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Cytomegalovirus Infection in Organ Transplant Recipients: Diagnosis, Prevention and Treatment

Singh N[1]*, Jain K[2], Rathore V[3] and Chowdhary PK[4]

[1]Department of Microbiology, Pandit Jawahar Lal Nehru Memorial Medical College, India

[2]Department of Community Medicine, Pandit Jawahar Lal Nehru Memorial Medical College, India

[3]Department of Nephrology, All India Institute of Medical Sciences, India

[4]Department of Nephrology, Ramkrishna Care Hospital, India

Review Article

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***Corresponding author:** Dr. Neha Singh, Virology Lab, Department of Microbiology, Pandit Jawahar Lal Nehru Memorial Medical College, Raipur, Chhattisgarh, 492001, India, Tel: +91 9010803331; Email: nehaashishsingh2015@gmail.com

Abstract

The most common infectious complication after first month of solid organ transplants is cytomegalovirus (CMV). Both direct such as viral syndrome, hepatitis, pneumonitis, colitis, etc. and indirect consequences such as rejection, infections by other microorganisms and graft dysfunction, are carried on by the virus. Latent infection, active infection, viral syndrome, and invasive disease are the four types of infection that can emerge due to transmission from the transplanted organ, reactivation of latent infection, or after a primary infection in seronegative individuals. Typically, this syndrome appears 30 to 90 days following transplantation. Several antiviral medications, including acyclovir, valacyclovir, ganciclovir, and valganciclovir, are being used for CMV prophylaxis and therapy. Furthermore, these antiviral medications are toxic and have serious adverse effects, including drug resistance, leukopenia, thrombocytopenia, renal failure, and neuropsychiatric symptoms. We attempted to discuss CMV risk factors, laboratory diagnosis, prevention, treatment and therapeutic in this review study with regard to organ transplantation.

Keywords: Risk Factors; Organ Transplants; Prevention; Diagnosis; Treatment

Introduction

Cytomegalovirus (CMV) is one of the most common opportunistic infections that affect the outcome of solid organ transplantation [1] and is a major cause of morbidity in these patients. CMV is widely distributed in the general population with seroprevalence ranging from 30 to 97% [2,3]. After primary infection, CMV establishes life-long latency. Without some form of prevention, CMV infection primarily occurs in the first 3 months following transplant. Onset may be delayed in patients receiving CMV prophylaxis. The following definitions are commonly used in the Transplant literature and are consistent with the AST recommendations for use in clinical trials [4]:

1. CMV infection: evidence of CMV replication regardless of symptoms (differs from latent CMV).
2. CMV disease: evidence of CMV infection with attributable

symptoms.

CMV disease can be further categorized as either a viral syndrome with fever and/or malaise, leukopenia, thrombocytopenia or as tissue invasive disease (e.g. pneumonitis, hepatitis, retinitis, gastrointestinal disease). In addition, several features unique to pediatric transplantation is discussed separately in this document. CMV has a predilection to invade the allograft, likely in part due to an aberrant immune response within the allograft [5]. To directly attributable morbidity, CMV likely has an immunomodulatory effect, and active CMV infection has been found to be an independent risk factor for the development of other infectious complications, such as bacteremia, invasive fungal disease and EBV-related PTLD [6]. CMV has also been implicated as a cause of acute and chronic allograft injury. There is evidence that CMV may play a crucial role in chronic graft vasculopathy resulting in lesions, such as chronic allograft nephropathy, bronchiolitis obliterans (lung transplant) and accelerated coronary artery disease (heart transplant) [7].

Risk Factors for CMV Infection

Patients undergoing organ transplants who are donor-positive but recipient-seronegative (D+R-), and who lack cellular and humoral immunity to the CMV, are most at risk for developing CMV illness. CMV R+ (D+/R+ or D-/R+) patients have a similar risk of CMV infection as CMV D+/R- patients but are at lower risk of CMV disease. The recipient's total level of immunosuppression, which is based on the immunosuppressive protocol's drug type, dose, timing, and duration, as well as different host characteristics like age, comorbidity, and neutropenia, are additional risk factors for illness. High rates of CMV illness are connected with antilymphocyte antibodies (ALA) as either induction or antirejection medication, such as thymoglobulin [8]. The danger is greatest when ALA therapy is used to treat organ rejection, and CMV infection is discovered three to four times more frequently in these patients than in patients who are not receiving ALA therapy [9]. The risk of CMV is also influenced by the type of transplant. Patients undergoing pancreas, small intestine, and lung transplants or multiorgan transplant are most at risk for developing CMV; recipients of liver and kidney transplants are at lower risk. This could be caused by the transplanted allograft's viral load or immunosuppressive level. Co-infection with closely related viruses like HHV-6 is a very important risk factor for CMV disease [10]. Therefore, it is advised that both donors and recipients undergo pretransplant CMV IgG screening. It is also advised that patients having a CMV D-/R- transplant receive CMV negative blood or leukodepleted blood both before and after the transplant.

Laboratory Detection

The diagnosis of the CMV infection has advanced significantly in recent years. The pp65 antigenemia assay and polymerase chain reaction (PCR), can be utilized for the early detection of CMV viral replication. However, there is a propensity to substitute molecular techniques for the antigenemia assay, particularly in assessing CMV viral replication following transplantation [11-14]. Traditional diagnostic techniques, including culture on human fibroblasts, take up to two weeks to produce a positive result, and even then, they do not necessarily indicate an infection that is actively spreading. As a result, these techniques are useless in clinical practice. The relevance of interferon-gamma release assay (IGRA)-based diagnostics like QuantiFERON and ELISpot in diagnosis and monitoring is not yet clear.

Molecular Techniques

Molecular diagnostic techniques, which can be qualitative or quantitative, can identify DNA or RNA. The majority of these tests have a high sensitivity for CMV detection. The assessment of quantitative CMV-DNA levels has grown in prominence and is recommended by most guidelines. A common assay that can be purchased or developed internally is a PCR test based on plasma or whole blood. Whole blood assays usually contain higher viral loads than plasma assays. There is significant overlap between these groups, although the lowest viral loads are frequently seen with asymptomatic CMV infection and intermediate-range viral loads are typically seen in those with CMV syndrome [15]. The rate of rise of the viral load is as important to take into account as its overall magnitude [16].

Serological Assays

IgM is the first antibody to manifest, and it may stay in the patient's serum for a very long time after the infection. Additionally, this antibody may emerge following reinfection, including infection by other virus strains, proving that IgM positive is not a reliable indicator of a primary or recent CMV infection. After 6 to 8 weeks of infection, the IgG antibody is detectable in the blood and can last indefinitely, though its levels may fluctuate. Because of this, the serological link between the donor and the recipient (D/R) is determined using this antibody. Serology results for the donor should be interpreted as positive if they are ambiguous or inconclusive. Serology should be repeated if there is a long wait before the transplant and the serology was negative during the initial pre-transplant evaluation, especially if the patient got a blood transfusion in the meantime. It's critical to keep in mind that having IgG antibodies does not shield a person from the reactivation of a latent viral infection or from

contracting a new infection with a different virus strain [17]. Immunocompromised individuals' decreased humoral responses make it challenging to evaluate serology in these patients. Additionally, they may have circulating IgG from transfusions or immunoglobulin therapy. CMV IgG/IgM antibody titers should not be used to diagnose active CMV infection or disease in transplant recipients.

Antigenemia Examination

It has been employed to quickly diagnose CMV infection in transplant recipients because it may detect CMV pp65 antigen in infected peripheral blood leucocytes [18]. Although it is more sensitive than viral culture, it may not be clinically useful in leucopenic patients and must process samples quickly for accuracy within 4–6 hours [19]. The antigenemia assay is also used to assess how well an antiviral treatment is working, and its elimination from the blood is regarded as a sign of therapeutic success [20]. The antigenemia assay has the advantages of being able to be done quickly after blood collection and having a quick processing time, allowing for quick results. it does not require even sophisticated and luxurious equipment and can be performed in medium-capacity laboratories.

Histopathology

To confirm tissue-invasive CMV illness, histopathology is employed. However, its invasive nature has limited its use in certain clinical settings. For instance, if the patient's blood has high levels of CMV, a biopsy may not be performed on a patient with gastrointestinal CMV disease. However, tissue invasive disease can occur without viremia. The traditional methods for diagnosing CMV infection/reactivation in biopsied tissues include histopatholgy and immunohistochemistry (IHC) studies to detect CMV intranuclear inclusions, and histopathological identification of virus-infected cells (viral cytopathic effect) on hematoxylineosin (H&E) stained slides [21]. IHC is frequently employed, despite the fact that it may not be the most sensitive approach for identifying CMV. There are currently no set guidelines for ordering IHC. There is considerable disagreement about whether CMV IHC should be routinely conducted on biopsies with moderate and severe inflammation [22].

Cell Culture

Viral culture has low sensitivity and a lengthy turnaround time, but it is highly specific for the detection of CMV [23]. Antigenemia and NAT have thus replaced the use of viral culture for the diagnosis of CMV in the transplant context. Since NAT are yet not fully optimized for these materials, the primary application of culture is the isolation of CMV from tissue specimens.

Immunologic Assays

Studies have attempted to correlate the patient's cellular immunity against CMV as a predictor of risk of developing later CMV disease [24] in addition to serology. In a recent study, the risk of CMV disease after the end of antiviral prophylaxis was connected with an assay that evaluates interferon-gamma levels following in-vitro stimulation in high-risk CMV D+/R- individuals. When compared to individuals with negative and indeterminate results, patients with a positive test had a lower risk of eventual CMV illness (6.4% vs 22.2% vs 58.3%, respectively; P 0.001) [25]. This study confirmed earlier research linking CD8+ T4 cell immunity to CMV infection in high-risk SOT recipients. When comparing patients with a detectable interferon-gamma response to those with a negative response, the incidence of late-onset CMV disease was lower in patients with the positive response (5.3% versus 22.9%, respectively), and the same pattern was seen in the D+/R- subgroup of patients (10% versus 40%) [26]. These results imply that in order to identify individuals who have a high likelihood of acquiring late CMV illness, immunological monitoring may be used in conjunction with viral load measurements. To evaluate the cellular immune response against CMV, numerous other tests have been developed and are being improved [27]. However, these tests need further validation before incorporating into clinical practice. For clinical usage, a CMV-specific T cell immunological competence assay should be accurate, repeatable, quick to run, and robust enough to allow shipping of specimens to specialized referral laboratories.

Prevention and Treatment

The goal of CMV infection prevention is to lower the prevalence of CMV disease and the collateral effects brought on by viral replication [28]. D+/R- patients, those receiving depleting antibodies (ATG), and lung transplant recipients are among the high-risk populations. Prominently, blood transfusions from CMV+ donors may well represent a danger for CMV- patients, who supposed to receive either transfusion from CMV donors or leukocyte-depleted transfusions. There are two strategies to prevent CMV: Universal prophylaxis and Preemptive therapy. Universal prophylaxis is use of antiviral medication to all transplant recipients or a subset of high-risk patients for a period of three to six month post-transplant. Pre-emptive therapy employs monitoring CMV in the blood using quantitative polymerase chain reaction at regular intervals and initiating antivirals when viral replication is detected at a certain threshold. In kidney transplant recipients, prophylactic options include intravenous ganciclovir, oral valganciclovir, and high dosages of oral valacyclovir, according to current guidelines [29]. Oral ganciclovir has been utilized, although some trials have revealed less ideal results. Valganciclovir is

the best medication for prophylaxis since it works well and can be taken orally [30].

Treatment

The most effective medication for treatment is intravenous ganciclovir [31]. Although valganciclovir treatment is an option for mild to moderate infections, intravenous ganciclovir is the treatment of choice for severe infections. Both valacyclovir and acyclovir are not recommended for use in therapy. The weekly monitoring of CMV viral loads determines the appropriate course of therapy; therapy should continue until viral eradication is confirmed in one or more assays after a minimum of two weeks. Reduction in Immunosuppression is an important strategy in the treatment of CMV disease, particularly stopping antimetabolities. Immune-based tests may be useful in the therapeutic setting for directing treatment duration and identifying patients who may benefit from subsequent prophylaxis if their assay results are negative at the end of treatment [32]. High viremia at the start of treatment and CMV recurrence are risk indicators that point to the necessity for extended treatment. Long-term antiviral drug exposure during active viral replication, intensive immunosuppressive therapy, and insufficient antiviral dosages are risk factors for resistance [33]. After two to three weeks of treatment, persistent viral replication, an increase in viral load, the presence of CMV prophylaxis, and/or clinical progression should all raise suspicions of drug resistance [34]. Foscarnet is a different option for treating ganciclovir-resistant CMV, although its use is constrained by frequent side effects, most notably nephrotoxicity [35].

Ganciclovir Resistant CMV Infection

Ganciclovir resistance in CMV has been happening more frequently, albeit it's still rare. Increased morbidity and death in organ transplant patients have been linked to ganciclovir-resistant CMV infection. The frequency is greatest in people who have had lung transplants. The UL97 phosphotransferase and, less frequently, the UL54 DNA polymerase genes are the main alterations in CMV that give treatment resistance. Ganciclovir-triphosphate is the substance in which ganciclovir is active. A viral kinase that is encoded by the UL97 gene performs the initial phosphorylation step. According to the location of the mutation, mutations in UL97 may result in modest or high level resistance to ganciclovir. By inhibiting DNA polymerase, which is encoded by the UL54 gene, competitively, ganciclovir triphosphate stops viral replication. Less often occurring and typically following UL97 mutations are UL54 mutations. Combination UL54-UL97 mutations result in high degree ganciclovir resistance. When resistance is indicated, genomic testing needs to be done. Although cidofovir has occasionally been utilized, the ideal medication for treating high levels of ganciclovir resistance is called foscaret. In the final phases of development for the treatment of CMV, maribavir has the potential to be a safer alternative to DNA polymerase inhibitors. Approaches for adoptive cell therapy and promising CMV vaccine candidates are being assessed. The best technique to apply cellular treatments in the letermovir era is still up for debate.

Conclusion

Despite significant advances in the prevention and management of CMV in organ transplant recipients, CMV remains at large and continues to have significant impact among organ transplant patients. Advances in the field of CMV and organ transplantation will be facilitated by the development of optimized threshold for viral diagnosis, effective vaccines for prevention, diagnostic assays to stratify risk of late onset CMV disease by immunological monitoring, and newer antiviral agents with unique mechanisms of action and ideally with much less toxicity. Major improvements in CMV prevention and therapy for transplant recipients have been done recently. We expect that continuous, meticulous research will further affect our capacity to enhance results for this demographic.

Authors Contributions

Neha Singh: conceptualization, review, visualization, writing – original draft; Kamlesh Jain: conceptualization, data validation, review, editing; Vinay Rathore: validation, writing – review and editing; Prawash Kumar Chauwdary: validation, review, editing.

Conflict of Interest

None

Ethics Statement

Not applicable

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