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Myroides Infection in a Baboon After Prolonged Pig Kidney Graft Survival

Hong Liu, MD,[1,2] Hayato Iwase, MD, PhD,[1] Martin Wijkstrom, MD,[1] Jagjit Singh, MD,[1] Edwin Klein, VMD,[3] Robert Wagner, DVM,[3] Abhinav Humar, MD,[1] William Pasculle, ScD,[4] and David K.C. Cooper, MD, PhD[1]

Background. Immunosuppressed patients and experimental nonhuman primates are at risk of opportunistic infection. We report a *Myroides* spp. infection in an immunosuppressed baboon that had received a life-supporting kidney from a genetically engineered pig. **Case Report.** The baboon received a costimulation blockade-based immunosuppressive regimen as well as 2 anti-inflammatory agents (tocilizumab and etanercept). Although the pig kidney functioned well, approximately 4 months after the transplantation, the baboon became less active and ate and drank poorly. On day 136, it collapsed and died despite inotropic and fluid support. A blood culture drawn before death grew *Myroides* spp. **Discussion and Conclusions.** To our knowledge, *Myroides* spp. has not been reported as a cause of opportunistic infection in either patients with organ allotransplants or experimental animals. We summarize what is known about this rare organism and suggest it should be considered in any immunocompromised patient or animal. In the present case, we suggest the baboon died of circulatory shock following infection through an indwelling intravenous catheter.

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Opportunistic infection is a common complication of both clinical allotransplantation (alloTx) and experimental xenotransplantation (xenoTx).[1-3] We here report a baboon that died (more than 4 months after a kidney transplant from a genetically engineered pig) in a state of circulatory shock and was found to have a blood culture positive for *Myroides* spp. The baboon had received an immunosuppressive regimen based on costimulation blockade, and also anti-inflammatory therapy with an IL-6R antagonist and a TNF-α antagonist.

A search of the literature has failed to identify *Myroides* spp. as an infectious agent in clinical alloTx or in patients receiving long-term anti-inflammatory therapy or in experimental alloTx or xenoTx in nonhuman primates (NHPs) previously.

CASE REPORT

Life-supporting pig-to-baboon kidney Tx was carried out on March 20, 2014. The baboon (B9313, *Papio* species, 8.3 kg, of blood type B) was from a specific pathogen-free facility at the Division of Animal Resources, Oklahoma University Health Sciences Center, Oklahoma City, OK.[4] The pig (*Sus scrofa*, 8.5 kg, blood group O; Revivicor, Blacksburg, VA) was an α1,3-galactosyltransferase gene-knockout pig transgenic for two human complement-regulatory proteins (CD46, CD55) and human coagulation-regulatory proteins (endothelial protein C receptor).

All animal care was in accordance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH publication no. 86-23, revised 1985). Protocols were approved by the University of Pittsburgh Institutional Animal Care and Use Committee.

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[1] Thomas E. Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, PA.

[2] Department of General Surgery, First Hospital of Shanxi Medical University, Taiyuan, China.

[3] Division of Laboratory Animal Resources, University of Pittsburgh, PA.

[4] Department of Microbiology, University of Pittsburgh, Pittsburgh, PA.

Hong Liu and Hayato Iwase contributed equally.

The authors declare no conflicts of interest.

The surgical procedures were carried out by A.H., M.W., H.L., H.I., and J.S. H.L., H. I., and J.S. took responsibility for management of the baboon after transplantation, with help from M.W., R.W., and D.K.C.C. The microbiological studies were by W. P., and the kidney biopsieswere interpreted by E.K. The original article was prepared by H.L., H.I., and D.K.C.C. All authors reviewed and approved the article, which was finalized by H.L., H.I., and D.K.C.C.

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Correspondence: David K.C. Cooper, MD, PhD, FRCS, Thomas E. Starzl Transplantation Institute, University of Pittsburgh Medical Center, Starzl Biomedical Science Tower, W1543, 200 Lothrop Street, Pittsburgh, PA 15261. (cooperdk@upmc.edu).

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TABLE 1.

Immunosuppressive, anti-inflammatory, and adjunctive therapy in a baboon recipient of a genetically engineered pig kidney graft

	Medication	Dose	Timing
Induction immunosuppression	Antithymocyte globulin	10 mg/kg	Day –3
	Anti-CD20mAb	10 mg/kg	Day –2
	Cobra venom factor	100u/Kg	Day –1, 0
Maintenance immunosuppression	Anti-CD40mAb	50 mg/kg	Days –1, 0, 4, 7, 10, 14, and weekly
	Rapamycin	0.01 mg/kg	×2 daily from day –3 : target level 8-12 ng/mL
	Methylprednisolone	5.0-0.25 mg/kg	5 mg/kg on day 0, tapering to 0.25 mg/kg by day 6
Anti-inflammatory	Tocilizumab	10 mg/kg	Days –1, 4, 7, 14, and every 2 weeks
Adjunctive	Etanercept	5 mg/kg	Days 0, 3, 7, 10, 28, 40
	Aspirin	40 mg	Alternate days

Immunosuppressive, anti-inflammatory, and adjunctive therapies are summarized in Table 1. In summary, the baboon recovered well from the operative procedure and showed good renal function (serum creatinine, 0.6-1.6 mg/dL) with no features of consumptive coagulopathy or protein-losing nephropathy for greater than 3 months (Figure 1). The indwelling intravenous (IV) catheter that had been inserted to facilitate management during the perioperative period was withdrawn on post-Tx day 26. After day 90, urine output gradually decreased and serum creatinine increased to 1.6-2.2 mg/dL. These changes were associated with the gradual development of a stricture of the ureter at the site of implantation into the bladder. Ultrasound indicated an increase in size of the kidney and dilatation of the ureter. On day 103, an operation was carried out to excise the ureteric stricture (which showed no infiltration with leukocytes or other features of rejection) and reimplant the ureter into the bladder. A renal biopsy was taken and showed no significant abnormality (not shown).

Subsequently, the serum creatinine remained slightly increased (1.5-1.9 mg/dL). The baboon was active, but was not drinking well and so on day 105 a single IV catheter was inserted into a branch of the right femoral vein using a jacket and tether system[5] and remained in place for the remainder of the experiment. The presence of the catheter was likely a major factor in the subsequent bloodstream infection.

On day 135, the baboon became much less active and quiet, but otherwise unchanged. On the evening of day 136, the baboon had what appeared to be a "neurological event" (conscious with some limb rigidity, but no paralysis), the cause of which remained uncertain. Its temperature was 36.2 °C. The white blood cell count was higher than previously at 8300/mm^3 (neutrophils, 6100/mm^3; monocytes, 1400/mm^3; lymphocytes, 800/mm^3), platelet count was 320,000/mm^3, hematocrit 27.4%, with basically normal electrolytes and metabolic parameters. With inotropic and IV fluid support, the baboon appeared to improve but, 2 hours later, suddenly died.

Blood drawn an hour before death of the baboon grew *Myroides* spp. Using the Bruker Biotyper MALDI-TOF instrument (Bruker Daltonics, Bilerica, MA), the isolates were identified as *Myroides odoratus* (blood had not been drawn for culture during the previous month.)

A necropsy was performed, and histopathology of the kidney graft showed patchy lesions in all 3 anatomic components of the transplanted kidney—glomerular, tubular, and interstitial—with thrombosis of primarily small vessels in both glomeruli and the interstitium, associated with focal infarction and tissue destruction, but little fibrosis (not shown). The pathologic features were not considered widespread or severe enough to account for the death of the animal.

DISCUSSION

This baboon represents the longest-surviving NHP supported by a pig kidney, all previous experiments having been

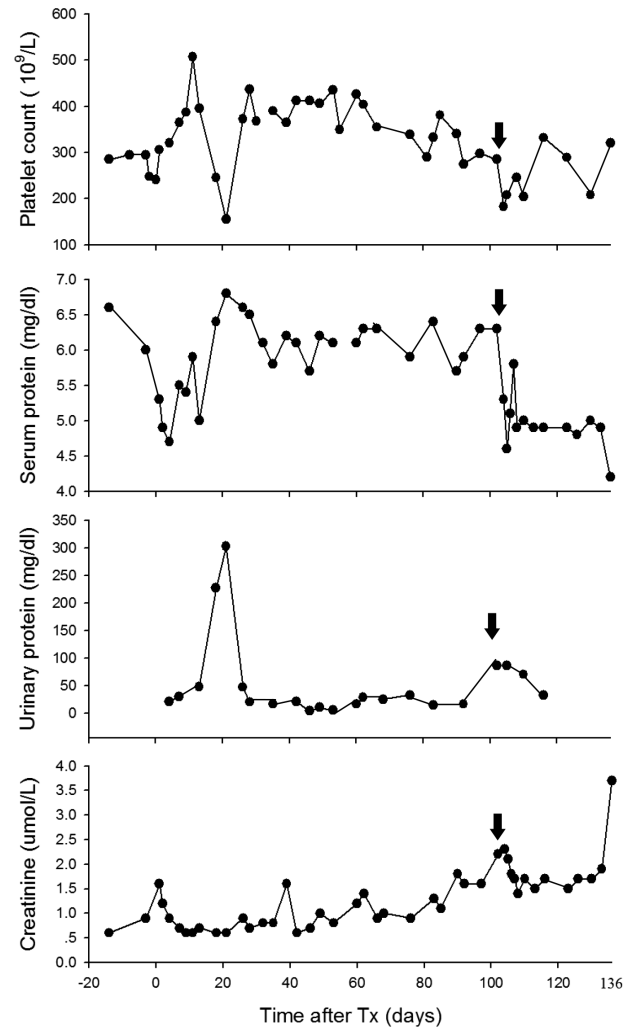

FIGURE 1. Platelet count, serum, and urinary protein, and serum creatinine in a baboon recipient of a life-supporting genetically engineered pig kidney. Graft survival (of 136 days) was longer than any previously reported case (arrows indicate the day of ureter reimplantation and renal biopsy.)

TABLE 2A.

Clinical reports of infection with *Myroides* spp

Infection site	Age (years unless stated)/sex	Underlying clinical conditions	Clinical features	Organism	Reference
Soft tissue	57/F	Alcoholism, bedsores, semi-comatose, malnourished	Fever, gangrene (left foot), amputation of toes	*M. odoratus*	Davis et al[33]
	71/F	Hepatitis B virus-related cirrhosis	Fever, hypotensive, confused, bacteremia, necrotizing fasciitis (left leg), septic shock, amputation (left leg)	*M. odoratus*	Hsueh et al[26]
	63/M	Chronic obstructive pulmonary disease, chronic steroid therapy	Cellulitis (both arms), bacteremia	*M. odoratus*	Bachman et al[27]
	69/M	Immunocompetent. Tinea pedis for 2 years (right foot)	Recurrent cellulitis (right leg), fever, sepsis	*M. odoratus*	Green et al[28]
	62/M	Diabetes	Cellulitis (right leg), fever, lethargy, septic shock	*M. odoratus*	Motwani et al[29]
	49/M	Alcoholic cirrhosis, trauma to legs	Cellulitis (right leg), fever, ascites, sepsis	*M. odoratimimus*	Bachmeyer et al[30]
	72/M	Immunocompetent. Traumatic left hemithorax and traumatized left arm (requiring amputation)	Fever, pneumonia, confusion, hypotension, septic shock	*M. odoratimimus*	Benedetti et al[34]
	13/M	Immunocompetent. Pig-bite (right leg)	Fever	*M. odoratimimus*	Maraki et al[32]
	55/F	Hepatitis C virus-related cirrhosis, morbid obesity, lymphedema	Necrotizing fasciitis (both legs), confusion, hypotension, bacteremia, septic shock, death	*M. odoratus*	Crum-Cianflone et al[31]
Pneumonia	45/F	Diabetes, pulmonary tuberculosis	Fever	*M. odoratus*	Deepa et al[35]
Endocarditis	56/F	Chronic renal failure (on hemodialysis)	Abscess around dialysis access site, fever, bacteremia	*M. odoratus*	Ferrer et al[36]
Cerebral ventriculitis	6 weeks /M	Prematurity, hydrocephalus	Fever	*M. odoratus*	Macfarlane et al[37]
Cholecystitis	76/M	Obstructive jaundice	None	*M. spp. (+ Oerskovia turbata)*	Thomas et al[38]

M indicates male; F, female

terminated within 90 days.[6,7] We attribute this relative success to the combination of (i) Tx of a kidney from a pig with multiple genetic modifications directed to prevent injury from the primate immune response and from the effects of coagulation dysfunction between pig and baboon,[8] (ii) an immunosuppressive regimen that has been demonstrated to prevent a T-cell response to pig cardiac xenografts,[9,10] and (iii) a regimen that reduces the inflammatory response.[11]

Using costimulation-based regimens, we have documented fewer infectious complications if all intravascular catheters are removed as soon as possible. In the present baboon, we felt forced to reinsert an IV catheter to ensure that the animal remained well hydrated, and we believe its presence may have been a major actor in the development of the *Myroides* infection. There were no features of infection in the organ-source pig or in the baboon before Tx. The clinical features in the baboon on day 136 were those of septic shock rather than acute rejection of the graft. Only 1 previous blood culture had been drawn from the baboon (day 7), which was negative, and so we have no record of the length of time the microorganism had been present in the baboon.

The positive blood culture indicated the presence of infection with *Myroides* spp., which is a rare cause of bloodstream infection, but which is widely distributed in nature. In recent years, novel species have been isolated from water and soil.[12-16] Although they are not usually components of human microflora, they have been isolated from several different clinical specimens,[17] and have been implicated in small nosocomial outbreaks.[18-20] (*Flavobacterium* spp. have also caused fatal infections in patients with human immunodeficiency virus.[21])

They are gram-negative, nonfermentative, obligately aerobic, yellow-pigmented, and nonmotile rods, with a characteristic fruity odor.[22] Whether the death of the baboon was solely a result of the *Myroides* infection remains uncertain, but the development of circulatory collapse would correlate with a septic cause (even though the white blood count remained within the normal range, which is not unusual in

TABLE 2B.

Clinical reports of nosocomial outbreaks of *Myroides* spp. infection

Infection site	No. cases	Causative factors	Organism	Reference
Urinary tract infection	22	Urological surgery	*M. odoratimimus*	Yagci et al[20]
Catheter-associated blood stream infection	20	Contaminated commercially-produced water for injection	*M. odoratus (+/– Burkholderia capacia)*	Douce et al[18]
Urinary tract infection	7	Urological surgery	*M. odoratimimus*	Ktari et al[19]

immunosuppressed baboons). Nevertheless, its culture from the blood, in the absence of other microorganisms, seems worthy of reporting.

After its first isolation in 1923,[23] the organism was designated as *Flavobacterium odoratum* and placed under genus Flavobacterium. However, it showed certain features that differentiated it from other Flavobacteriaceae, such as lack of gliding motility, good growth at 37 °C, halotolerance (tolerance to high salt concentration), and differences in the fatty acid profile. Based on genotypic and phenotypic data, the new genus *Myroides* was created in 1996,[24] in which 2 species, *Myroides odoratus* (formerly *F. odoratum*) and *Myroides odoratimimus,* were included.

The diagnosis of *Myroides* spp. depends on culture and molecular techniques. Schröttner et al[25] analyzed 22 strains using 3 identification methods. The results demonstrated that VITEK2 reliably identifies the genus *Myroides,* but cannot differentiate between *Myroides odoratus* and *Myroides odoratimimus*. In contrast, both MALDI_TOF MS and 16S rDNA sequencing efficiently distinguish between the species.

Myroides spp. microorganisms usually behave as low-grade opportunistic pathogens, though clinical infection caused by this organism is rare. A significant number of patients have been to some extent immunocompromised through, for example, liver cirrhosis, diabetes mellitus, or chronic obstructive pulmonary disease on long-term corticosteroid treatment. The organism has been responsible for soft tissue infection,[26-31] including after a pig bite,[32] surgical wound infection,[33,34] pneumonia,[35] endocarditis,[36] cerebral ventriculitis,[37] and cholecystitis[38] (Table 2A). One patient died with a necrotizing fasciitis of both lower extremities and septic shock.[31] Perhaps, surprisingly, we have not been able to identify any reports of infection caused by these microorganisms after solid organ alloTx.

Nosocomial outbreaks have been reported (Table 2B), including urinary tract infections, sometimes associated with urological surgery.[19,20] An outbreak of central venous catheter-associated bloodstream infection was reportedly caused by commercial ampoules of sterile water contaminated by *Myroides odoratum* and/or *Burkholderia capacia*.[18]

Myroides spp. is characterized by resistance to a wide range of antimicrobial agents that have satisfactory activity against other gram-negative bacteria. Most strains are resistant to the β-lactams, including aztreonam and carbapenems, and exhibit variable susceptibility to aminoglycosides, quinolones, and sulfamethoxazole.[39,40] Resistance to β-lactams is due to the production of chromosome-encoded metallo-β-lactamases, both in *M. odoratum* (TUS-1) and *M. odoratimimus* (MUS).[41] The importance of an accurate and reliable susceptibility test has been stressed when significant infection with *Myroides* strains is encountered.

To our knowledge, the present report is the first of a bloodstream infection caused by *Myroides* spp. in an immunosuppressed NHP host. Indeed, we have been unable to identify a report of a *Myroides* complication in either patients with organ allografts or those receiving anti-inflammatory agents or in any NHP (whether immunosuppressed or not). Whether the nature of the immunosuppressive regimen (costimulation blockade) or the addition of a potent anti-inflammatory agent (tocilizumab) contributed to the development of this rare infectious complication remains uncertain. However, we would suggest that it should be suspected in any patient receiving immunosuppressive therapy following organ Tx or for an autoimmune disorder.

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