The Contribution of Cytomegalovirus to Atherosclerotic Events after Kidney Transplantation

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(See the major article by Courivaud et al on pages 1569–75.)

With improvements in management of acute rejection and allograft function over the past decades, short-term survival after solid-organ transplantation is excellent, and death with a functioning graft has become the outcome for the majority of solid-organ transplant recipients. Thus, there is a necessity to focus not only on interventions to maintain graft function, but also to address other posttransplantation complications contributing to death among transplant recipients. Chief among these concerns is posttransplantation atherosclerosis. Atherosclerosis resulting in cardiovascular events is now the major cause of death in long-term survivors of renal, cardiac, and hematopoietic stem cell transplantsations [1–3]. In a cohort of 2202 adult kidney transplant recipients with >10-year graft survival, cardiovascular disease (CVD) was the major cause of mortality, followed by malignancy and infection [4].

The cause of posttransplantation atherosclerosis is multifactorial. Risk factors resembling those for atherosclerosis in the general population include pretransplantation CVD, diabetes, hypertension, hyperlipidemia, tobacco use, obesity, and renal disease [1]. For transplant recipients, additional contributors include transplant-related medications such as steroids, transplant nephropathy, posttransplantation diabetes, and posttransplantation dyslipidemia. Thus, identifying comorbidities that influence the progression of CVD in transplant recipients might provide interventions to prolong survival and quality of life.

Cytomegalovirus (CMV) has been associated with atherosclerosis in large seroepidemiologic studies of nontransplant recipients [5–7]. In one longitudinal prospective study (the Atherosclerosis Risk in Communities [ARIC] study), patients who developed elevated carotid intimal-medial thickening had higher CMV antibody titers measured 13–18 years prior to onset of the carotid lesions, compared with matched control patients who did not develop carotid intimal-medial thickening [5]. In the ARIC study, high CMV antibody titers also correlated to later onset of coronary heart disease [6]. In the Heart Outcomes Prevention Evaluation study, CMV-positive serostatus was associated with increased risk of myocardial infarction, stroke, or cardiovascular death [7]. In an elderly Latino population (the Sacramento Area Latino Study on Aging), high CMV antibody titers were related to increased risk for both all-cause mortality and mortality from CVD [8]. Among these patients, serum tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) quantities were covariates with CMV titers, suggesting a relationship between ongoing inflammation, high CMV titers, and observed mortality. These studies suggest that the magnitude of the antibody response, and not CMV seropositivity itself, is associated with the observed risk. However, as for all seroepidemiologic studies, a mechanistic etiology cannot be assigned directly to CMV.

To address pathogenesis, animal models have been developed to analyze the contribution of CMV to cardiovascular events. In murine models, murine CMV infection exacerbates atherogenesis in apoE-knockout mice [9, 10] and increases arterial blood pressure in mice fed a high-fat diet [11]. In the latter study, murine CMV–infected mice also had elevated serum levels of the proinflammatory cytokines TNF-α, IL-6, and monocyte chemoattractant protein 1 (MCP-1). In vitro human CMV–infected endothelial cells can secrete a number of proinflammatory cytokines and chemokines, including IL-6, interleukin 8, TNF-α, regulated and normal T-cell expressed and secreted chemokine, MCP-2, CXC ligand 6, and interferon γ–induced protein 10, among others [12]. These studies provide potential mechanistic pathways by which CMV might contribute to atherosclerosis in human populations.
Some investigators have identified CMV DNA in atherosclerotic plaques but not nonatherosclerotic vessels by polymerase chain reaction [13, 14], but others have shown the presence of CMV DNA in both patients with and without atherosclerotic disease [15], atherosclerotic and nonatherosclerotic vessels of individual patients [16], or no relationship between CMV DNA and atherosclerotic lesions [17]. Identification of viral antigens or recovery of virus by culture from atherosclerotic plaques has not been consistently described. Since CMV can infect endothelial cells and has been identified pathologically in other types of inflammatory lesions, the significance of the CMV DNA in atherosclerotic plaques in the general population remains unclear.

In the context of transplantation, some seroepidemiologic associations between human CMV infection and posttransplantation atherosclerosis exist, but this literature is sparse. In a study of 301 cardiac transplant recipients, CMV infection was associated with graft rejection and more severe graft atherosclerosis contributing to graft loss and death [18]. Another group found no increase in cardiac allograft vasculopathy (CAV) with CMV infection alone but did find an increased incidence of CAV in CMV-infected patients with persistent (duration, ≥4 months) viremia [19]. In a cohort of 1859 kidney transplant recipients in the era prior to routine use of ganciclovir prophylaxis and current immunosuppressive regimens, CMV disease was associated with an increased risk of cardiac complications [20]. Antiviral prophylaxis has been associated with decreased severity of CAV [21, 22], but the impact of antiviral prophylaxis on transplant-associated atherosclerosis has not been evaluated in other solid organ transplant populations.

Animal models support a role of CMV in the development of CAV. In a rat cardiac transplant model, CAV is accelerated by rat CMV infection and is ameliorated by use of antiviral prophylaxis [23–25]. Studies in the animal model and in vitro demonstrate that CMV genes encode functions that stimulate migration of infected vascular smooth muscle cells, contributing to CAV in the animal model [26–28]. In vitro CMV infection of vascular endothelium, smooth muscle cells, fibroblasts, and mononuclear cells can induce expression of numerous proinflammatory cytokines and chemokines, adhesion molecules, growth factors, and matrix metalloproteases, which can be associated with recruitment of inflammatory cells, stimulation of angiogenesis, and induction of wound-healing responses thought to contribute to atherosclerotic plaques [29]. Transcriptional upregulation of many inflammatory, angiogenesis, and wound-healing molecules has been demonstrated in rat CMV-infected cardiac allografts [30]. These studies provide possible mechanisms by which CMV might accelerate CAV in transplant recipients.

However, cardiac allograft vasculopathy may represent a form of rejection specific to cardiac transplants, the pathogenesis of which may not generalize to the posttransplantation atherosclerosis observed in recipients of noncardiac solid-organ transplants. In this issue of the Journal of Infectious Diseases, Courivaud et al analyzed data from 570 consecutive adult kidney transplant recipients for the relationship between human CMV serostatus and posttransplantation atherosclerotic events. CMV status was stratified according to infection (any CMV DNA–positive PCR result), disease (viral replication requiring treatment according to clinician’s judgment), or exposure (positive donor and/or recipient serostatus, infection, and/or disease). Patient factors associated with risk for atherosclerotic events were included in the analysis, and atherosclerotic events were defined by objective evidence of coronary heart disease, cerebrovascular disease, or aortic/extremity arterial disease. A higher rate of atherosclerotic events occurred among patients who had CMV viremia after transplantation, compared with those without replication and with CMV-negative patients. Patients with viremia also had an increased risk of atherosclerotic events and death. A secondary analysis of blood samples from a subset of patients identified a greater frequency of T cells with surface markers characteristic of exhaustion (CD57+/CD28−) in CMV-exposed patients, compared with CMV-naïve patients. By use of the last available C-reactive protein measurement as a marker of systemic inflammation in surviving patients, C-reactive protein levels were highest in patients with CMV replication, lower in CMV-exposed patients, and lowest in CMV-naïve patients. These ancillary studies suggest the possibility that immune senescence and/or inflammation might contribute to the atherosclerotic events observed in the patients with CMV replication.

This is only the second study to analyze a large population of kidney transplant recipients for the association of CMV with atherosclerotic events, and it is the first to study a population largely treated with current induction and immunosuppression protocols. In this study, atherosclerotic events were characterized by specific categories (coronary, cerebrovascular, and peripheral vascular disease) and defined by objective clinical and imaging criteria. As such, this study supports and advances the known body of literature linking CMV and atherosclerotic events in recipients of noncardiac solid-organ transplants. However, as direct causation cannot be assigned to the observed associations, further studies are needed to define whether CMV contributes directly to atherosclerotic events or instead serves as a marker of immune dysregulation or ongoing inflammation in the transplant-recipient population. For example, an alternative explanation for the observed association might be that CMV viremia and atherosclerotic events constitute independent responses to ongoing inflammation in the affected subjects, rather than a causal relationship. CMV
is well known to reactivate in the setting of inflammation, so an inflammatory host milieu resulting in both viremia and development of atherosclerosis in transplant recipients could be postulated. Such a mechanism could also explain the association of high CMV antibody titers with atherosclerotic events in the general population, so that patients with greater systemic inflammation are predisposed independently to atherosclerotic events and to CMV reactions resulting in more robust antibody responses. To date, no animal models or in vitro studies have interrogated the pathogenesis by which CMV might intensify atherosclerotic events in the setting of immunosuppression. Studies such as the one performed by Courivaud et al support the possibility that CMV may contribute to postransplantation atherosclerotic events and emphasize the need for further investigation in human, animal, and in vitro studies.

As the major cause of late patient demise, atherosclerotic events now constitute a postransplantation complication of significant concern. Understanding the multifactorial etiology of this complication will be important to improve long-term outcomes after transplantation. Whether CMV is a marker or a direct contributor to atherosclerotic events in this population remains to be firmly established, but studies such as that by Courivaud et al suggest that this viral infection deserves further study and that it might provide one potential target of clinical intervention to prevent atherosclerotic events and improve long-term mortality in kidney transplant recipients.

Notes

**Financial support.** This work was supported by the National Institutes of Health (grants 5K08AI059428-02 and 1R56AI101138-01) and the Kaul Pediatric Research Initiative of the Children’s Hospital of Alabama.

**Potential conflicts of interest.** Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**


