after the initial regimen and the third dose of vaccination against COVID-19. The specific ex vivo cellular immune study against spike of SARS-CoV-2 by interferon gamma release assay (IGRA) also remained at non-response levels at different time points despite an optimal non-specific cell immune response assessment. However, the cellular immunity test by delayed-type hypersensitivity (DTH) with spike of SARS-CoV-2 was always positive since the vaccination scheme began. Only after COVID-19 infection has there been a seroconversion of the patient's antibody tests along with IGRA positivity. The use of DTH test to measure the immune response could be a better and earlier parameter of the actual immune status that helps us to predict the immune response in real life. Hybrid immunity combining vaccine and natural infection could be a stronger stimulator of the specific global immune response.

BACKGROUND

Since the start of the SARS-CoV-2 pandemic, there have been hundreds of millions of reported cases and millions of deaths.[1 2] Compared with the general population, kidney transplant recipients are at increased risk of adverse effects in case of SARS-CoV-2 infection, including higher mortality. In the absence of effective specific treatment, vaccination has become the most effective preventive strategy, and this group of patients was the first to receive a booster dose of the vaccine against COVID-19. However, there is clear evidence that immunosuppressed patients such as kidney transplant recipients have a reduced immune response. Various studies show that kidney transplant recipients, compared with the non-immunocompromised population or compared with dialysis patients, show a lower response rate to two doses of the vaccine.[3–5]

To assess the adaptive immune system after COVID-19 vaccination, the humoral response by antibody detection is being used globally.[6 7] However, in many cases, this response is truncated or inhibited in patients with immunomodulatory or immunosuppressive treatments. In these cases, the cellular response would give a complete view of the immune response.[8] Ex vivo cellular response measurement mechanisms are laborious due to the time and cost involved. As an alternative, delayed-type hypersensitivity (DTH) tests have been seen as a useful additional test to observe the presence or absence of response.[9 10]

CASE PRESENTATION

A woman in her 50s with end-stage kidney disease after a membranoproliferative glomerulonephritis underwent a deceased donor kidney transplant, 20 years ago. On debut, it presented as advanced chronic renal failure, with the need for dialysis from the beginning and significant chronicity data in the biopsy, for which she only received a cycle of oral corticosteroids with prednisone 1 mg/kg for 4 weeks and a subsequent reduction until it was withdrawn. She had been on haemodialysis for 8 months before transplantation. She received an induction therapy with lymphocyte-depleting antibodies and was maintained on prednisone, ciclosporin and azathioprine. Her immediate post-operative course was uneventful with a serum creatinine of 1 mg/dL upon discharge. Two months after transplant, she presented with cytomegalovirus disease that was treated with intravenous ganciclovir. Six year later, an acute cellular rejection was observed that required treatment with methylprednisolone boluses (total dose of 1500 mg). A second episode of acute cellular rejection was diagnosed 18 months later, which was again treated with methylprednisolone (total dose of 1500 mg). Therefore, maintenance immunosuppression was changed to prednisone (5 mg/day), mycophenolate (1 g/day) and tacrolimus (to maintain levels of 8–10 ng/mL for the first 6 months and 6 ng/mL later). Her serum creatinine returned to its baseline of 1.3 mg/dL.

At 20 years post-transplantation, a kidney biopsy was performed due to elevated serum creatinine up to 1.7 mg/dL, with no evident explanation. The biopsy showed mild interstitial fibrosis and tubular atrophy with less than 25% (grade 1 in score). There was no evidence of rejection or disease recurrence. Maintenance immunosuppressants were continued. Subsequently, as remarkable events, the patient presented with recurrent urinary tract infections, a community-acquired pneumonia 22 years after transplantation and a deep vein thrombosis of the lower left limb in the setting of a thrombophilia that required the start of oral anticoagulation 1 year later. Five years earlier, she was diagnosed with a low-grade intraepithelial lesion in the cervix associated with human papillomavirus infection.

The patient continued her regular follow-up without other major events, with stable kidney

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Table 1 Levels of specific humoral immune response to RBD throughout last year and after infection (levels of specific IgA and IgG in OD ratio; positive >0.8); levels of specific cellular immunity IGRA to RBD (levels in mIU/mL; positive >5)

	Day							
	0	20	21	35	230	235	364	394
Vaccine	X		X		X			
Infection							X	
IgG anti-RBD		0.1		0.1		0.1		**0.8**
IgA anti-RBD		0.1		0.1		0.1		**7.7**
IGRA		ND		0		0		**263**
Classification		NR		NR		NR		R
DTH		+		+		+		++
Classification		R		R		R		R

Classification: response classification according to the results.

DTH, delayed-type hypersensitivity; IGRA, interferon gamma release assay; ND, Not done; NR, non-responder; OD ratio, Optical density ratio; R, responder; RBD, receptor-binding domain.

function and no proteinuria. According to local health policies, she was vaccinated against SARS-CoV-2 with the first dose of the Pfizer-BioNTech COVID-19 vaccine by intramuscular injection. The second and third doses of the Pfizer-BioNTech COVID-19 vaccine were administered 3 weeks and 7 months after the first dose (see table 1).

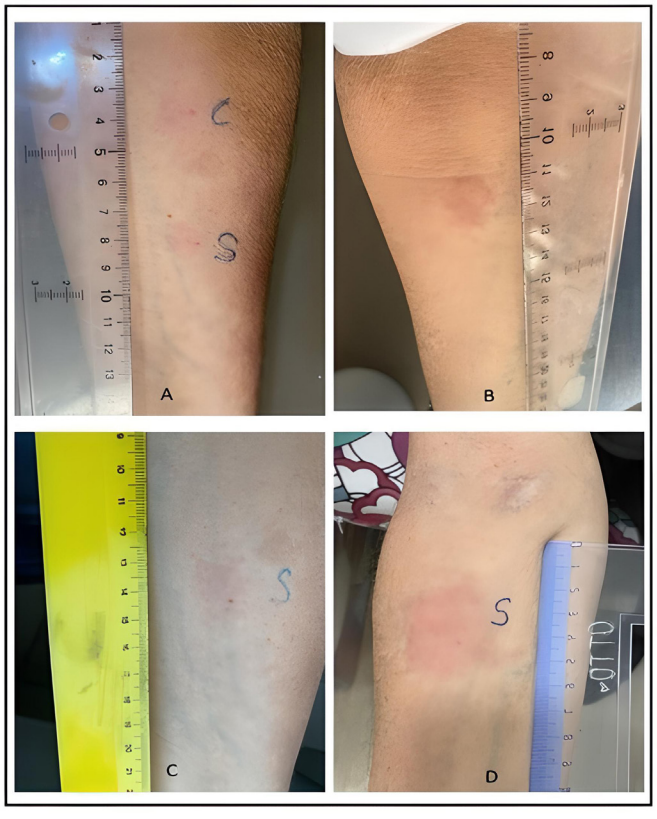

Figure 1 Pictures of delayed-type hypersensitivity skin response 20 days after first dose of COVID-19 vaccine (A), 14 days after second shot (B; day 35) and 14 days after third shot of COVID-19 vaccine (C, day 200). Last picture was taken 4 weeks after the end of SARS-CoV-2 infection (D, day 360).

Three months after the third dose of Pfizer-BioNTech COVID-19 vaccine, she presented with mild respiratory symptoms and tested positive with SARS-CoV-2 infection. There was no fever, fatigue, oxygen requirements, myalgia, diarrhoea, loss of taste or loss of smell. These mild respiratory symptoms persisted for less than 48 hours. Since the patient presented with a mild case of SARS-CoV-2 infection, she did not require hospital admission and she was not treated with dexamethasone, monoclonal antibodies or any other medications, nor was any reduction in immunosuppressants necessary. After a period of isolation of 21 days, she began her usual follow-up.

INVESTIGATIONS

- Blood samples were collected from the patient before vaccination, before the second dose, 15 days after the second dose, after the third dose and 2 weeks after infection. A commercial ELISA to detect specific antibodies IgG to the S1 protein of SARS-CoV-2 was used as described before.[9 10]
- An automated commercial ex vivo diagnostic method that measures a component of cell-mediated immune reactivity to the S1 protein of SARS-CoV-2 was performed (SARS-CoV-2 interferon gamma release assay), as described before.[11]
- On the same day as the blood collection, after oral and written informed consent and after sterilisation with alcohol in the volar part of the arm, a reconstituted lyophilised SARS-CoV-2 recombinant protein of the receptor-binding domain (25 µL (final concentration of 0.1 mg/mL)) similar to the dose normally used in the tuberculin test[9] was administered as the intradermal test (IDT) puncture, with an immediate reading after 15 min.[9 10] IDT was carried out 15 days after the second dose, after the third dose and 2 weeks after infection (see figure 1).
- The patient signed a written document called a 'Patient Information Sheet', which contained relevant and necessary information for the patient to decide whether they wanted to participate in the study.

OUTCOME AND FOLLOW-UP

Six months after COVID-19 infection, the patient remains asymptomatic, with stable renal function and receiving maintenance immunosuppression.

DISCUSSION

The lower efficacy of the vaccine in kidney transplant recipients is observed in both humoral and cellular responses.[12 13] Various risk factors have been related to a lower immune response, including older age, the first year of transplant compared with subsequent ones, the use of triple therapy versus double therapy,[13] and the use of mycophenolate versus mTOR inhibitors,[14] and the BNT162b2 vaccine instead of the MRNA-1273.[13] In the case of our patient, the factors that could influence the poor response to vaccination included the use of immunosuppression for more than 20 years with triple therapy including mycophenolate. In favour of the role of immunosuppression in our patient is the fact that throughout her follow-up, she presented with other complications of infectious aetiology.

However, while the evidence indicates that kidney transplant recipients have a reduced response to vaccination, there is a clear improvement in clinical outcomes in terms of reducing complications secondary to SARS-CoV-2, with a lower rate of admission and of mortality compared with the waves prior to vaccination, and even to the waves immediately after the first doses of vaccination.

In our patient, despite three doses of vaccine, no immunity was detected by in vitro methods. However by using DTH, an in vivo method, it was possible to detect a vigorous cellular immune response (CIR) in this patient. Despite being a patient with a high immunosuppressive burden, with infectious complications prior to the SARS-CoV-2, the patient experienced a mild COVID-19 infection. It is possible that this good outcome was possible partly because in vitro methods are not fully representative of immunity in this patient, whereas an in vivo method, like DTH, could reflect better the immune scenario.

Knowledge on the vaccine-induced CIR and humoral immune response (HIR) and on immunogenicity of mRNA vaccines in solid organ transplant recipients is limited. Immunocompromised individuals such as patients after solid organ transplantation are at higher risk of suffering from more severe courses of disease.[15] Moreover, little is known about the correlation of protection from severe disease and the results of HIR or CIR measurements. This group of immunocompromised patients had been vaccinated using a boosted protocol trying to obtain the maximum titres of neutralising antibodies because HIR to measure antibodies is the more extended method to measure immunogenicity elicited by the COVID-19 vaccines. However, it is well-known that humoral immunity towards other vaccines such as influenza or hepatitis B is decreased in solid organ transplant recipients.[16–18] Several groups have reported that in transplant recipients immunised with mRNA-based COVID-19 vaccines, SARS-CoV-2-specific antibodies were only induced in 6%–17% after the first dose,[19–21] and up to 59% after the second dose,[4 19 22 23] respectively. For these reasons, it is of main importance to have an easy and informative method to measure CIR in immunocompromised patients that can be used to understand the correlation with the protection from severe disease and to optimise vaccine schedules in this group of patients. Our group has validated the CoviDCELL-DTH test both in immunocompetent individuals and in patients with primary immunodeficiency[24] and in patients with immunosuppression.[25] This DTH test of measuring the immune response could help us predict the real-life response to SARS-CoV-2 infection in correctly vaccinated transplant recipients. Likewise, we must emphasise that as the pandemic has progressed, seroprevalence surveys estimate that more than one-third, and possibly more than half of the world population, has already been infected with SARS-CoV-2 by the beginning of 2022. This fact, together with the increasing vaccination coverage in all countries, should remind us of the sometimes forgotten concept of hybrid immunity, both in immunocompromised patients and in healthy individuals.

Patient's perspective

The results of the rest of the antibody tests and in vitro cell tests over the months made me uncertain about the possible response I would have to the infection. However, the DTH test produced a certain calm and tranquility, and even happiness, every time it was positive. This gave me confidence in the Immunology team that was doing the follow-up.

Learning points

- The study of the cellular immune response complements and sheds light on the adaptive immune response after vaccination against COVID-19.
- The delayed-type hypersensitivity (DTH) test to measure immune response could be an early parameter of the immune response after COVID-19 vaccination.
- The DTH test is less expensive than ex vivo cellular response measurement techniques that are more laborious, time-consuming and expensive.
- There is some evidence that the hybrid immunity acquired by vaccination, and then by natural infection, might be a more potent defence system in both healthy and immunocompromised patients.

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Contributors YB is responsible for the immunological follow-up of the case. DM-M is responsible for the nephrological follow-up of the case. CA-C is responsible for the patient's DTH tests. VM is responsible for writing the case and for the global assessment of the case.

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Competing interests YB is currently a medical advisor to BioVaxys. The rest of the authors declare that they have no competing interest.

Patient consent for publication Obtained.

Ethics approval The protocol was approved by the ethical committee of the hospital (CHUC_2021_04) and was conducted in accordance with the requirements expressed in law.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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REFERENCES

1 World Health Organization. WHO coronavirus dashboard. Available: https://covid19.who.int
2 Jager KJ, Kramer A, Chesnaye NC, *et al*. Results from the ERA-EDTA registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. *Kidney Int* 2020;98:1540–8.
3 Boyarsky BJ, Werbel WA, Avery RK, *et al*. Antibody response to 2-Dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA* 2021;325:2204–6.
4 Grupper A, Rabinowich L, Schwartz D, *et al*. Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. *Am J Transplant* 2021;21:2719–26.
5 Quiroga B, Soler MJ, Ortiz A, *et al*. Safety and immediate humoral response of COVID-19 vaccines in chronic kidney disease patients: the SENCOVAC study. *Nephrol Dial Transplant* 2022;37:1868–78.
6 Meyer B, Torriani G, Yerly S, *et al*. Validation of a commercially available SARS-CoV-2 serological immunoassay. *Clin Microbiol Infect* 2020;26:1386–94.
7 Doria-Rose N, Suthar MS, Makowski M, *et al*. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for Covid-19. *N Engl J Med* 2021;384:2259–61.
8 Mangge H, Kneihsl M, Schnedl W, *et al*. Immune responses against SARS-CoV-2-questions and experiences. *Biomedicines* 2021;9:1342.
9 Barrios Y, Franco A, Sánchez-Machin I, *et al*. A novel application of delayed-type hipersensitivity reaction to measure cellular immune response in SARS-CoV-2 exposed individuals. *Clin Immunol* 2021;226:108730.
10 Barrios Y, Franco A, Sánchez-Machín I, *et al*. The beauty of simplicity: delayed-type hypersensitivity reaction to measure cellular immune responses in RNA-SARS-Cov-2 vaccinated individuals. *Vaccines* 2021;9:575.

11 Barrios Y, Alava-Cruz C, Franco A, *et al*. Long term cell immune response to COVID-19 vaccines assessment using a delayed-type hypersensitivity (DTH) cutaneous test. *Diagnostics* 2022;12:1421.
12 Bertrand D, Hamzaoui M, Lemée V, *et al*. Antibody and T cell response to SARS-CoV-2 messenger RNA BNT162b2 vaccine in kidney transplant recipients and hemodialysis patients. *J Am Soc Nephrol* 2021;32:2147–52.
13 Stumpf J, Siepmann T, Lindner T, *et al*. Humoral and cellular immunity to SARS-CoV-2 vaccination in renal transplant versus dialysis patients: a prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine. *Lancet Reg Health Eur* 2021;9:100178.
14 Cucchiari D, Egri N, Bodro M, *et al*. Cellular and humoral response after MRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. *Am J Transplant* 2021;21:2727–39.
15 Danziger-Isakov L, Blumberg EA, Manuel O, *et al*. Impact of COVID-19 in solid organ transplant recipients. *Am J Transplant* 2021;21:925–37.
16 Birdwell KA, Ikizler MR, Sannella EC, *et al*. Decreased antibody response to influenza vaccination in kidney transplant recipients: a prospective cohort study. *Am J Kidney Dis* 2009;54:112–21.
17 Manuel O, Pascual M, Hoschler K, *et al*. Humoral response to the influenza A H1N1/09 monovalent AS03-adjuvanted vaccine in immunocompromised patients. *Clin Infect Dis* 2011;52:248–56.
18 Sester M, Gärtner BC, Girndt M, *et al*. Vaccination of the solid organ transplant recipient. *Transplant Rev* 2008;22:274–84.
19 Boyarsky BJ, Werbel WA, Avery RK, *et al*. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA* 2021;325:1784.
20 Benotmane I, Gautier-Vargas G, Cognard N, *et al*. Weak anti-SARS-CoV-2 antibody response after the first injection of an mRNA COVID-19 vaccine in kidney transplant recipients. *Kidney Int* 2021;99:1487–9.
21 Yi SG, Knight RJ, Graviss EA, *et al*. Kidney transplant recipients rarely show an early antibody response following the first COVID-19 vaccine administration. *Transplantation* 2021;105:e72–3.
22 Boyarsky BJ, Werbel WA, Avery RK, *et al*. Antibody response to 2-Dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA* 2021;325:2204–6.
23 Korth J, Jahn M, Dorsch O, *et al*. Impaired humoral response in renal transplant recipients to SARS-CoV-2 vaccination with BNT162b2 (Pfizer-BioNTech). *Viruses* 2021;13. doi:10.3390/v13050756. [Epub ahead of print: 25 Apr 2021].
24 Barrios Y, Franco A, Alava-Cruz C, *et al*. Easy approach to detect cell immunity to COVID vaccines in common variable immunodeficiency patients. *Allergol Immunopathol* 2022;50:101–5.
25 Barrios Y, Rodriguez A, Franco A, *et al*. Optimizing a protocol to assess immune responses after SARS-CoV-2 vaccination in kidney-transplanted patients: in vivo DTH cutaneous test as the initial screening method. *Vaccines* 2021;9:1315.