Systemic inflammation in xenograft recipients (SIXR) or undetected PCMV/PRV transmission?

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Transplantation of pig organs into non-human primates has often been associated with clinical symptoms described as systemic inflammation in xenograft recipients (SIXR). Systemic inflammation precedes and promotes activation of coagulation after pig-to-nonhuman primate xenotransplantation, irrespective of immunosuppressive therapy. Inflammation can be described as a complex biological response of an organism to harmful stimuli and chronic inflammation is observed in various diseases, for example, diabetes, infection, or atherosclerosis. Inflammation is associated with the release of a wide range of cytokines and chemokines, recruiting immune cells to the site of inflammation and modulating the maturation of immune cells. Among these molecules are tumor necrosis factor (TNF) and interleukin 6 (IL-6), which are highly elevated in animals with SIXR. Innate immune cells expressing tissue factor (TF) are activated after xenotransplantation and expression of the TF by activated endothelial cells is an initial mechanism in the development of thrombotic microangiopathy in the transplant and consumptive coagulopathy (CC) in the recipient. Thrombotic microangiopathy and CC are characteristic features associated with xenotransplant failure. TNF-alpha and IL-6 are known to promote TF expression. SIXR is always associated with the activation of coagulation and the interaction between inflammation and coagulation results in an amplification circuit, promoting the production of both inflammatory mediators and coagulation factors. The influence of IL-6 on coagulation has been well studied in baboons. However, transmission of the porcine cytomegalovirus/porcine roseolovirus (PCMV/PRV) to non-human primate recipients of pig organs is also associated with CC. The word transmission is used, because there is no evidence that PCMV/PRV infects human or non-human primate cells. Obviously, the virus replicates in the transplant and interacting with endothelial and lymphoid cells of the baboon, causing the changes in cytokine release and coagulation.

The name PCMV/PRV was chosen to indicate that this virus is not a cytomegalovirus, but a roseolovirus and that it is not closely related to the human cytomegalovirus (HCMV), also called human herpesvirus 5 (HHV-5), but that it is closely related to the roseoloviruses HHV-6 and HHV-7. Most importantly, early weaning was shown to prevent PCMV/PRV transmission to the pigs, organs of PCMV/PRV-free animals obtained by early weaning did not induce CC. An activation of the porcine TF in porcine aortic endothelial cells by a PCMV/PRV infection was observed in vitro. Although no correlation between TF expression and PCMV/PRV infection was observed in vivo, decreased levels of PCMV/PRV activation were, however, associated with the prolongation of xenotransplant survival. An expression of the TF by activated endothelial cells was also observed in reported cases of SIXR; however, the expression of TF on immune cells (macrophages and peripheral blood mononuclear cells), another SIXR feature reported was not yet studied after PCMV/PRV infection. Interestingly, IL-6 was only elevated when immunosuppression was given, indicating that PCMV/PRV could replicate to a titer able to induce IL-6 and coagulation dysfunction only under immunosuppression. When we analyzed baboons after the orthotopic transplantation of pig hearts with and without PCMV/PRV, we observed that the baboons, which presented clear pathological alterations, had very high levels of tissue-type plasminogen activator (tPA) – plasminogen activator inhibitor type 1 (PAI-1) complexes. This indicates a hypercoagulable state, defined as an increased tendency to develop blood clots (thrombosis). In an older report, it had been shown that IL-6 treatment induces a 20-fold increase of PAI-1 within 8 hours in a
The strong similarity of the clinical symptoms described for animals with SIXR and for animals which have received SIXR suggests the question as to whether the described SIXR represents an undetected PCMV/PRV transmission. The fact that PCMV/PRV induces similar features does not automatically mean that SIXR can be fully explained by a PCMV/PRV infection. Alternatively, a PCMV/PRV transmission may enhance SIXR. Unfortunately, the donor pigs in most of the investigations had not been tested with appropriate methods for PCMV/PRV detection, so they were believed to be PCMV/PRV-free, but were PCMV/PRV-positive in reality, as for example the donor pig of the heart for the patient in Baltimore. After orthotopic transplantation of a heart from a PCMV/PRV-free donor pig, baboons do not show such features. The transplants of small (2 x 1 cm) pig artery patches into baboons are of special interest. These patches, neither high levels of IL-6 nor high levels of tPA-PAI-1 complexes were observed.

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CONFLICT OF INTEREST

The author has no conflict of interest.

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