

Cytomegalovirus infection in non-human immunodeficiency virus-infected patients: a hematologist perspective

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Abstract

Cytomegalovirus is an opportunistic pathogen in immunocompromised patients, particularly those infected with the human immunodeficiency virus. In non-human immunodeficiency virus-infected patients, including patients with hematological malignancies and those undergoing hematopoietic stem cell transplantation, cytomegalovirus infection also leads to significant morbidity and mortality. The high cytomegalovirus seroprevalence in our locality explains the vulnerability of immunocompromised subjects to cytomegalovirus reactivation. Recipients of allogeneic hematopoietic stem cell transplantation and patients treated with certain chemotherapeutic drugs for hematological malignancies are at high risk of cytomegalovirus reactivation. Cytomegalovirus disease is associated with a wide range of clinical manifestations, as almost any organ can be involved. Histopathology remains the gold standard to confirm end-organ cytomegalovirus involvement, although pp65 antigenemia assay and quantitative polymerase chain reaction of viral DNA are useful tools in daily practice. Nevertheless, peripheral blood-based assays may not be positive in patients with cytomegalovirus involving organs including the gastrointestinal tract, brain and eye. Different treatment approaches are used in the

management of cytomegalovirus infection, including prophylactic, preemptive and therapeutic strategies. Ganciclovir and its oral prodrug valganciclovir remain the cornerstone treatment of cytomegalovirus disease, albeit at the risk of increased myelosuppression. Alternatively, foscarnet may be used in cytopenic patients. Clinical vigilance and multidisciplinary collaborations are of paramount importance in the management of cytomegalovirus infection.

Key words: Cytomegalovirus infections; Hematopoietic stem cell transplantation; Immunosuppressive agents; Virus activation

Introduction

Cytomegalovirus (CMV) is a double-stranded DNA virus in the herpesvirus family. The majority of the human populations have been exposed to CMV, as judged by seroprevalence studies. CMV establishes a lifelong latent state in the host once infection has occurred.

Cytomegalovirus infection, reactivation and disease

Primary CMV infection is asymptomatic in immunocompetent individuals, and this is followed by a latent state without active viral replication. In immunocompromised subjects, however, primary CMV

infection may lead to an infectious mononucleosis-like syndrome with atypical lymphocytosis, lymphadenopathy, and widespread organ involvement of the brain, liver, lung and gut; which is potentially fatal. In most instances, clinical problems arise from CMV reactivation in seropositive subjects due to advanced age, or diseases and treatment that result in an immunocompromised state. The latter category includes infection by the human immunodeficiency virus (HIV), autoimmune diseases treated with immunosuppressants and high-dose corticosteroids, cancers treated with chemotherapy, treatment with lymphoablative drugs, and organ transplantations including hematopoietic stem cell transplantation (HSCT). Although reinfection with a CMV strain different from the endogenous latent strain in seropositive subjects is also possible, there is differentiation between endogenous reactivation and exogenous reinfection in clinical practice. Notably, CMV infection/reactivation and CMV disease are not synonymous. CMV infection/reactivation refers to the presence of CMV replication regardless of symptoms. It might allude to CMV DNA- or RNA-emia, CMV antigenemia, or CMV viremia, depending on the detection method used. Conversely, CMV disease is defined as CMV infection/reactivation with presence of clinical signs and symptoms compatible with CMV end-organ damage.¹ Tissue-invasive CMV disease can affect various organs and cause significant morbidity and mortality.

Among cancer patients and those who have undergone HSCT, Asians have been shown to have the highest CMV antigenemia rate and viral burden.² In fact, CMV seroprevalence varies in different populations, being highest in South America, Africa and Asia.³ The seropositive rate of our local population is over 90%.^{4,5} Therefore, the importance of recognizing this disease entity and managing it properly cannot be overemphasized.

Hematological patients at risk

Patients with hematological malignancies are very often immunocompromised, due to the underlying diseases and their treatment. Allogeneic HSCT recipients are at the highest risk of CMV reactivation. Without anti-CMV prophylaxis, about 80% of CMV-seropositive allogeneic HSCT recipients have CMV infection; the incidence of CMV disease in the early post-HSCT period being as high as 35%.⁶⁻⁸ Other risk factors include graft-versus-host disease (GVHD), increased or prolonged courses of immunosuppression, human leukocyte antigen-mismatched or -unrelated HSCT, and administration of T-cell depleting agents.^{7,9} Autologous HSCT recipients are at a lower risk of CMV infection. Because CMV infection is a major post-transplantation complication, different strategies of prophylactic and preemptive therapies have been incorporated into standard HSCT protocols to reduce the risk of CMV disease.

For non-HSCT patients, susceptibility to CMV infection is increased with particular types of drug. Fludarabine, a purine analogue, is a potent suppressor of T cells and increases the risk of opportunistic viral and fungal infections. It is

mainly used to treat patients with chronic lymphocytic leukemia. Rituximab is an anti-CD20 monoclonal antibody widely used in the treatment of B-cell lymphomas.¹⁰ In our population with a high seropositive rate, combination of fludarabine-based chemotherapy regimens with rituximab is associated with a significantly higher risk of CMV retinitis.¹¹ Alemtuzumab is a monoclonal antibody against CD52. It is active against chronic lymphocytic leukemia and other low-grade B- and T-cell lymphoproliferative diseases. As CD52 is expressed on all B-cells and T-cells, treatment with alemtuzumab leads to profound lymphoablation. Hence, alemtuzumab strongly predisposes to CMV reactivation, with reported frequencies varying from 10% to 100%.^{12,13} Therefore, it is recommended that regular virologic surveillance and/or anti-CMV prophylaxis are needed in patients treated with these drugs.^{14,15}

Clinical manifestations of cytomegalovirus infection

CMV infection without any clinical manifestations is specified as 'asymptomatic CMV infection'.¹ Patients with CMV disease, however, have a wide range of clinical manifestations, as almost any organ can be involved. CMV pneumonia is the most serious complication, with a high mortality of >50%.¹⁶ CMV retinitis is sight-threatening and affected patients might present with non-specific, subtle blurring of vision. It is most often associated with HIV infection, and is the most common manifestation of CMV end-organ disease in HIV-infected patients. CMV retinitis is increasingly recognized in hematological patients.¹¹ CMV gastrointestinal disease is becoming more prevalent in recipients of allogeneic HSCT.¹⁷ Because it often overlaps with GVHD, which is itself an important predisposing factor to CMV reactivation, the differentiation between the 2 conditions is challenging. Other rare manifestations of CMV diseases include hepatitis and encephalitis.

Laboratory workup and pitfalls

The diagnosis of CMV infection requires judicious application of laboratory tests in the appropriate clinical contexts. Commonly available tests for the diagnosis of CMV infection involve detection of a component of or the whole virus in blood or other bodily fluid/specimen. These tests include the pp65 antigenemia assay, molecular tests for detection of DNA or mRNA, viral culture and histopathology. The CMV antigenemia assay detects pp65 proteins in CMV-infected peripheral blood leukocytes. It is a semi-quantitative and rapid test, with results generally available the same day. Thus it is the preferred tool for regular surveillance when a preemptive strategy is adopted, and is useful for monitoring treatment response. Yet, it has limited utility in neutropenic patients as an adequate number of polymorphonuclear leukocytes is a prerequisite for the test.¹⁸ Quantification of viral DNA by polymerase chain reaction (PCR) has become more popular, due to its high sensitivity and ability to measure viral load. The burden and the rate of increase of viral load are useful parameters to

assess risks of CMV disease.¹

Histopathology remains the gold standard for diagnosing end-organ CMV disease, although its application is limited by the risk of the invasive diagnostic procedure and availability of other non-invasive methods for documentation of CMV infection in blood. Nevertheless, histopathology is still needed in certain clinical scenarios, for example, to exclude other concomitant pathology or co-pathogens, or when patients do not respond to anti-CMV treatment.

There are 2 major pitfalls in laboratory diagnosis of CMV infection. Firstly, absence of CMV in blood does not exclude CMV disease.¹⁹ It has been well reported that peripheral blood-based CMV assays might be negative in CMV disease affecting various organs, including the gastrointestinal tract, lungs and eyes.^{8,11,16} Circulating pp65 and CMV DNA can remain undetectable even in CMV infection affecting multiple anatomic sites.²⁰ Given the limitations of blood-based CMV assays, clinicians should always be vigilant and maintain a high index of suspicion when managing at-risk patients.

Conversely, it is important to understand that detection of CMV in blood or other body fluid does not necessarily indicate CMV disease. High sensitivity and good negative predictive value of PCR make it a useful test to exclude CMV disease.^{7,8,21} Nevertheless, detection by PCR alone in bodily fluid or biopsy specimen is insufficient for the diagnosis of most CMV end-organ diseases.²² When neurologic symptoms are present, detection of CMV by PCR in cerebrospinal fluid samples is diagnostic of central nervous system involvement. For CMV retinitis, its diagnosis is conventionally based on characteristic retinal lesions, and an ophthalmoscopic examination performed by an experienced ophthalmologist remains indispensable.²²⁻²⁴ PCR-based analysis of ocular fluids serves as a valuable confirmatory tool, as opportunistic infection by other herpesviruses including varicella zoster virus and Epstein-Barr virus may give similar appearance on fundoscopic examination.²⁵ CMV DNA may be detected in the vitreous humour in approximately 80% of CMV retinitis, and a positive result is highly suggestive of the pathogenic role of CMV.²⁶

Management

There are 3 major strategies in the management of CMV infection, namely prophylactic, preemptive and therapeutic.⁹ The prophylactic approach is used in patients at high risk, such as recipients of allogeneic HSCT from unrelated donors and patients prescribed alemtuzumab therapy. Antiviral drugs are routinely administered to at-risk patients without any evidence of CMV reactivation. Preemptive therapy refers to initiation of antivirals when there is evidence of CMV replication in blood, by the presence of CMV pp65 antigen, CMV DNA or mRNA. This strategy is commonly used in standard-risk allogeneic and autologous HSCT recipients. The threshold to initiate antiviral treatment, however, varies across different centers. In patients diagnosed with CMV

end-organ disease, a therapeutic dose of systemic anti-CMV treatment should be commenced.

Antiviral agents

Intravenous ganciclovir remains the first-line agent in the treatment of CMV infection. Induction dose is 5 mg/kg every 12 hours for 2 to 3 weeks, followed by 5 mg/kg/day as maintenance. The duration of therapy depends on the severity of disease and resolution of signs and symptoms. The most significant side-effect of ganciclovir is marrow suppression, and neutropenia can occur in up to 30% of HSCT recipients during ganciclovir treatment. Hence extra caution is needed for ganciclovir therapy in patients with hematological malignancies, with or without prior HSCT. Ganciclovir can also be given as an intravitreal injection, resulting in a high intraocular concentration of the drug. Based on the experience of treating HIV-infected patients, a combination of systemic and intravitreal anti-viral drugs should be used in patients with CMV retinitis.²⁶

Valganciclovir is an alternative to intravenous ganciclovir for the treatment of CMV infection in patients who tolerate oral medication with normal or minimally impaired gastrointestinal absorption. It is an orally available prodrug of ganciclovir, achieving blood concentrations equivalent to intravenous ganciclovir. The usual regimen of valganciclovir for induction therapy is 900 mg twice daily. Similar to ganciclovir, valganciclovir is also myelosuppressive and may lead to profound neutropenia. Both ganciclovir and valganciclovir require dose reduction in patients with impaired renal function.

For patients who cannot tolerate ganciclovir or valganciclovir, particularly those with significant pre-existing cytopenia, the less myelosuppressive but also less-effective drug foscarnet can be used. It is administered intravenously. Nephrotoxicity and electrolyte disturbances are the most important side-effects. It chelates divalent cations, causing hypocalcemia, hypomagnesemia and hypokalemia. Monitoring of renal function and electrolytes is mandatory for patients treated with foscarnet. The recommended regimen is 90 mg/kg every 12 hours.

At the beginning of preemptive treatment, viral load might continue to rise due to replication of virus, underlying immunosuppression and delayed onset of action of the drug.⁹ Unless there is clinical progression to CMV disease, or rapidly rising viral copy numbers, switching of drugs for preemptive therapy earlier than 2 weeks is generally not recommended. In patients unresponsive to or intolerant of ganciclovir and foscarnet, other antivirals such as cidofovir and maribavir can be considered as third-line treatment. The novel antiviral drug letermovir has been shown in a phase II study to provide effective prophylaxis against CMV reactivation in HSCT patients,²⁷ but it is not widely available.

In addition to antiviral therapy, intravenous immunoglobulin is often given to immunocompromised patients with CMV

infection. Reduction in immunosuppressant(s), if any, is strongly recommended. Chemotherapy and/or monoclonal antibodies should also be withheld until CMV infection is under control. Dose reduction or even cessation of therapy will have to be considered, especially in severe/refractory cases.

Conclusion

CMV infection is increasingly recognized in non-HIV subjects. CMV retinitis, once considered exceptionally rare outside the clinical context of HIV infection and organ allografting, can be found in hematological patients,

particularly those prescribed potent chemotherapy or lymphoablative monoclonal antibodies. As CMV infection can involve different organs, a multidisciplinary approach to its management is essential. Goal-directed investigations with appropriate microbiological workup depend on which organs are affected. Systemic antiviral drugs are warranted in the treatment of CMV disease. As such, clinicians from different disciplines should be familiar with their toxicity profile.

Declaration

All authors have disclosed no conflicts of interest.

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