BRIEF REPORT

Xenotransplantation of a Porcine Kidney for End-Stage Kidney Disease

Tatsuo Kawai, M.D., Ph.D.,[1,4] Winfred W. Williams, M.D.,[1,4] Nahel Elias, M.D.,[1,4] Jay A. Fishman, M.D.,[1,4] Kerry Crisalli, R.N.,[1,4] Alban Longchamp, M.D.,[1,4] Ivy A. Rosales, M.D.,[2,4] Michael Duggan, D.M.D.,[3,4] Shoko Kimura, M.D., Ph.D.,[1,4] Leela Morena, M.D.,[1,4] Thiago J. Borges, Ph.D.,[1,4] Toshihide Tomosugi, M.D., Ph.D.,[1,4] Ahmad Karadagi, M.D., Ph.D.,[1,4] Tsukasa Nakamura, M.D., Ph.D.,[1,4] Kassem Safa, M.D.,[1,4] Alessia Giarraputo, Ph.D.,[2,4] Claire T. Avillach, M.D.,[2,4] Eva D. Patalas, M.D.,[2,4] R. Neal Smith, M.D., Ph.D.,[2,4] David H. Sachs, M.D.,[1,4] A. Benedict Cosimi, M.D.,[1,4] Joren C. Madsen, M.D., D.Phil.,[1,4] David K.C. Cooper, M.D.,[1,4] Richard Pierson, M.D.,[1,4] Steve Perrin, Ph.D.,[5] Ranjith P. Anand, Ph.D.,[6] Sagar Chhangawala, Ph.D.,[6] Matthew Coscarella, M.S.,[6] Alexandre Daigneault, B.S.,[6] Feng Li, Ph.D.,[6] Owen Pearce, B.S.,[6] Wenning Qin, Ph.D.,[6] William T. Serkin, B.S.,[6] Vincent Yeung, Ph.D.,[6] Kristen Getchell, M.A.,[6] Susan C. Low, Ph.D.,[6] Michael Curtis, Ph.D.,[6] Robert B. Colvin, M.D.,[2,4] and Leonardo V. Riella, M.D., Ph.D.[1,4]

SUMMARY

Xenotransplantation offers a potential solution to the organ shortage crisis. A 62-year-old hemodialysis-dependent man with long-standing diabetes, advanced vasculopathy, and marked dialysis-access challenges received a gene-edited porcine kidney with 69 genomic edits, including deletion of three glycan antigens, inactivation of porcine endogenous retroviruses, and insertion of seven human transgenes. The xenograft functioned immediately. The patient's creatinine levels decreased promptly and progressively, and dialysis was no longer needed. After a T-cell–mediated rejection episode on day 8, intensified immunosuppression reversed rejection. Despite sustained kidney function, the patient died from unexpected, sudden cardiac causes on day 52; autopsy revealed severe coronary artery disease and ventricular scarring without evident xenograft rejection. (Funded by Massachusetts General Hospital and eGenesis.)

Author affiliations are listed at the end of the article. Dr. Kawai can be contacted at tkawai@mgh.harvard.edu or at the Department of Surgery, Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114. Dr. Riella can be contacted at lriella@mgh.harvard.edu at the Department of Medicine, Massachusetts General Hospital, 165 Cambridge St., 3rd Fl., Boston, MA 02114.

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Kidney transplantation has become the ideal standard of care for end-stage kidney disease, but organ shortage remains critical.[1] One promising approach to address this critical shortage is xenotransplantation of porcine organs. Advances in CRISPR–Cas9 gene editing have enabled porcine kidney xenografts to survive for more than 2 years in nonhuman primates.[2] We treated a 62-year-old man with long-standing diabetes and advanced vasculopathy who had lost nearly all viable hemodialysis-access options. His chance of receiving a transplant within 5 years was only 16%, with a 76% likelihood of dying or becoming too ill to receive a transplant, according to the decision-aid calculator for kidney transplantation of the Scientific Registry of Transplant Recipients.[3]

With no living donor available, we pursued a gene-edited pig kidney transplant under a single-patient, expanded-access authorization. The patient's candidacy un-

derwent rigorous evaluation by an independent psychiatrist, the Optimum Care Ethics Committee at Massachusetts General Hospital, and external transplant experts. After iterative protocol review by the Food and Drug Administration and final approval by the institutional review board at Massachusetts General Hospital, we transplanted a gene-edited porcine kidney with deletion of three major glycan xenoantigens (3KO), inactivation of porcine endogenous retroviruses, and insertion of seven human transgenes.

METHODS

PIG KIDNEY XENOGRAFT

A Yucatan miniature pig was engineered to carry 69 genomic edits, eliminating three major glycan antigens, overexpressing seven human transgenes (*TNFAIP3*, *HMOX1*, *CD47*, *CD46*, *CD55*, *THBD*, and *EPCR*), and inactivating porcine endogenous retroviruses[2] (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

RECIPIENT EVALUATION

The patient was a 62-year-old man with end-stage kidney disease caused by type 2 diabetes mellitus who had exhausted nearly all viable vascular access for dialysis. His history included myocardial infarction, severe vasculopathy, heart failure, total parathyroidectomy, and receipt of a deceased-donor kidney in 2018. After having graft failure in May 2023 associated with BK virus infection and recurrent diabetic nephropathy, he returned to receiving hemodialysis. Comprehensive evaluation by the multidisciplinary team at Massachusetts General Hospital, along with ethical assessments conducted by an independent psychiatrist and ethics committee, are detailed in the Supplementary Appendix and in Table S1.

TRANSPLANT PROCEDURE AND IMMUNOSUPPRESSION PROTOCOL

The transplant procedures are detailed in the Supplementary Appendix and the protocol, available at NEJM.org. The immunosuppressive regimen was based on our preclinical studies in nonhuman primates[2,4,5] and included antithymocyte globulin (rabbit), rituximab, Fc-modified anti-CD154 monoclonal antibody (tegoprubart), and anti-C5 antibody (ravulizumab) in combination with maintenance immunosuppression with tacrolimus, mycophenolic acid, and prednisone (Fig. 1A and Supplementary Appendix).

DISEASE SURVEILLANCE, HISTOPATHOLOGICAL REVIEW, AND TRANSCRIPT ANALYSIS

Extensive microbiologic testing of the donor swine herd and the specific porcine donor was conducted before transplantation. Post-transplantation monitoring for both human and porcine pathogens and pathological analyses of biopsy samples are detailed in Tables S2, S3, and S4.

RESULTS

EARLY POSTOPERATIVE PERIOD

The transplantation procedure was completed with a cold ischemic time of 4 hours 38 minutes. The xenograft (Fig. 1B and 1C) produced urine within 5 minutes after implantation and more than 6 liters in the first 48 hours. Thereafter, urine output stabilized at 1.5 to 2 liters per day (Fig. S2). The patient's plasma creatinine level dropped from 11.8 to 2.2 mg per deciliter by day 6 (Fig. 1D).

The patient recovered from the transplantation procedure. Aside from chills and fever after the first infusion of antithymocyte globulin, he did not have overt problems with the immunosuppressive regimen. Because the patient's T cells were sufficiently depleted after the initial dose of antithymocyte globulin (Fig. S3), a second dose was not administered. Immunosuppression with anti-CD154 monoclonal antibody resulted in serum trough levels exceeding 1000 μg per milliliter on day 0, after which levels were consistently above 800 μg per milliliter (Fig. 1E). Tacrolimus trough levels were maintained below 4 ng per milliliter during the first week after transplantation (Fig. 1E), combined with a lowered dose of 360 mg of mycophenolic acid twice daily owing to concern about overimmunosuppression with lymphocyte depletion, intensive immunosuppression, and his history of BK virus nephropathy.

XENOGRAFT REJECTION EPISODE

On day 8, the patient's plasma creatinine level increased from 2.2 (day 7) to 2.9 mg per deciliter, accompanied by fever, allograft tenderness, and decreased urine output. An infectious disease workup was negative. Empirical therapy with glucocorticoid pulse (500 mg of methylprednisolone) and monoclonal antibody against interleukin-6 receptor (tocilizumab at a dose of 8 mg per kilo-

gram of body weight) was initiated for suspected antibody-mediated rejection. A pretreatment, same-day biopsy confirmed acute T-cell–mediated rejection, Banff grade 2A, without evidence of thrombotic microangiopathy or antibody-mediated rejection (Table 1 and Table S5; Fig. 2A, 2B, and 2C; and Fig. S4A, S4B, and S4C). Two glucocorticoid pulses (500 mg each) and antithymocyte globulin (1.5 mg per kilogram) were administered on days 9 and 10, and the doses of tacrolimus and mycophenolic acid were increased. Given the C3 deposition in the biopsy sample (Fig. S5), we administered pegcetacoplan, a targeted C3 and C3b inhibitor. Since the biopsy sample showed no evidence of antibody-mediated rejection, no additional doses of tocilizumab were administered. After these interventions, the patient's urine output increased, and the plasma creatinine level started to decline (Fig. 1D). The patient was discharged on day 18 with a plasma creatinine level of 2.5 mg per deciliter.

On day 34, another xenograft biopsy was performed because of an increase in the creatinine level (to 2.65 from 1.9 mg per deciliter), which showed resolution of the T-cell–mediated rejection but with C3 deposition, focal interstitial fibrosis, and tubular atrophy without evidence of antibody-mediated rejection or thrombotic microangiopathy (Table 1 and Fig. 2D, 2E, and 2F; Fig. S4D and S4F; and Fig. S5). The plasma creatinine level decreased to 1.57 mg per deciliter with hydration on day 36. Antiporcine antibody titers remained lower than values in human serum controls (Fig. S6). No new anti-HLA antibodies were detected, and levels of preexisting anti-HLA antibodies were reduced (Fig. S7).

KIDNEY FUNCTION, HEMODYNAMICS, AND FLUID-ELECTROLYTE BALANCE

Although the plasma creatinine levels occasionally fluctuated with the patient's volume status, baseline levels ranged from 1.5 to 2.0 mg per deciliter, with an estimated glomerular filtration rate (eGFR) of 40 to 50 ml per minute per 1.73 m^2 of body-surface area (Fig. 1D). The measurement of 24-hour urine creatinine clearance on days 7 and 28 after transplantation was 37 and 59 ml per minute per 1.73 m^2, respectively. The mean blood pressure was 131/70 mm Hg (Fig. S8), and a loop diuretic (furosemide) was used to maintain euvolemia.

The electrolyte levels remained mostly within normal limits (Figs. S9 and S10). However, the plasma total calcium level was low (Fig. S11) in association with the patient's previous parathyroidectomy with undetectable levels of parathyroid hormone, which was managed with vitamin D and calcium supplementation. Plasma phosphate levels were elevated throughout the clinical course, necessitating the addition of phosphate binders. There was no hematuria or albuminuria, with a urine albumin-to-creatinine ratio (with both measured in grams) in the range of 0 to 0.2. Although the patient's hemoglobin levels remained stable, erythropoietin was initiated on day 15 after transplantation because of the low reticulocyte count with appropriate iron stores.

INFECTIOUS COMPLICATIONS

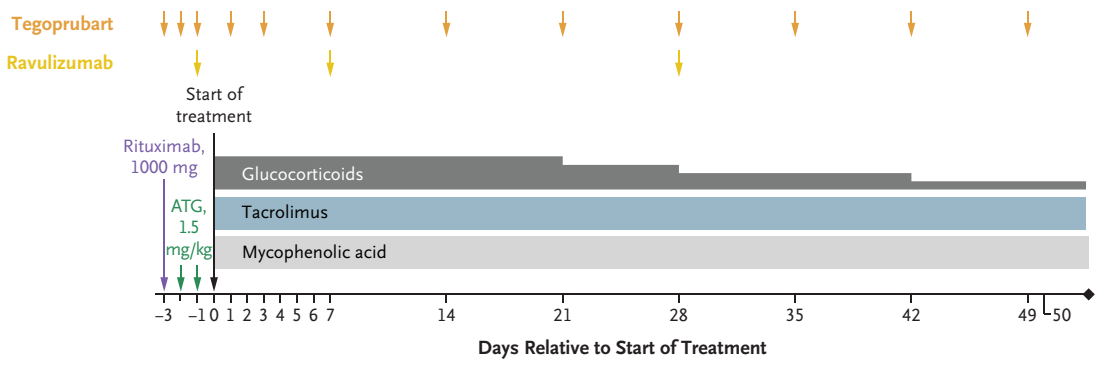
On day 25, a subcutaneous wound infection led to a partial surgical opening of the incision and initiation of antibiotics (linezolid and meropenem). A retroperitoneal fluid collection, positive for *Pseudomonas aeruginosa*, was drained through percutaneous drain placement. The surgical incision was successfully closed on day 37. After 2 weeks of negative cultures and resolution of the fluid collection confirmed by abdominal computed tomography, the drain was removed on day 51.

CARDIAC COMPLICATION

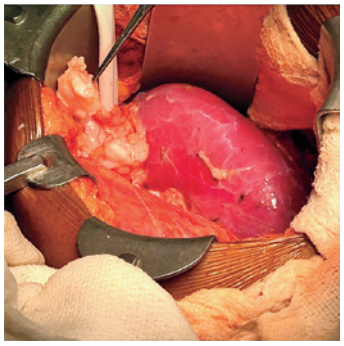
The patient was also evaluated in the outpatient clinic on day 51 after transplantation. He reported low fluid intake, and the plasma creatinine level of 2.7 mg per deciliter was relatively elevated, despite tacrolimus trough levels within target range. He had no symptoms of congestive heart failure or worrisome findings on physical examination, and kidney ultrasonography showed no abnormalities. The overall presentation was similar to a previous episode of an elevated creatinine level on day 34, which had resolved with hydration. Intravenous magnesium (2 g) and a 500-ml bolus of normal saline were administered over a 30-minute period to address hypomagnesemia and presumed volume depletion. The patient's blood pressure, heart rate, and respiratory rate were all normal.

Later that evening, the patient had respiratory distress and rapidly became unresponsive. Despite resuscitative efforts, he died. Autopsy revealed an enlarged heart with severe, diffuse coronary artery disease, diffuse left ventricular fibrosis, and a remote posterior infarct with a subacute ischemic

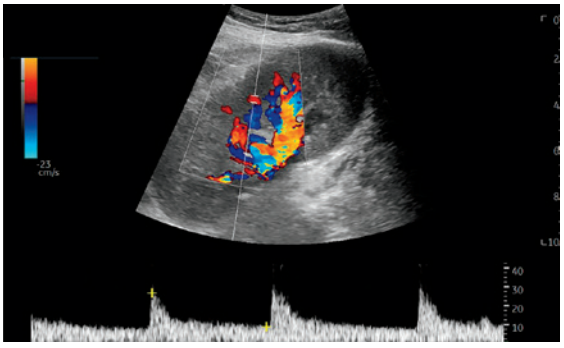
A Planned Immunosuppressive Regimen



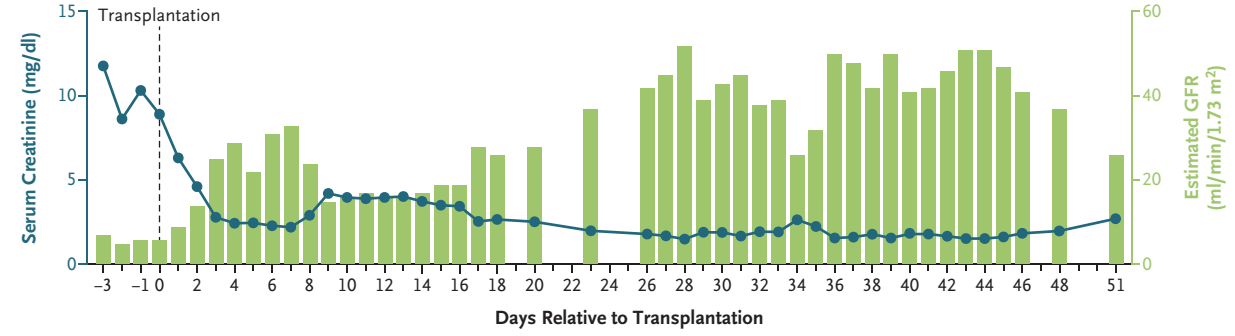
B Intraoperative View of Xenograft Immediately after Reperfusion



C Renal Ultrasound after Transplantation



D Plasma Creatinine and Estimated GFR Following Transplantation



E Drug Levels of Tegoprubart and Tacrolimus after Transplantation

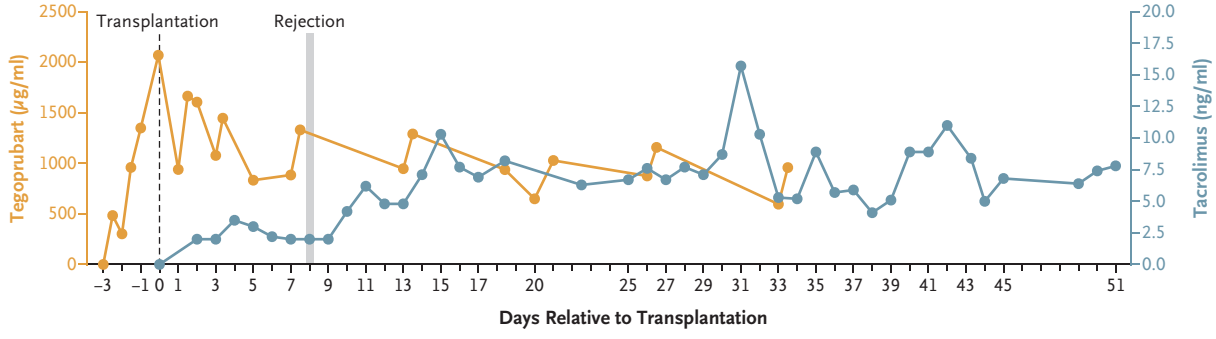


Figure 1 (facing page). Immunosuppressive Regimen and Post-Transplantation Clinical Course.

Panel A shows the planned immunosuppressive regimen including antithymocyte globulin (ATG) (1.5 mg per kilogram of body weight on days –2 and –1), rituximab (anti-CD20 antibody) (1000 mg on day –3), Fc-modified anti-CD154 monoclonal antibody (tegoprubart at a dose of 20 mg per kilogram on days –3, –2, –1, 1, 3, 7, and then weekly), and anti-C5 antibody (ravulizumab at a dose of 3330 mg on days –1, 7, and 28) combined with a conventional immunosuppressive regimen of tacrolimus, mycophenolic acid (540 mg twice a day), and glucocorticoids (starting on day 0). As T cells were completely depleted from the circulation after the first dose and the patient had a severe reaction, the second dose of ATG was not administered. Panel B shows an intraoperative view of the xenograft immediately after reperfusion. Panel C shows a renal ultrasound performed after transplantation indicating excellent blood flow within the kidney xenograft with normal resistive index of 0.67. Panel D shows the plasma creatinine and estimated glomerular filtration rate (GFR) after transplantation. Plasma creatinine levels decreased to 2.2 mg per deciliter by day 6. An increase in the creatinine level was observed after day 8 after a rejection episode, but levels returned to baseline by day 20 after rejection treatment. Since the kidney graft was relatively small in relation to the patient's size (155 g from a 75-kg donor to a 100-kg recipient), the baseline creatinine level was 1.5 to 2.0 mg per deciliter with an eGFR of approximately 45 ml per minute per 1.73 m^2. Panel E shows levels of tegoprubart (Fc-modified anti-CD154 monoclonal antibody) and tacrolimus after transplantation. Tegoprubart administration was initiated on day –3 and its drug level reached more than 1000 μg per milliliter by day 0 (dashed line). Tacrolimus levels were maintained below 4 ng per milliliter during the first post-transplantation week but rose to therapeutic levels (>6 ng per milliliter) after rejection. Tegoprubart levels were subsequently tapered down to 500 to 800 μg per milliliter.

extension, all of which were considered to have been caused by diabetic and ischemic cardiomyopathy (Fig. S12). There was no evidence of acute myocardial infarction, pulmonary embolism, pneumonia, inflammation in other organs, or drug toxicity. We concluded that the patient had probable sudden cardiac death caused by dysrhythmia in the context of severe ischemic cardiomyopathy. The xenograft showed focal fibrosis (attributed to sequelae of the episode of T-cell–mediated rejection) and no histologic evidence of active T-cell– or antibody-mediated rejection or thrombotic microangiopathy (Table 1; Fig. 2G, 2H, and 2I; and Fig. S4G, S4H, and S4I). No porcine pathogens were detected in cultures, on nucleic acid testing, or on metagenomic assays during the clinical course. Retrospective transcriptomic analyses of biopsy samples are shown and discussed in Figure S13 and Table S4.

DISCUSSION

This report documents the transplantation of a 3KO kidney xenograft with seven human transgenes into a patient with end-stage kidney disease, which built on our preclinical studies.[2,4,5] Tegoprubart, an Fc-modified anti-CD154 monoclonal antibody in phase 2 trials for kidney allotransplantation, was part of the immunosuppressive regimen.[6] This agent has shown potent inhibition of antibody production,[7] as well as suppression of innate immune responses by blocking CD11b,[8] another receptor of CD154. The pattern and timing of rejection in this patient suggested that early subtherapeutic levels of tacrolimus and mycophenolic acid may have contributed to the development of T-cell–mediated rejection, which was successfully treated with standard antirejection therapy. On biopsy, there was no evidence of antibody-mediated rejection, a common complication observed in the preclinical and decedent models of kidney xenotransplantation.[2,4,9]

Thrombotic microangiopathy has been a frequent cause of xenograft loss in previous studies in nonhuman primates.[2,4] This condition can arise from incompatibilities between porcine endothelial cells and the human complement system.[10] Therefore, we included an anti-C5 monoclonal antibody, ravulizumab, in the patient's regimen, and no thrombotic microangiopathy was observed in the xenograft. Upon encountering T-cell–mediated rejection with C3 deposition and inflammation on biopsy, we also added pegcetacoplan to inhibit the proximal complement pathway. Our intention was to cautiously taper the use of anticomplement agents while closely monitoring for the development of thrombotic microangiopathy through protocol biopsies, as the clinical necessity for these agents remains to be fully established.

Comprehensive monitoring for zoonotic pathogens was performed with the use of targeted nucleic acid testing and metagenomic sequencing. No porcine-derived pathogens were detected throughout the clinical course.

Certain physiological differences between porcine and human kidney function remain to be elucidated. In studies involving nonhuman primates, porcine renin did not efficiently cleave angiotensin I from angiotensinogen, resulting in

Table 1. Banff Scores on Xenograft Biopsy Samples.*

Variable	Interstitial Inflammation	Tubulitis	Endarteritis	Glomerulitis	Peritubular Capillaritis	C4d Deposition in Peritubular Capillaries	Thrombotic Microangiopathy
Contralateral donor kidney not transplanted	0	0	0	0	0	0	None
Timing after transplantation							
5 minutes after reperfusion	0	0	0	0	0	0	None
Day 8	3	1	1	1	2	0	None
Day 34	0	1	0	0	0	0	None
Day 52 on autopsy	0	0	0	1	0	0	None

* Banff scores range from 0 to 3, with higher scores indicating increasing extent or severity of the variable. An expanded version of these data with additional categories is provided in Table S5 in the Supplementary Appendix.

a dysfunctional renin–angiotensin–aldosterone system (RAAS).[5] Given the incompatibility of primate antidiuretic hormone[11] in nonhuman primates that have received xenografts, dehydration accompanied by elevated creatinine levels often develops.[12] In our patient, blood pressure was well maintained at an average of 131/70 mm Hg, with stable plasma sodium levels and the use of diuretics to maintain euvolemia. Although reversible kidney dysfunction was observed on day 34 and improved with hydration, additional studies are needed to clarify potential differences in the hemodynamic regulation of glomerular filtration by porcine kidneys transplanted to humans. Whether this diuretic requirement in our patient stemmed from the propensity for sodium reabsorption of the porcine kidney or the patient's preexisting heart disease (cardiorenal syndrome) is unclear and warrants further investigation in future xenotransplant recipients. In contrast with the hypercalcemia and hypophosphatemia that are observed in nonhuman primate recipients,[5] our patient had hypocalcemia and hyperphosphatemia,[13] findings that potentially could be attributed to the patient's previous parathyroidectomy. Finally, although the 155-g kidney xenograft obtained from a 75-kg pig donor was relatively small for the 100-kg patient, the average creatinine level was 1.85 mg per deciliter after recovery from the rejection episode — a level that was reasonable for kidney function, given the size difference.

The patient died from unanticipated, sudden cardiac causes, despite a functioning kidney xenograft. An autopsy revealed severe coronary artery disease with diffuse ventricular scarring but no evidence of acute thrombi, and we surmise that the cause of death was probably due to ventricular dysrhythmia. With such severe ischemic heart disease, the risk of sudden death from dysrhythmia remains substantial in any patient,[14] especially after a major surgical procedure.[15] However, we cannot exclude the possibility that frequent fluctuations in intravascular volume, possibly caused by a dysfunctional RAAS in the pig kidney,[5] may have increased the risk of cardiac dysrhythmia in a patient with severe ischemic heart disease.

Despite the short observation period, this case demonstrated that a genetically modified kidney xenograft with human transgenes provided life-supporting kidney function in a living human

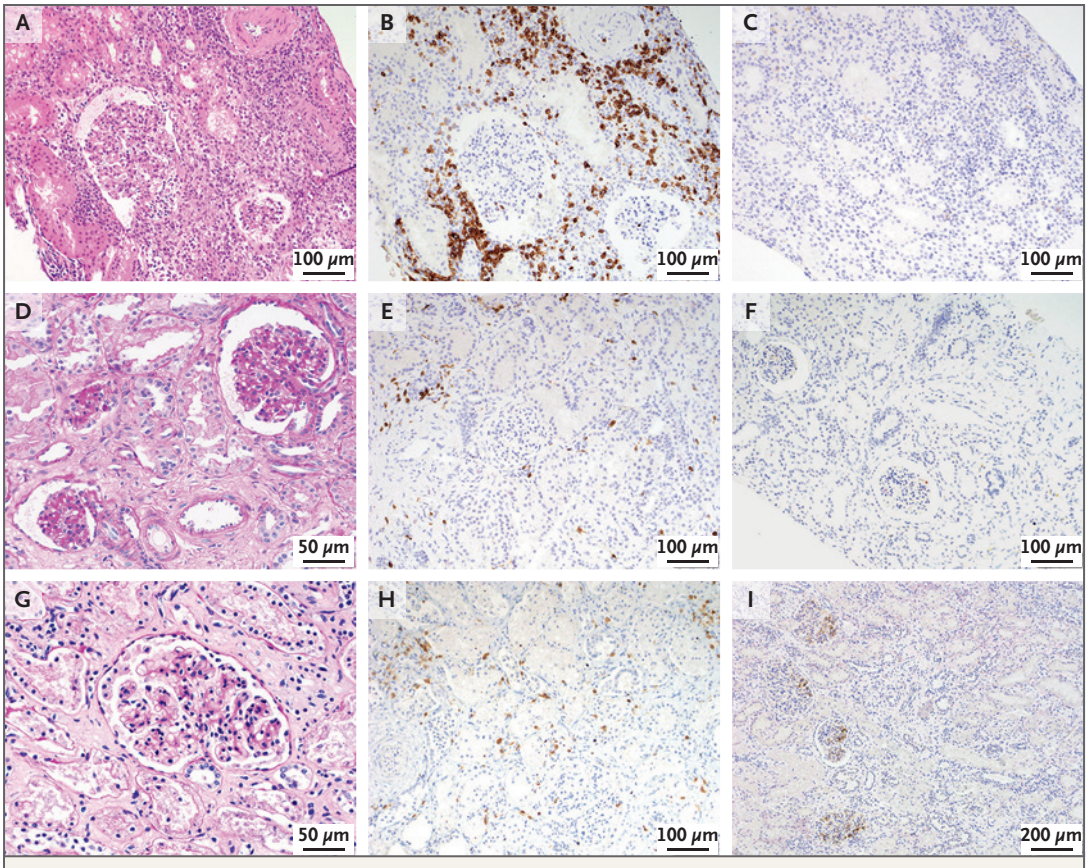


Figure 2. Pathological Analyses of Biopsy Samples Obtained from the Kidney Xenograft.

A biopsy sample obtained 8 days after transplantation shows a prominent, extensive mononuclear infiltrate in the cortex that was associated with tubulitis and focal endarteritis, which is typical of T-cell–mediated rejection (Panel A). Abundant CD3+ cells are seen in the interstitium and focally in an artery (Panel B), and staining for C4d is negative (Panel C). At 34 days, the sample shows normal arteries and glomeruli with mild interstitial fibrosis (Panel D). The CD3+ infiltrate is sparse and substantially reduced from the 8-day biopsy (Panel E), and the C4d stain is negative (Panel F). At 52 days after transplantation in a sample obtained on autopsy, the glomeruli are normal except for minimal glomerulitis (Panel G); sparse CD3+ cells are seen (Panel H), similar to the biopsy sample at 34 days. The C4d stain is segmentally present in glomerular capillaries and not detected in peritubular capillaries (Panel I). Analyses include hematoxylin and eosin staining (Panels A, D, and G) and immunohistochemical analyses of CD3 (Panels B, E, and H) and C4d (Panels C, F, and I).

patient. This outcome supports the feasibility of using genetically modified pig kidney xenografts to expand transplant access for patients with end-stage kidney disease. Although the identification of suitable candidates for kidney xenotransplantation is complex and debated, a small, pilot clinical trial for well-informed dialysis patients who face a high risk of dying while awaiting a human transplant may be a logical next step.

Despite stable kidney function, our study patient who had undergone kidney xenotransplantation died from apparent sudden cardiac causes on day 52. The autopsy revealed severe coronary artery disease and ventricular scarring but no evidence of xenograft rejection.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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AUTHOR INFORMATION

[1]Transplant Center, Massachusetts General Hospital, Boston; [2]Department of Pathology, Massachusetts General Hospital, Boston; [3]Center for Comparative Medicine, Massachusetts General Hospital, Boston; [4]Harvard Medical School, Boston; [5]Eledon Pharmaceuticals, Irvine, CA; [6]eGenesis, Cambridge, MA.

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