Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Patient 2 commenced pembrolizumab 200 mg every 3 wk in November 2016; his PSA was 0.43 μg/l and scans revealed bilateral pelvic nodes, a large pelvic mass (53 mm), and a complex fistula between the rectum and bladder. He received 11 pembrolizumab courses with no immunological toxicity and experienced a partial response. However, pembrolizumab was stopped because of fistula worsening requiring intravenous antibiotics and surgical intervention. He made a full recovery and remains disease-free 40 mo after starting pembrolizumab (Fig. 1F,G). Tumour NGS had indicated an MSH6 mutation (Y214*), high MutLoad, and high MSINGS score, with MSH6 loss but incomplete MSH2 loss on IHC, as well as PD-L1 positivity (1%). IHC showed high TILs; most of these cells were $CD4^+$FOXP3 and Tregs ($CD4^+FOXP3^+$; Fig. 1H).

We previously showed that a small but important subset of mCRPC tumours have evidence of MMRd by IHC and this is associated with high MutLoad and MSI-NGS. However, only some MMRd cancers present with high T-cell infiltration, PD-L1 protein expression, and elevated T-cell–associated transcripts [2].

The rearrangement identified for patient 1 was associated with immune evasion and PD-L1 overexpression in mouse models using an N-terminal binding antibody [4]. This could explain his PD-L1 negativity (since the antibodies routinely used target the C-terminus) and extraordinary response to pembrolizumab in an otherwise immune "cold" tumour.

Patient 2, besides MMRd, presented with a highly inflamed cancer, mainly represented by Tregs and $CD4^+$FOXP3 cells. Interestingly, in mCRPC models, ICIs reprogram $CD4^+$ cells towards a Th1 rather than Th17 lineage in nodal disease, possibly explaining this responsiveness [5].

In conclusion, elucidation of the mCRPC subset benefiting from ICIs requires multiple orthogonal assays, including genomic analyses, IHC, and tumour microenvironment studies.

Conflicts of interest: Johann S. de Bono has served on advisory boards for MSD, Merck Serono, Pfizer, Genentech/Roche, AstraZeneca, Astellas, Janssen, GSK, Genmab, Amgen, Daiichi Sankyo, and Bayer. The remaining authors have nothing to disclose.

Acknowledgements: Christian Poehlein is an employee of Merck Sharp&Dohme. Pasquale Rescigno is supported by a Prostate Cancer Foundation (PCF) Young Investigator Award.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.06.056.

References

[1] Antonarakis ES, Piulats JM, Gross-Goupil M, et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label phase II KEYNOTE-199 study. J Clin Oncol 2020;38:395–405.

[2] Rodrigues DN, Rescigno P, Liu D, et al. Immunogenomic analyses associate immunological alterations with mismatch repair defects in prostate cancer. J Clin Invest 2018;128:4441–53.

[3] Daud AI, Loo K, Pauli ML, et al. Tumor immune profiling predicts response to anti–PD-1 therapy in human melanoma. J Clin Invest 2016;126:3447–52.

[4] Kataoka K, Shiraishi Y, Takeda Y, et al. Aberrant PD-L1 expression through 3′-UTR disruption in multiple cancers. Nature 2016;534:402–6.

[5] Jiao S, Subudhi SK, Aparicio A, et al. Differences in tumor microenvironment dictate T helper lineage polarization and response to immune checkpoint therapy. Cell 2019;179, 1177–90.e13.

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June 24, 2020

COVID-19–related Mortality During the First 60 Days After Kidney Transplantation

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The COVID-19 pandemic prompted the decision to suspend most organ transplantation programs in affected countries, especially in Europe [1]. A recent large population-based report revealed that the cohort at highest risk of in-hospital death due to COVID-19 was the organ transplant population, with a hazard ratio of 4.27 [2]. Published experiences

Table 1 – Characteristics of 24 patients who suffered from COVID-19 during the first 60 d after kidney transplantation.

Variable	Alive (n = 13)	Dead (n = 11)	p value
Male, n (%)	6 (46.2)	5 (45.5)	0.97
Median age, yr (range)	61.1 (40–74)	69.6 (60–75)	0.006
Age ≥65 yr, n (%)	4 (30.8)	8 (72.7)	0.04
Hypertension, n (%)	12 (92.3)	10 (90.9)	1
Diabetes, n (%)	8 (66,7)	4 (36.4)	0.15
Deceased donor, n (%)	13 (100)	10 (91)	0,46
Delayed graft function n (%)	5 (38.5)	7 (63.6)	0.41
Acute rejection, n (%)	2 (15.4)	0 (0)	0.48
Median time from KT to COVID-19 Dx, d (range)	39 (15–59)	28.8 (8–56)	0.07
Baseline immunosuppressive treatment, n (%)			
Prednisone	13 (100)	11 (100)	1
Tacrolimus	13 (100)	11 (100)	1
Mycophenolate	12 (92,3)	9 (81.8)	0.58
mTOR inhibitors	0 (0)	2 (18.2)	0.2
Fever, n (%)	9 (69.2)	6 (54.5)	0.67
Cough, expectoration, and/or rhinorrhea, n (%)	6 (46.2)	8 (72.7)	0.24
Dyspnea, n (%)	6 (46.2)	8 (72.7)	0.24
Pneumonia, n (%)	12 (92.3)	10 (90.9)	1
Digestive symptoms, n (%)	1 (7.7)	2 (18.2)	0.58
Lymphopenia, n (%)	13 (100)	11 (100)	1
Hospitalization, n (%)	13 (100)	11 (100)	1
Renal failure, n (%)	6 (46.2)	7 (63.6)	0.26
Ventilator support, n (%)	2 (15.4)	7 (77.8)	0.007
Intensive care unit admission, n (%)	2 (15.4)	2 (18.2)	1
COVID-19 treatment, n (%)			
Hydroxychloroquine	12 (92.3)	10 (90.9)	1
Glucocorticoids	3 (25)	9 (81.8)	0.006
Lopinavir/ritonavir	4 (30.8)	4 (36.4)	1
Tocilizumab	5 (38.5)	3 (27.3)	0.68
Median time from admission to death or recovery, d (range)	23 (4–48)	13.7 (6–36)	0.08

KT = kidney transplantation; Dx = diagnosis.

have been restricted to long-term stable kidney transplant (KT) recipients. Despite initial low mortality reported from China [3], further case series have shown mortality rates of up to 75% [4]. The decision to suspend KT programs has been arbitrary, as no reports of COVID-19 in the most vulnerable population, that is, patients with a very recent KT and profound immunosuppression, are available.

A registry to collect information regarding dialysis or KT patients with COVID-19 in Spain started to gather information on March 18, 2020 (www.senefro.com). A confirmed COVID-19 diagnosis was defined as a patient with positive reverse transcriptase-polymerase chain reaction (RT-PCR) assay of a specimen collected via nasopharyngeal swab or bronchoalveolar lavage. Comparisons between groups were made using a two-sided χ^2 test with a significance level of 0.05, using SPSS v22. The study was approved by the ethics committee of Hospital del Mar.

Among the 502 KT patients with COVID-19 included until May 9, 2020, 24 had received a KT less than 60 d before being diagnosed as having COVID-19. Cases were diagnosed in 12 Spanish transplant centers between March 17 and April 18, 2020 and had at least 1 mo of follow-up. During the period and 60 d before the first case, 275 KT surgeries were performed in those 12 centers. Therefore, the cumulative incidence of COVID-19 was 9%.

The median age of the 24 patients was 66.5 yr (range 40–75) and immunosuppression regimens were conventional (Table 1). Fever, cough, and pneumonia were the usual COVID-19 signs and symptoms and all of the patients were hospitalized. Respiratory failure led to ventilatory support in eight patients and intensive care unit (ICU) admission in four. ICU admission was initially indicated but finally denied in nine patients. Specific COVID-19 management was attempted with immunosuppression reduction (mycophenolate withdrawal in 96% and tacrolimus withdrawal in 62.5%) and different combinations of hydroxychloroquine, antiviral agents, and steroids. Interestingly, eight patients were treated with the anti-IL6 antibody tocilizumab and five of them recovered. No relevant surgical or urological complications were recorded.

The fatality rate was 45.8%, which is markedly higher than the usual very low 2-mo mortality observed outside the COVID-19 pandemic. Compared with survivors, patients who died were older, were infected closer to transplantation, more frequently needed ventilator support, and were treated less often with high-dose steroids.

The maximum effect of immunosuppression is exerted in the first months after transplantation and recipients are at maximum risk of viral infection and severity in this period. A short time since transplantation was associated with more severe disease in the 2009 pandemic of influenza A (H1N1) [5]. In cities and areas with very high incidence of COVID-19, KT is not a safe option for renal patients, especially those aged >60 yr. When COVID-19 significantly decreases, and as part of

the measures to open up after lockdown, KT programs may be resumed under strict preventive measures.

Conflicts of interest: The authors have nothing to disclose.

Acknowledgments: We are indebted to the many physicians and nurses who take care of these patients and are facing the COVID-19 pandemic in our country. The registry for COVID-19 renal patients is supported by the Spanish Society of Nephrology.

CRediT authorship contribution statement

Julio Pascual: Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing - original draft. **Edoardo Melilli:** Investigation, Writing - review & editing. **Carlos Jiménez-Martín:** Investigation, Writing - review & editing. **Esther González-Monte:** Investigation, Writing - review & editing. **Sofía Zárraga:** Investigation, Writing - review & editing. **Alex Gutiérrez-Dalmau:** Investigation, Writing - review & editing. **Veronica López-Jiménez:** Investigation, Writing - review & editing. **Javier Juega:** Investigation, Writing - review & editing. **Miguel Muñoz-Cepeda:** Investigation, Writing - review & editing. **Inmaculada Lorenzo:** Investigation, Writing - review & editing. **Carme Facundo:** Investigation, Writing - review & editing. **María del Carmen Ruiz-Fuentes:** Investigation, Writing - review & editing. **Auxiliadora Mazuecos:** Investigation, Writing - review & editing. **Emilio Sánchez-Álvarez:** Investigation, Writing - review & editing. **Marta Crespo:** Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing - original draft.

References

[1] Loupy A, Aubert O, Reese PP, Bastien O, Bayer F, Jacquelinet C. Organ procurement and transplantation during the COVID-19 pandemic. Lancet 2020;395:e95–6. http://dx.doi.org/10.1016/S0140-6736(20)31040-0.

[2] The OpenSAFELY Collaborative. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv preprint. https://doi.org/10.1101/2020.05.06.20092999.

[3] Zhang H, Chen Y, Yuan Q, et al. Identification of kidney transplant recipients with coronavirus disease 2019. Eur Urol 2020;77:742–7. http://dx.doi.org/10.1016/j.eururo.2020.03.030.

[4] Abrishami A, Samavat S, Behnam B, Arab-Ahmadi M, Nafar M, Sanei Taheri M. Clinical course, imaging features, and outcomes of COVID-19 in kidney transplant recipients. Eur Urol 2020;78:281–6. http://dx.doi.org/10.1016/j.eururo.2020.04.064.

[5] Cordero E, Pérez-Romero P, Moreno A, et al. Pandemic influenza A (H1N1) virus infection in solid organ transplant recipients: impact of viral and non-viral co-infection. Clin Microbiol Infect 2012;18:67–73. http://dx.doi.org/10.1111/j.1469-0691.2011.03537.x.

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June 12, 2020