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LETTER TO THE EDITOR

Kidney xenotransplantation in a brain-dead donor: Glass half-full or half-empty?

To the Editor:

We congratulate Dr. Locke and colleagues for their contributions to xenotransplant biology through their manuscript reporting the results of a genetically engineered (GE) porcine kidney transplanted into a brain-dead human.[1] We join the research team in expressing gratitude to the family of the donor for allowing their loved one to participate in such important research. Here we offer our interpretation of the data presented and recommendations for next steps.

The reported case demonstrates the surgical feasibility of intra-abdominal bilateral sequential kidney xenotransplantation. Based on the clinical appearance of the kidney xenografts and the initial production of urine by the first kidney, the authors conclude that the pair of 'ten-GE' pig kidneys were protected from hyperacute rejection, as predicted based on extensive prior work with GE pigs in non-human primate recipients (NHP).[2,3] However, the cause of the rapid appearance of thrombotic microangiopathy on the first xenograft biopsy and the absence of significant creatinine clearance over the subsequent 3 days following the transplant needs to be addressed.

Thrombotic microangiopathy (TMA) in the reperfusion biopsy at POD1 could be a sign of antibody-mediated xenograft rejection; however, the negative historical crossmatch argues against this interpretation. Distinguishing TMA from antibody-mediated rejection (AMR) remains a challenge in xenotransplantation.[4] The patient exhibited systemic evidence of TMA before nephrectomy, as indicated by an elevated D-dimer, prolonged prothrombin and partial thromboplastin times, and abnormal kidney function, presumably attributable to the inflamed, hypercoagulable state caused by traumatic brain injury (TBI).[5] While marked thrombocytopenia and anemia are also compatible with the consumptive coagulopathy observed occasionally in NHP renal and heart recipients of pig xenografts, these typically arise later after those transplants. Because there was rapid clearing of the lesions on repeated biopsies with reduction in glomerular thrombi reported at POD3, we believe that the lesions are unlikely to be due to antibody-mediated rejection and more likely due to the hypercoagulable state of the recipient.

To promote a wider understanding of the results of these initial and future limited experiments, we encourage these and other authors to include high-resolution images and additional routine diagnostic stains (e.g., for fibrin and platelets) in future reports, or in supplemental material with digital images placed on a public server, analogous to how genomic data are publicly curated. Lastly, standard analysis should include electron microscopy, as is routine in clinical kidney biopsies, to assess the presence and extent of TMA and the status of the endothelium and podocytes.

Most NHP xenotransplant studies have demonstrated that the calcineurin-inhibitor-based immunosuppression prevalently used in humans is inferior to costimulation pathway blockade to prevent organ xenograft rejection. Costimulation blockade of CD40-CD40L pathway was required for long-term graft survival in preclinical heart and kidney studies,[6] and was used by the Maryland group in their recent heart xenograft case. Indeed, Adams and colleagues[7] and Kawai and colleagues (manuscript in preparation) have kidney xenotransplants surviving over 1 year without rejection or TMA in nonhuman primates. Unfortunately, the 3-day duration of follow-up in the current report does not contribute to our evidence base in this regard. The authors' clinical description of the GE pig kidneys' tissue qualities, which included "*soft to palpation, thin capsule and larger diameter ureters*" are typical of pig kidneys and do not necessarily raise concerns about the potential impact of the genetic mutations on the kidney phenotype. Nonetheless, the mid- and long-term impact of those kidney characteristics in human recipients remains to be determined.

Finally, while Porrett et al showed that the right kidney produced more than 500 ml of urine within 24 h of transplant, the clearance function of the transplanted kidneys was effectively absent, as evidenced by the rising creatinine and low concentration of creatinine in the urine. The cause of the persistent kidney dysfunction was not clarified; the only reported histologic correlate was acute tubular injury (ATI). Impaired kidney function due to ATI could have been aggravated by hemodynamic instability of the decedent, who demonstrated an increased pressor requirement (dopamine and phenylephrine) and steadily declining MAPs, and by the coagulopathic, inflamed physiologic environment associated with brain death and trauma. To separate this model's potential shortcomings from pathophysiology ascribable to the potentially pro-inflammatory pig-human interface, and to thus better assess the compatibility of the GE pig kidney with

Summary Sentence: In this letter to the editor, the authors discuss a recent report of a genetically engineered porcine kidney transplanted into a brain-dead human, providing some additional insights and suggestions as next steps.

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humans, we suggest the next step should be to transplant GE pig kidneys into dialysis-dependent, otherwise stable ESKD patients with no living donor and on the bottom of the waiting list.

KEYWORDS

translational research/science, clinical research/practice, immunobiology, xenotransplantation, solid organ transplantation, xenoantigen, xenoantibody, kidney (allograft) function/dysfunction

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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REFERENCES

1. Porrett PM, Orandi BJ, Kumar V, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model [published online ahead of print 2022]. *Am J Transplant*. 10.1111/ajt.16930.
2. Iwase H, Hara H, Ezzelarab M, et al. Immunological and physiologic observations in baboons with life-supporting genetically-engineered pig kidney grafts. *Xenotransplantation*. 2017;24. 10.1111/xen.12293
3. Ma D, Hirose T, Lassiter G, et al. Kidney transplantation from triple-knockout pigs expressing multiple human proteins in cynomolgus macaques. *Am J Transplant*. 2022;22(1):46-57.
4. Rosales IA, Colvin RB. The pathology of solid organ xenotransplantation. *Curr Opin Organ Transplant*. 2019;24(5):535-542.
5. Lisman T, Leuvenink HG, Porte RJ, Ploeg RJ. Activation of hemostasis in brain dead organ donors: an observational study. *J Thromb Haemost*. 2011;9(10):1959-1965.
6. Bikhet MH, Iwase H, Yamamoto T, et al. What therapeutic regimen will be optimal for initial clinical trials of pig organ transplantation? *Transplantation*. 2021;105(6):1143-1155.
7. Kim SC, Mathews DV, Breeden CP, et al. Long-term survival of pig-to-rhesus macaque renal xenografts is dependent on CD4 T cell depletion. *Am J Transplant*. 2019;19(8):2174-2185.