

The spectrum of CMV disease in solid organ transplant recipients

Masoud Mardani*

Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University, M.C., Tehran, Iran

Cytomegalovirus (CMV), a member of the *Betaherpesviridae* family, infects most humans. Epidemiologic studies report a prevalence of anti-CMV immunoglobulin (Ig) G antibody positivity in adults of up to 80% to 90%. Primary CMV infection generally occurs during the first two decades of life either as an asymptomatic infection or as a benign infectious mononucleosis-like syndrome.

Cell mediated immunity and neutralizing antibodies, subsequently develop, but, possibly because of CMV's immune system evasion mechanisms, the cellular and humoral immune responses do not completely eliminate the virus. Like the other members of the human herpesvirus (HHV) family, CMV establishes latency, with intermittent reactivation leading to low levels on viral persistence. This infection occurs predominantly among those with a suboptimal immune response. CMV infection is normally defined as evidence of viral replication regardless of symptoms, whereas CMV disease typically describes the presence of viral replication and associated symptoms, and can occur in the form of a viral syndrome or tissue invasive disease. This infection is particularly challenging to treat and manage among solid organ transplant recipients. CMV appears to have indirect immunomodulatory

effects and may lead to higher rates of bacterial and fungal infections, acute allograft rejection, posttransplant lymphoproliferative disease (PTLD), chronic allograft rejection, and allograft loss. The ideal preventive strategy for CMV infection and disease has yet to be identified, and although treatment of this condition with antiviral agents is often effective, antiviral toxicity and the development of drug-resistant strains can pose significant barriers to long-term success. In this regard, patients and healthcare providers alike can benefit from new insights into the diagnosis, treatment, and management of this virulent infection.

Cytomegalovirus (CMV) is specifically problematic to transplant patients (1). Approximately 40% to 90% of healthy individuals are CMV-seropositive, reflecting exposure to CMV and subsequent development of antibodies against the virus at some point during their lifetime. CMV may be acquired at birth during delivery (via placental or vaginal transmission), or the virus may be transmitted through body fluids, blood, and transplanted stem cells and organs. After initial infection, the virus establishes life-long latency. The reactivation of CMV with progression of CMV infection to clinical disease depends largely on the host's immune status; immunocompromised hosts are more likely to develop clinical disease than immunocompetent hosts, primarily due to impaired cell-mediated immunity.

Received: 15 June 2009 Accepted: 20 June 2009

Reprint or Correspondence: Masoud Mardani, MD.
Infectious Diseases and Tropical Medicine Research Center
Shahid Beheshti University, M.C., Tehran, Iran.

E-mail: mmardani@hotmail.com

CMV viral load is an important predictor of CMV disease; the level of viremia has been directly associated with risk of CMV disease following solid organ transplant (SOT) (2).

The host immune response also plays an important role; patients who are donor seropositive and recipient seronegative (D+/R-) lack both cell-mediated and humoral immunity to CMV and are at highest risk for disease. Clinical studies have demonstrated that both in healthy controls and in renal transplant recipients, CMV-specific T-cell levels strongly correlate with CMV serostatus (3). Recently, cell mediated immune responses have been utilized to help predict CMV infection and disease. In this setting, detectable CMV-specific CD8+ T-cell response is predictive of a low risk of subsequent CMV disease. Innate immunity also likely plays a role in the control of CMV (4).

Three types of CMV infection can develop in SOT recipients: primary infection, reactivation, and superinfection (1). Primary infection is the result of viral transmission from a seropositive donor (D+) to a seronegative recipient (R-) or transmission of latent virus through blood transfusion or through community exposure. Reactivation refers to the reactivation of endogenous latent CMV in a recipient who was seropositive (R+) prior to transplantation. Superinfection describes transmission and reactivation of donor-derived CMV in a seropositive recipient. D+/R- patients are considered to be at highest risk of CMV infection and disease development. Without prophylaxis, approximately 80% to 100% of D+/R- SOT recipients will develop CMV infection. Among these patients, up to 50% to 70% will go on to develop clinical CMV disease. D+/R+ and D-/R+ patients are considered to be at moderate risk of CMV infection, and D-/R- patients have the lowest risk of CMV. Approximately 16% to 21% of moderate-risk SOT patients will develop CMV infection, and this condition rarely occurs in low-risk groups provided

that CMV seronegative or leukodepleted blood products are used (5).

Recipients of certain types of SOT are at increased risk of CMV infection. The highest incidence of this infection is in lung allograft recipients. Pancreas and heart transplant patients are at intermediate risk, and liver and kidney recipients are generally at lower risk, however, significant variation exists based on the type of immunosuppression used. Additionally, the risk of CMV disease is significantly greater in patients receiving highly immunosuppressive therapies (e.g., antithymocyte globulin or OKT3) than in those receiving less potent immunosuppressive therapy.

In the absence of prophylactic therapy, CMV infection typically develops within 3 months of SOT, with a median time to onset of 1 to 2 months (6). Symptoms of CMV disease can range from a viral syndrome to tissue-invasive disease and severe end-organ involvement (e.g., pancreatitis, pneumonitis, hepatitis, myocarditis, nephritis, or gastrointestinal disease) (1). In addition to directly attributable morbidity, CMV may also have an immunomodulatory effect. The indirect effects of active CMV disease can include development of other infectious complications, such as bacteremia, invasive fungal infections (IFI), and Epstein-Barr virus (EBV)-related PTLD (1). Several studies of liver transplant patients have identified CMV infection or disease as an independent risk factor for IFI (7). In these studies, patients who developed IFI had higher 1-year mortality rates than those observed in patients without IFI. Heart, lung, and liver transplant recipients with CMV disease are also at increased risk for invasive aspergillosis infection (8). In patients at high risk of developing PTLD, (D+/R- for EBV), CMV disease has been shown to be an independent predictor of this outcome. Moreover, the risk of developing PTLD is increased by 7.3-fold in those with CMV disease (9).

CMV also appears to be associated with infection or reactivation of HHV-6 and/or HHV-7, although the factors surrounding this relationship have yet to be elucidated (1). Among liver transplants, CMV disease has been associated with elevated CMV, HHV-6, and HHV-7 viral loads. Renal transplant recipients who were coinfecting with both CMV and HHV-7 were found to experience higher rates of CMV disease and HHV-7-associated allograft rejection. Similarly, CMV has also been coupled with poor outcomes when occurring in tandem with hepatitis C virus (HCV) infection. In liver transplant recipients who were infected with HCV, CMV reactivation was independently associated with allograft failure and mortality (10). Again, the factors that contribute to the pathogenesis of HCV and CMV infection have yet to be identified. Additional indirect effects of CMV infection include acute allograft rejection, chronic allograft rejection, and allograft loss (1). Among kidney transplant recipients, both CMV infection and CMV disease have been associated with acute allograft rejection, and CMV disease has been found to predict allograft loss—underscoring the importance of preventing the progression of CMV infection to CMV disease. SOT recipients with CMV infection may also have increased risk of posttransplant diabetes mellitus. CMV infection also appears to facilitate inflammatory processes, leading to endothelial cell damage by alloreactive T cells and chronic allograft rejection (1). Chronic allograft nephropathy, vanishing bile duct syndrome, bronchiolitis obliterans, and accelerated coronary atherosclerosis have been linked to CMV infection in kidney, liver, lung, and heart transplant patients, respectively (1).

REFERENCES

1. McDevitt LM. Etiology and impact of cytomegalovirus disease on solid organ transplant recipients. *Am J Health-Syst Pharm* 2006;63(Suppl 5):S3-S9.
2. Griffiths P, Whitley R, Snyderman D, Singh N, Boeckh M. Contemporary management of cytomegalovirus infection in transplant recipients: guidelines from an IHMF workshop, 2007. *Herpes* 2008;15:4-12.
3. Radha R, Jordan S, Puliyanda D, Bunnapradist S, Petrosyan A, Amet N, et al. Cellular immune responses to cytomegalovirus in renal transplant recipients. *Am J Transplant* 2005;5:110-17.
4. Kijpittayarit S, Eid AJ, Brown RA, Paya CV, Razonable RR. Relationship between Toll-like receptor 2 polymorphism and cytomegalovirus disease after liver transplantation. *Clin Infect Dis* 2007;44:1315-20.
5. Gane E, Saliba F, Valdecasas GJ, O'Grady J, Pescovitz MD, Lyman S, et al. Randomized trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver transplant recipients. The Oral Ganciclovir International Transplantation Group [corrected]. *Lancet* 1997;350(9093):1729-33.
6. Ho M. Advances in understanding cytomegalovirus infection after transplantation. *Transplant Proc* 1994;26(Suppl 1):7-11.
7. Collins LA, Samore MH, Roberts MS, Luzzati R, Jenkins RL, Lewis WD, et al. Risk factors for invasive fungal infections complicating orthotopic liver transplantation. *J Infect Dis* 1994;170:644-52.
8. Munoz P, Rodriguez C, Bouza E, Palomo J, Yañez JF, Dominguez MJ, et al. Risk factors of invasive aspergillosis after heart transplantation: protective role of oral itraconazole prophylaxis. *Am J Transplant* 2004;4:36-43.
9. Hornef MW, Bein G, Fricke L, Steinhoff J, Wagner HJ, Hinderer W, et al. Coincidence of Epstein-Barr virus reactivation, cytomegalovirus infection, and rejection episodes in renal transplant recipients. *Transplantation* 1995;60:474-80.
10. Razonable RR, Burak KW, van Crujisen H, Brown RA, Charlton MR, Smith TF, et al. The pathogenesis of hepatitis C virus is influenced by cytomegalovirus. *Clin Infect Dis* 2002;35:974-81.