1. INTRODUCTION

The cytomegaloviruses are ubiquitous pathogens that commonly infect animals and humans (1–3). Their classification is based on the biological properties of host specificity, length of replication cycle, and the cytopathic effects (4). The genera Cytomegalovirus (human cytomegalovirus; HCMV) together with the genera Muromegalovirus (murine cytomegalovirus) belong to the subfamily Betaherpesvirinae of the family Herpesviridae. A nonexclusive characteristic of the subfamily Betaherpesvirinae is a restricted host range. Their reproductive cycle is prolonged, with the infection progressing slowly in culture (4).

Also known as betaherpesviruses, the human cytomegaloviruses (CMVs) are highly species-specific both for replication and pathogenesis. Whereas some host cells are more susceptible to infection, others do not succumb to the virus but may play an important role in harboring the pathogen. The latter may persist for longer periods of time, after which it may establish latency. It is likely that the thousands of genetically different strains of HCMV currently in existence, circulate in the general population throughout the world (5). Humans are believed to be the only reservoir for HCMV. Cytomegalovirus infection is acquired throughout life with over 50% of adult population being infected by 50 years of age. Although neonatal HCMV infections can be severe, in healthy populations the disease is usually asymptomatic. Transmission is carried out by direct or indirect person-to-person contact (2,6). Among the various sources of infection, oropharyngeal secretions, cervical and vaginal excretions, spermatic fluids, urine, feces, breast milk, tears, and blood are predominant (7–9). Oral and respiratory spread appear to be the primary routes of transmission during childhood and possibly adulthood. Multiple or large quantities of blood transfusion also convey a greater risk of both primary and recurrent HCMV infections (2).

Infection with HCMV may be acquired throughout the year and does not appear to be seasonal or dependent on climate (10).

HCMV infection in immunocompetent hosts (11,12) usually is benign and asymptomatic, although occasionally it may be associated with a heterophile-negative mononucleosis syndrome. In both cases there may be shedding of virus in urine and oral secretions for several months to several years after the primary infection (13).

After primary infection, HCMV remains latent in the cells. However, similarly to other herpesviruses, HCMV can reactivate in immunosuppressed hosts. The primary HCMV infection is frequently followed by persistent and/or recurrent infections. Although most often recurrent infections result from latent viral reactivation, reinfection may also occur possibly because of the antigenic diversity of the cytomegaloviruses (2,14).
In severe disseminated disease, evidence of HCMV presence can be seen in virtually all organs, (2,15–18), but ductal epithelial cells are the major site of involvement. In infants and young children, salivary glands are most frequently affected (16,18). Viruria resulting from renal infection is consistently observed in all age groups. The lungs are another organ affected by HCMV, especially in immunosuppressed older patients and bone marrow and lung transplant recipients (19).

Other organs, although less frequently involved in HCMV infection, include the adrenals, ovaries, bones, pancreas, and the skin (2,15). Gisserot et al. (20) have described HCMV infection of the submandibular gland in an HIV-infected patient. A case was also presented of an immunocompromised patient with a locally advanced hypopharyngeal carcinoma who developed a severe cytomegalovirus colitis after his first chemotherapy course with 5-fluorouracil (5-FC), decetaxel, and cisplatin (21).

It is noteworthy to mention that the term “recurrent infection” is generally used to refer to intermittent excretion of virus from single or multiple sites over a prolonged period of time, and should be differentiated from “chronic” or “prolonged excretion” of virus that characterizes certain forms of HCMV infection (2).

The most common clinical manifestations of HCMV infection in immunocompromised hosts include chorioretinitis, gastrointestional disorders (esophagitis, colitis, cholangitis), Central Nervous Systems (CNS) infection, pneumonitis, and adrenal gland disease. Addison’s disease as an unusual manifestation of HCMV-end organ disease in pediatric AIDS has also been reported (22).

2. HCMV INFECTION IN IMMUNOCOMPROMISED HOSTS

HCMV has long been considered to be an immunosuppressive agent capable of inhibiting the host immune response and contributing to the persistence of infection (23). In a symptomatic primary HCMV infection, the cell-mediated immunity is depressed with T-cell abnormalities most readily defined (24). Consequently, the likelihood of CMV infections is markedly increased in the immunocompromised host (25–30). By some accounts (27) between 46 and 80% of the immunocompromised population may be infected. In renal allograft recipients (31–39) the primary infections varies from 22%–100% (average 53%) and recurrent infections from 46%–100% (average 85%). Similar rates of infections have been seen among cardiac and bone marrow transplant recipients (2,40–43). HCMV is the most commonly isolated opportunistic pathogen associated with hepatitis following orthotopic liver transplantation (44–50). HCMV infection is also a major cause of morbidity following lung transplantation (51).

Although HCMV infection is frequently observed in allograft recipients, not all infected individuals will develop disease. In solid organ-transplant recipients, HCMV infection develops largely when a seropositive organ containing the virus is transplanted into a recipient (44,45). If the recipient has a pre-existing immunity against HCMV, this can partially ameliorate the disease (35,52). However, in bone marrow allograft recipients, HCMV infection usually ensues from reactivation of latent infection in the recipient (53).

The fact that after renal transplantation, most patients become productively infected indicates frequent reactivation of latent HCMV (24,54). Reactivation occurs despite of the serologic status of donors.

Owing to the high rate of seropositivity (90–100%) among AIDS patients, HCMV was originally thought by some to be the etiologic agent of AIDS (25,26). Approximately 40% of patients with AIDS present with HCMV visceral involvement at the advanced stage of the disease (55,56). The most common localizations are retinitis and gastrointestinal infection (57) and to a lesser extent CNS disorders. When compared to HCMV infection in non-human immunodeficiency virus (HIV) immunosuppressed patients, retinitis in HIV-positive individuals is much more prevalent than pneumonitis. To this end, despite the presence of HCMV in the lungs, Millar et al. (58) found no evidence of HCMV-induced pneumonitis in AIDS patients, presumably owing to the inability of the lungs to