Introduction

Cytomegalovirus (CMV) is the most prevalent viral diseases globally [1], with an estimated positive infection rate of 80% to 90% of the US population [2,3]. CMV is a ubiquitous DNA virus belonging to the β-herpes virus family that causes severe disease with high morbidity and mortality in immunocompromised patients, and is the predominant infectious cause of congenital birth defects [4,5]. Most patients are infected early in life, which results in a lifelong latent infection [5]. The immune system can tolerate the viral infection but cannot eradicate the virus [6]. The public health annual burden in the US alone for CMV infection and co-infection was estimated to exceed $4.4 billion [7]. CMV shedding is persistent during the latent infection in multiple body fluids (blood, saliva, tears, urine, genital secretions, and breast milk). Active CMV replication and to some extent gene expression [8] occurs continuously as indicated by the frequency of CMV shedding[9], kinetics of reactivation after transplantation (immune suppression) [10], and the CMV-specific T cell response [11,12]. The persistent CMV latent infection together with the frequent immune system stimulation, which leads to a low grade inflammatory response may contribute or involved in the development of chronic diseases, such as atherosclerosis, restenosis and transplant vascular sclerosis [13]. CMV is genetically diverse large virus with more than 200 open reading frame producing effector proteins [14], of which, one-quarter is committed to replication [15,16]. Hence, the majority of viral proteins may potentially alter the host cellular responses; of all herpes viruses, CMV expresses the most genes that alter innate and adaptive host immune responses [17]. Several regions of the CMV genome are used to genotype the virus based on clustering of polymorphism. Frequently, mixed infection with multiple CMV strains occurs in various patient populations including both immune-competent and immunocompromised subjects [18-23]. In Congenital CMV infection, there is strain diversity and infection with multiple CMV strains occurs in congenital CMV infection. Neither, the pathogenesis nor the long-term effect of specific or co-infecting genotypes is currently known [24]. CMV genome is composed of linear, double-stranded DNA, surrounded by a matrix protein lining containing phosphoproteins, which causes the dysregulation of the host’s cell cycle. The protein lining is enveloped by several glycoproteins that are necessary for the virus’s infectivity, including entrance to the host cell, cell-to-cell dissemination and maturation [25]. The fusion between the virus and the cell is mediated by the viral glycoprotein [25,26], which is followed by the entrance of the nucleocapsid and protein lining of the host cell cytoplasm. The nuclei are translocated, an infection marker that may be detected in serum within an hour. Many host cells act as the main reservoirs of CMV, which includes the monocytes, fibroblasts, myeloid cells, epithelial and endothelial cells [25]. Endothelial cells and macrophages play an important role in latency and seem to be critical for maintaining CMV in the host [27]. After cell infection, viral replication begins within 12-24 hours, with the cytopathic effect seen in-vitro after 7-14 days [28]. Through inhibiting RNA formation, CMV has the ability of thwarting its host’s immune response, by preventing antigen presentation mechanism and blocking apoptosis [21]. These mechanisms may lead to reactivation of a latent infection, often seen in transplant patients [29]. Currently, there are three forms of active CMV infection: a) primary infection, when the virus infects a CMV-naïve subject; b) endogenous infection in CMV-seropositive individuals who undergo reactivation from latency, and c) exogenous reinfection in previously infected individuals who acquire infection by a different strain [30]. Either active or latent CMV infection induces sustained systemic inflammatory responses that are accompanied by a type 1 cytokine signature [31]. Viral persistence is established in all infected individuals and is chronically productive or occurs as a latent infection in
which viral gene expression is limited [3]. CMV reactivation can also occur as a result of elevated Tumor necrosis factor-α (TNF-α) [32]. Furthermore, CMV reactivation through cyclic-AMP also occurs as a result of proinflammatory prostaglandins and/or stress catecholamine’s stimulation [33,34]. Cells of the myeloid lineage are also potent carriers of latent CMV [35,36]. CMV can reanimate from latency by allogeneic stimulation of monocytes from seropositive donors [37].

CMV/ EBV Co-infection

Both CMV and Epstein-Barr virus (EBV) infection causes infectious mononucleosis (IM) characterized by fever, pharyngitis and lymphadenopathy [1]. Each virus shares the ability to persist in latent form after primary infection [1,38] with the ability to reactivation later under immunosuppression conditions. EBV is the most common cause of IM, but primary CMV infection will cause up to 7% of IM cases with almost indistinguishable symptoms [39]. Co-infection with CMV and EBV occurs occasionally in children [40,41]. EBV/CMV can infect immuno competent patients simultaneously with other agents including respiratory syncytial virus (RSV). Chlamydia pneumoniae (CP), human herpes virus 6 or 7, measles virus and others [40,42-46], and it has been reported that EBV/CMV-immune-competent infected children suffers from mixed infections with other agents [44,46].

Children who show both EBV and CMV primary infection are typically presented with the typical manifestations of IM together with high occurrence of hepatomegaly (57.1%), splenomegaly (57.1%) and liver function abnormalities (80.0%). The co-infection rate with other pathogens is high as 100%, and the prevalence of multi-pathogen infection is 80%, which is higher than that of the children with a single EBV or CMV infection [47]. EBV and CMV co-infection could have synergistic influence on allergen-specific B-cell responses and NK-cell cytokine production [48,49]. EBV and CMV co-infection in children also increases the frequencies of differentiated NKG2C+ and CD57-NKG2C+ NK-cell subsets through unknown mechanism. Weather EBV and CMV co-infection leads to a more pathological consequences or synergistic effect on the subject long term heath, remains to be elucidated. Research on multiple infections accompanying EBV/CMV infection is relatively rare, and warrant more extensive immunological investigations.

CMV co-infection with upper respiratory tract viruses

Common RNA and DNA viruses that usually causes self-limited upper respiratory tract infections in immuno competent adults is known as Community respiratory viruses (CRV) [50]. However, CRV infections in the immunocompromised patient, often involves the lower respiratory tract and are associated with significant morbidity and mortality [51]. The immunopathological mechanisms of respiratory viral infections remain to be investigated. In normal hosts, Paramyxoviruses (RSV) primarily infect airway epithelial cells, with subsequent immune responses that may lead to either resolution or chronic airways disease [52]. RSV infection of respiratory epithelial cells induces toll-like receptor (TLR4), which is a potent activator of T-helper 1 (Th1), which leads to interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin-2 (IL-2) production, as well as cytolytic T cell responses that are responsible for the resolution of the infection [53]. Influenza viruses infection result in a toll-like receptor 3 (TLR3) mediated innate immune response, activation of CD8+, and induction of IFN-γ and TNF-α [54]. Regulation of this response to limit lung injury is complex due to the attenuation of lung inflammation that is dependent on IL-10 production by CD8+ T lymphocytes, or development of a protective Th17 response in IL-10 deficient hosts that enhances survival after influenza infection [55,56]. The immunopathogenesis of CMV infection is highly complex as it engages both the innate and adaptive immunity, in addition to humoral immunity from B cells and plasma cells [56]. In immunocompromised patients or lung transplant recipient, where immunosupression is intense will limit the memory T cell immune responses that are important for optimal CMV immune control [57]. Investigational studies of CMV and other upper respiratory virus’s co-infection are rare, and warrant more studies.

CMV/HHV6, 7 Co-infection

Human herpesvirus6 (HHV-6) is a frequently detectable pathogen after transplantation [58,59], and is considered as a cofactor for increased CMV replication in the blood [60]. HHV-6 DNA is detected in the epithelial lining fluid (BAL) of the lung transplant recipient (LTRs) at lower frequencies and concentrations than CMV or EBV and only in a limited part of the samples in co-infection with the other herpes viruses. But so far a possible pathogenic role of HHV-6 or CMV/HHV-6 co-infection in LTRs is unknown [61]. Active co-infection with CMV and HHV-7 in immunocompetent patients resulted in the development of encephaloradiculomyelitis, indicating infection of the central and peripheral nervous systems, caused by CMV and HHV7 [62]. Such viral co-infection has only been described in immunocompromised patients with CMV disease, in which HHV-7 was presumed to be to a cofactor, enhancing clinical manifestations. The actual immunopathological mechanisms involved are unknown [63]. Primary infection is uncommon in solid organ transplant adult recipients, but reactivation of endogenous latent viruses occur very frequently [64]. The indirect effect of these viruses appears to be an interaction with CMV that may promote replication and persistence of the latter virus [65]. The cause of such interactions is unknown, but may be due to cytokine dysregulation induced by viral gene products or due to more direct effects of viral co-infection within a single cell [64].

CMV/HSV Co-infection

The majority of infections with herpes simplex virus (HSV) and CMV are clinically mild or even asymptomatic, primary infection in the fetal and perinatal periods can be neurologically devastating or fatal [66]. HSV generally infects a limited number of cell types, including mucosal and cutaneous epithelial cells and neurons, and may be clinically silent or cause ulcerative lesions. Spread of the virus to other tissues is associated with an inability of the immune system to limit viral replication to the mucosa, and
latent infection is largely restricted to neurons [67]. While CMV and HSV infections were critically reviewed, no data are available for the CMV/HSV co-infections [68].

CMV/TB Co-infection

*Mycobacterium tuberculosis* (TB) infection is second to HIV as an infectious cause of death globally and is still one of the life-threatening infections worldwide among renal transplants, because of their chronic immunosuppression, often with delayed diagnosis [69-71]. The incidence of both multidrug-resistant and extensively drug-resistant TB continues to rise [72]. Inhalation of infectious droplets expectorated by a patient with active pulmonary disease starts the life cycle of TB. The immune response to TB infection is mainly based on the matrix metalloproteinases (MMP) derived from the monocytes and leukocytes (infected or influxed to the lungs). Despite the wide spread of CMV infections and its hampering consequences of the immune system, little work has been done to identify the immunopathological relation in CMV and TB co-infection. Some TB patients will develop TB meningitis (TBM). The immune response within the brain is poorly understood or explored [73]. In TBM, CSF shows increased levels of inflammatory mediators, including TNF, IFN-g, IL-8, IL-10, MMPs, and their corresponding tissue inhibitors, the exact role of those cytokines remains to be clarified. TB is more common in allograft recipients than the general population. CMV infection is common post transplantation, and may predispose the patients to secondary bacterial or fungal infections. However, simultaneous co-infection is rare in allograft recipients and often makes diagnosis difficult [74,75].

CMV/HCV Co-infection

Chronic hepatitis C virus (HCV) infection leads to exhaustion and death of HCV-specific T-cells, but also causes defects in the overall immune defense [76]. This notion is supported by the fact that peripheral dendritic and naïve CD4+ T-cells are reduced both in number and function in individuals with chronic HCV [77,78]. Peripheral CD4+ T-cell numbers are also reduced in patients with HCV-associated cirrhosis. Therefore, chronic HCV infection will affect the immune response against CMV in a similar fashion to that seen with age and HIV infection [79]. In liver transplant patients and those receiving HCV antiviral therapy the association of HCV with CMV pathogenesis is documented [80,81]. Post-transplantation, CMV is well documented to be a potential threat to renal transplant recipients and is a significant cause of morbidity and mortality [82,83]. Also, it is well established that CMV infection facilitates renal allograft rejection and may result in a varied spectrum of diseases ranging from respiratory tract to gastrointestinal diseases, retinitis, myelosuppression and neurological involvement [15]. In addition, CMV pneumonitis in renal transplant patients is a well-known complication with high mortality and morbidity rates [84]. Immune suppression and aggravation of other viral diseases is a consequence of CMV infection. CMV infection enhances HCV pathogenesis by preventing the normal mechanisms responsible for HCV clearance, thus playing vital role in HCV persistence and pathogenicity [85].

CMV/HIV Co-infection

CMV and human immunodeficiency virus (HIV) share common features, including route of transmission, immunosuppression, and the negative impact on the immune system [1]. Co-infection with both viruses is common, with serious complications. The genito-urinary tract is known to support both HIV and CMV replication [86]. Levels of CMV DNA in semen are correlated with the number and activation state of CD4+ T-lymphocytes found in the same compartment [87]. CMV DNA viral load detected in semen correlates positively with the semen HIV-1 viral load. CMV replication in the male genital tract may lead to local immune activation and enhanced HIV-1 replication. Therefore, the connections between CMV and HIV-1 are likely important [88]. In CMV infected patients, there is an increased CMV-specific CD8+ T-cell responses once HIV infection has been established, even before the loss of peripheral CD4+ T cells [89,90]. CMV also induces a proinflammatory state in the genital tract that activates HIV-1 and that anti retrovirus therapy (ART) does not have an impact on this interaction [91]. CMV IgG may be associated with increased carotid artery stiffness and carotid artery lesions in HIV-infected women, with those on effective antiretroviral therapy may be at higher risk to develop vascular lesions in association with CMV co-infection [92]. CMV co-infection is highly prevalent in HIV patients at a rate of 75% and 90% [93,94]. Unfortunately, many areas of HIV research have not taken in consideration the effect or the impact of CMV co-infection on the immunopathology of HIV infection as evident in the literature.

CMV/Other Pathogen Co-infection

CMV co-infections with other pathogens or in association with other inflammatory disorders is poorly understood, as most of the information available relied on case reports or smaller studies [95,96].

Conclusion

The strength of the humoral and cellular immune responses depends on interaction of viruses that are present during co-infections of the host. CMV is one of the most prevalent infectious viruses worldwide, which infects a wide range of cell types and establishes a life-long, persistent infection. CMV infection, latent or active is a major health risk with huge public health burden. The lack of current treatment and reliable vaccine highlight the urgent need to focus more research resources, and emphasis the importance of considering CMV status in clinical assessment. The pathophysiological and immunopathological effects of CMV co-infections are still to a large extent speculative especially with the emerging new viruses. Additional research is need because CMV co-infections increase the morbidity and mortality of patients.

Most of the work done to date, did not take in account the effect of the genetic makeup of the hosts in relation to the different virus stains. We are not aware of any laboratory studies that addressed the CMV co-infection and established the relationship between CMV and other pathogen infections. Future efforts are needed to explain and characterize the pathological effects of CMV co-infection. Whether CMV would change, inhibit,
or promote the other pathogen course of infection, is the current question to be answered, as it will have many implications on the patient treatment and outcomes. With the advances in anti-viral technology and genetics, future efforts should be directed toward the eradication of the silent viruses such as CMV or EBV.

References


Immunopathology of CMV Co-Infection: Review


