Invited Commentary: Human Cytomegalovirus, Inflammation, Cardiovascular Disease, and Mortality

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Human cytomegalovirus (CMV) is a human herpesvirus, and infection is widespread in the human population. Prevalence of seropositivity for human CMV increases with age. CMV establishes persistent infection in vascular arterial and venous endothelial tissue. It has been associated with atherosclerosis and graft rejection in heart transplant recipients. The antiviral drug ganciclovir prevents CMV disease in heart transplant patients, and valganciclovir and CMV immune globulin reduce rejection rates and cardiovascular disease. Human CMV infection has been associated with proinflammatory cytokine increases and nonresponsiveness to antiinfluenza vaccine in the elderly. Enhanced expression of proinflammatory cytokines has also been associated with enhanced mortality in the elderly. In this issue of the Journal, Roberts et al. report that, in a large population-based cohort of elderly Sacramento area Latino subjects in California followed from 1998 to 2008, more than 95% were seropositive for human CMV. In that study, Kaplan-Meier survival curves suggested worse cardiovascular disease survival for individuals in the highest quartile of human CMV immunoglobulin G antibody titers over 9 years of follow-up. Theirs is the first study known to report a relation between high human CMV antibody levels and mortality.

cardiovascular diseases; cytomegalovirus; immune system; infection; inflammation

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G; IL-6, interleukin 6; TNF-α, tumor necrosis factor-alpha.
as shown by the appearance of new antibody specifications against epitopes on gB and gH of CMV (7). Elderly patients may also undergo reinfecction with new strains of CMV as well as reactivate existing latent virus.

Human CMV has been implicated in cardiovascular disease in a major way; a study found that heart transplant recipients positive for human CMV antibody had a higher incidence of atherosclerosis and graft rejection in the recipient heart than human CMV–negative recipients did (8). Studies by investigators in the Division of Cardiovascular Medicine at Stanford University (California) showed that CMV replication contributed to acute graft rejection and cardiac allograft vascular disease (9). The use of the antiviral drug ganciclovir effectively prevented CMV disease in heart transplant patients (10), and prolonged use of valganciclovir plus CMV–immune globulin reduced circulating CMV viremia, acute rejection, and cardiac allograft vascular disease (9). These observations provide evidence for the role of CMV infection in acute rejection and cardiac allograft vascular disease. CMV has also been implicated to cause restenosis of coronary arteries following coronary angioplasty and to interact with p53 to promote vascular smooth muscle cell proliferation (11).

Animal model experiments involving murine CMV or rat CMV have also shown the development of atherosclerotic lesions in blood vessels (12). In a recent study of a model of mice fed a high-fat diet and infected with murine CMV, an increase in arterial blood pressure was observed during a 6-week period (13). This increase was enhanced in infected mice fed a high-cholesterol diet, and the murine-CMV-infected mice had a significant increase in proinflammatory cytokines, tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), and MCP-1 (13). In other studies, CMV infection has been associated with an increase in a large number of proinflammatory cytokines including TNF-α, IL-6, MCP-1, interleukin 1, leukotrienes, vascular endothelial growth factor, and vascular cell adhesion molecules (5, 14, 15). Induction of proinflammatory cytokines by CMV infection may also sequentially up-regulate expression of intracellular adhesion molecules in uninfected neighboring cells through paracrine action (16). Human CMV is able to establish a persistent infection in vascular endothelial cells of venous and arterial origin, where viral replication continues without destruction of cells (13). Viral replication is necessary for the enhanced expression of some cellular proteins because ultraviolet-inactivated virus is not able to up-regulate expression of cellular genes involved in hypertension.

Enhanced expression of proinflammatory cytokines such as IL-6 and C-reactive protein has previously been associated with mortality in the elderly (17). Systemic inflammation, as measured by C-reactive protein, has been associated with acute myocardial ischemia, coronary artery disease, and strokes. In a randomized trial, men with higher C-reactive protein levels who used aspirin had a lower risk of myocardial infarction than those who did not use aspirin (18). Because C-reactive protein is a product of acute-phase reaction, it may not be controlled by posttranscriptional regulation, and it may not measure all relevant effectors of inflammation. IL-6 is the major contributor of acute-phase response by hepatocytes and induces the synthesis of C-reactive protein (19). The combined use of proinflammatory cytokines as a measure of inflammation may provide a better predictor of risk associated with inflammation than would the use of C-reactive protein alone.

As a persistent viral infection of vascular endothelial cells, human CMV is well suited to induce proinflammatory cytokines, which results in inflammation and disease in the elderly. A previous report found a correlation between the carrier status of human CMV, proinflammatory cytokine levels, and nonresponsiveness to an antiinfluenza vaccine in the elderly (20). The elderly human CMV-infected patients had high levels of TNF-α and IL-6 and failed to respond to an antiinfluenza vaccine with protective titers of antibodies against the influenza antigens following vaccination. The authors showed the coexistence of high levels of IL-6 and anti-CMV immunoglobulin G (IgG) and speculated that the high proinflammatory state from a chronic human CMV infection in the elderly resulted in depletion of the immune system and “immune senescence,” with the inability to respond to an antiinfluenza vaccine (20).

The article by Roberts et al. (4) provides important new information on the relation among the immune response to human CMV, levels of proinflammatory cytokines, and all-cause and cardiovascular disease mortality in an elderly Latino population followed for 9 years. The data were derived from a cohort of 1,468 Sacramento Area Latino Study on Aging (SALSA) participants aged 60–101 years followed in 1998–2008. Levels of human CMV IgG, IL-6, TNF-α, and high-sensitivity C-reactive protein were measured from blood draws at baseline. In this sample population, only 54 (3.7%) were seronegative for human CMV. The highest levels of CMV IgG were associated with a high all-cause mortality rate even after adjusting for covariates such as age, gender, education, and baseline health conditions. The participants in the highest quartile of human CMV–IgG antibody titers had 1.43 (95% confidence interval: 1.14, 1.79) times higher all-cause mortality compared with those in the lower quartiles. In fully adjusted models, the risk of cardiovascular disease mortality was elevated as well (hazard ratio = 1.35, 95% confidence interval: 1.01, 1.80). A substantial proportion of the relation between human CMV and mortality was mediated by TNF-α and IL-6 levels, but C-reactive protein was excluded because it was found not to be associated with mortality in this sample. The Kaplan–Meier survival curves suggested significantly worse all-cause and cardiovascular disease survival for individuals in the highest quartiles of CMV IgG antibody titers over the 9 years of follow-up.

The authors (4) claim that this study is the first known to report on the relation between high human CMV antibody levels and mortality in a population-based cohort. The high CMV antibody levels probably reflect more frequent CMV reactivation and higher levels of replication in this elderly population, leading to an increase in the proinflammatory cytokines TNF-α and IL-6 and enhanced vascular damage. The study is well done, the statistical analysis is compelling, and the results support the conclusions. The authors do point out several limitations of their study. They were unable to look at cellular immune markers of CMV infection because peripheral blood mononuclear cells were not available. They
also considered other infectious agents such as *Chlamydia pneumoniae*, *Helicobacter pylori*, and herpes simplex virus as causes of chronic inflammation. They were able to show, however, only that herpes simplex virus-1 exposure was not associated with the mortality they observed. Additional studies to examine the role of these pathogens are needed.

The important research questions concerning CMV remain to be addressed. These questions include defining the cellular immune parameters of CMV infection and the CMV genes that activate these functions. The CMV genes that activate cellular cytokines to accelerate arteriosclerosis and vascular injury also must be defined.

Such studies will add precision to the mechanism of how CMV produces inflammation leading to enhanced vascular injury and mortality. They will also reveal new viral targets for intervention. Improved antiviral drugs against CMV and an effective CMV vaccine remain high priorities to improve the care of immunosuppressed patients and to improve outcomes of CMV infection in the elderly. A controlled trial with intervention by an antiviral drug or an effective vaccine against CMV will be needed to definitively prove that CMV infection in the elderly is a significant cause of cardiovascular disease mortality in the elderly.

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