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Special Theme Issue:

CLASSIC ARTICLES IN HEART TRANSPLANTATION

REVIEW:

Grattan MT, Moreno-Cabral CE, Starnes VA et al. Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis. *JAMA* 1989; 261: 3561-3566.

Cardiac allograft vasculopathy (CAV) remains the Achilles heel of heart transplantation, and it remains the most common indication for re-transplantation (1). Rapidly progressive diffuse intimal proliferation is the characteristic hallmark of CAV, but it may also present as focal stenosis or simply lack of distal vasculature (so-called “angiographic pruning”). Many non-invasive modalities have been studied, but coronary angiography remains the gold standard for diagnosis. Some patients with discrete focal lesions may be treated with percutaneous coronary intervention, but this has not been shown to prolong survival, perhaps because the microvasculature is usually involved at the time of presentation (2). The International Society for Heart and Lung Transplantation has established consensus nomenclature for grading CAV, and this correlates with prognosis (3).

Early and subclinical post transplant endothelial injury and dysfunction are thought to be the inciting events in the development of CAV (4,5). Cytomegalovirus (CMV) infection has been recognized for decades as one of the major endothelial insults associated with development of CAV. The recognition of this clinical association between infection and vascular injury has led to extensive research and practice pattern changes, and therefore management of CMV including risk assessment is part of standard transplant care. Given the importance of CMV, we decided to review the original landmark paper which first reported the association between this ubiquitous virus and CAV (6). The findings in this paper have been validated in a number of subsequent studies (7-9).

In this seminal 1989 paper, Grattan and others evaluated a cohort of 301 patients undergoing orthotopic heart transplantation at Stanford University between December 1980 and October 1988. Of these, 210 patients were CMV naïve (no evidence of prior infection), and 91 patients developed CMV infection (CMV group). The definition of infection (which preceded PCR techniques) was a fourfold rise in the IgG anti-CMV antibody titer, demonstration of typical CMV inclusion bodies in tissue, or positive cultures for the CMV virus. Angiographic disease was classified as mild (< 30% luminal stenosis), moderate (31-69%) or severe (> 69%) and occurred significantly more frequently and earlier in the CMV group. Autopsy data were available in 31 of 41 patients who died in the CMV group and in 49 of 57 patients who died in the non-CMV group. Estimation of the degree of coronary obstruction in each of the major coronary arteries in these autopsy specimens was made using a

segment of the patient's own coronary artery for comparison. These patients were then grouped into those with one or more major coronary arteries showing $\geq 50\%$ obstruction and those with no such obstruction. The CMV cohort had significantly more severe CAV in this autopsy analysis.

The immunosuppression regimen in that era consisted of cyclosporine, azathioprine, prednisone, and antithymocyte globulin (ATG) induction therapy. In terms of CMV therapy, 12 patients in the CMV group received ganciclovir due to life-threatening CMV infection, and 32 patients received it prophylactically.

An important highlight of this study is the description of the heterogeneous clinical presentation of CMV infection related to what we now know to be "characteristic" subclinical or smoldering CMV disease in heart transplant recipients: CMV infection was not localized clinically in 67 of 91 patients in which diagnosis was based only on antibody titer. Forty-five and 22 patients respectively had a titer rise and "CMV syndrome" (fever, malaise, leucopenia and rise in serum transaminase levels). The rest of the patients (24/91) had infection localized to one or more organs. In patients in whom CMV infection was identified after heart transplantation, symptoms related to infection appeared in 44 patients, and 47 were asymptomatic. In terms of pre-transplant CMV status, 58 of the 91 (63.7%) patients in the CMV group were seropositive pre-transplant. Interestingly, the donors' CMV serostatus were not reported in this study. The vast majority of the patients were not treated with ganciclovir, which was quite new at the time and not easily available. Twelve patients were treated for life-threatening CMV infections with a compassionate use indication, and 32 patients were given ganciclovir as prophylaxis in a randomized trial, reported in another landmark publication (10).

Another interesting aspect of this study is the reported rejection rate. Most of the patients were treated for rejection at least once by the end of the first year in both groups; however, rejection was seen more frequently in the CMV group (91%) as compared to the non-CMV patients (84%), $P < 0.05$. This is markedly higher than current reports, and issues such as the lack of standardization of biopsy grading as well as use of azathioprine may explain the high incidence noted in this trial.

The major finding of the study was that "graft atherosclerosis" / CAV occurred more frequently and earlier in the CMV group, with 90% of the patients in the non-CMV group being free of severe angiographic disease as compared to 70% in the CMV group at 5 years after the transplant surgery ($p < 0.05$). CAV was similar in both symptomatic and asymptomatic CMV patients. Perhaps most notable in this paper is the survival difference according to CMV status (Original figure 4). The survival of those patients without CMV was 68.2 % versus the 32.3% 5-year survival in the CMV group. The rate of graft loss, which was defined as death of the patient or re-transplantation, was also significantly greater in the CMV group as compared to the non-CMV group. The most common cause of death in both cohorts was infection, with a higher percentage seen in the CMV group (43.9 vs. 31.6%). The other major causes of death were similar in both groups, with CAV and rejection predominating.

It is noteworthy that 20 years later, CMV continues to be a critically important virus and one that we can suppress but not eradicate. We therefore continue to explore the answers to the question raised in the conclusion of the paper:

"What are the potential mechanisms for an interaction between host infection with a virus, heart allograft rejection, and the development of allograft atherosclerosis? Possible direct mechanisms include a viral mediator of endothelial hyperplasia. Another direct cause could be endothelial cell damage by viruses, leading to ineffective repair and eventual plaque formation."

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