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COMMENTARY

Porcine cytomegalovirus: A very unwelcome stowaway

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The announcement of the first pig-to-human heart transplantation early this year was the culmination of a very long and arduous path. The groundbreaking first life-sustaining pig-to man heart transplantation by the team of University of Maryland at Baltimore under the lead of Professor Griffith provided the long-awaited proof that it can work–even if survival was cut short by a hitherto still to be defined process. In a fascinating webinar, Professor Griffith described in detail the course of the patient.[1] One potential element in the deterioration was the increase of porcine cytomegalovirus (PCMV) DNAemia, detected in the blood of the patient. The exact role of PCMV in the sequence of events is unclear and currently analyzed in detail, and will undoubtedly increase our knowledge.

As a young researcher in the laboratory of Jay Fishman, I had the privilege to play a small role in early pig-to-baboon xenotransplantation experiments done in the Transplantation Biology Research Center at MGH, headed by Professor David Sachs. Organ- and recipient survival was short in the early 2000s, and reasons were explored on many different angles. From the experience in human-to-human solid organ transplantation, one avenue was to look for activation or primary infection of latent viruses, primarily from the herpesvirus family. PCMV had been identified as a potential zoonotic agent before.[2] Using quantitative PCR assays, we demonstrated activation of PCMV and baboon cytomegalovirus (BCMV) in a series of pig-to primate organ kidney xenotransplantations. High copy numbers of PCMV DNAemia were detected in recipient baboon tissue and particularly in the transplanted porcine graft tissues.[3,4] In a model of primary porcine aortic endothelial cells infected in vitro with PCMV, an increase in porcine tissue factor was observed, and we hypothesized that this was a potential cofactor in the development of an often fatal consumptive coagulopathy observed in pig-to baboon kidney xenotransplantation.[5] Using PCMV-free pig donors, which was achieved by early weaning of piglets, consumptive coagulopathy was prevented in pig-to-baboon heart transplantation, resulting in an improved graft survival.[6] Given the many modifications in the protocols over time, it was not possible to establish PCMV as the sole cause of this coagulopathy. Nevertheless, at this point elimination of PCMV was the clear goal given the harmful potential of this virus.[7] Eradication protocols were developed and successfully tested.[8] This was all the more important, as ganciclovir failed to control PCMV activation.[9] BCMV activation in the recipient baboons, on the other hand, by then was controlled by prophylactic use of ganciclovir in the majority of recipients and had become part of all protocols.

The most comprehensive study on the role of PCMV was recently published by Denner et al. in 2020. In a series of orthotopic pig-to-baboon heart transplantations, transmission of PCMV was observed from PCMV-positive donor pigs in some but not all baboon recipients, whereas no transmission events occurred for a number of other potentially harmful latent porcine viruses tested, including porcine lymphotropic herpesviruses, and porcine endogenous retroviruses. In baboons transplanted with a heart from a PCMV-positive donor pig, survival was reduced, inflammatory cytokines such as IL-6 and TNF-α were increased and tPA-PAI-1 complexes circulated in high concentrations in the recipients, pointing to substantial alterations of the coagulation system. This detailed report provided additional evidence for the deleterious effects of PCMV, and reiterated the need for elimination of PCMV from the pig donor.[10]

Why then are PCMV-positive donor pigs still an issue? Breeding pathogen-free pigs was shown to be feasible, but the effort to achieve this is considerable. In a publication on virus prevalence in different minipig breeds in 2021, PCMV was still detected in some but not all breeds.[11] Recent work did primarily focus on porcine endogenous retroviruses, as elimination of these viruses is incomparably more challenging than that of traditional latent viruses. Testing for elimination requires not only the use of PCR for detection PCMV DNAemia, but also by serology, as PCR can be negative in swabs from a healthy swine.

Validated serological assays for PCMV are not readily available. Efforts did understandably concentrate on the genetic modifications of donor pigs. Given the potential unfavorable role in the first human case of orthotopic heart transplantation, the focus must be redirected to the elimination of PCMV. It is a feasible and necessary step. The amazing initial clinical course of the patient is a huge incentive to keep the momentum going and continue on this path.

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