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Review

The Advent Of Cytomegalovirus Infection In HIV Infected Patients – A review

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Abstract
Cytomegalovirus is considered as one among the long list of latent infections in humans that although normally controlled by the cellular immune response, gets activated after HIV infection takes its role on infecting the T4 lymphocytes. Clinical disease due to Cytomegalovirus has been recognized in up to 40% of patients with advanced HIV disease. The clinical syndromes most commonly associated include chorioretinitis, esophagitis, colitis, pneumonitis, adrenalitis and neurological disorders. Cytomegalovirus infections are usually diagnosed clinically and by serological tests for CMV immunoglobulin. Chemotherapy using systemic agents, including ganciclovir, intravenous foscarnet and intravenous cidofovir is effective. New agents, as for example an anti-sense agent against cytomegalovirus, appear promising.

Keywords: Cytomegalovirus infection, Human immunodeficiency virus, CMV colitis, CMV retinitis, AIDS.

Key Messages:
Cytomegalovirus is contracted from close personal contact with persons who excrete the virus in their bodily fluids, hence CMV infection is one among the major cause of secondary infections in patients with AIDS.

Introduction

Cytomegaloviruses (CMVs) are ubiquitous beta herpes viruses that infect animals as well as humans. Primary infection with CMV is followed by persistence of the virus in a latent form.

Later during life, the virus can reactivate, thus resulting in development of disease.(1) CMV has been found as a major cause of morbidity and mortality in patients with acquired immune deficiency syndrome (AIDS).(2) Cytomegalovirus infection is one of a long list of latent human infections that, although controlled by the cellular immune response, is activated after human immunodeficiency virus takes its role on the T4 lymphocytes.(3) Epidemiological studies suggest that since 1992 nearly half of HIV infected patients eventually develop CMV as an end-organ disease with its most prominent manifestations being chorioretinitis, oesophagitis, colitis, pneumonitis and central nervous system disease.(4) The introduction of highly active antiretroviral therapy (HAART) has dramatically improved prognosis for patients infected with HIV and has had a profound impact on the incidence of CMV disease.(5) The diagnosis of CMV disease can be based on clinical evaluation (eg, CMV retinitis) but often requires tissue biopsy with histologic evidence of viral inclusions and inflammation (eg, CMV colitis).(6) Significant progress has been made in the last few years in detecting CMV antigens or nucleic acids in tissue specimen, CMV culture of blood, urine or even biopsy tissue which may

reflect active infection rather than end-organ disease. The most sensitive molecular amplification methods such as polymerase chain reaction (PCR) are also be employed in the diagnosis of CMV. Ganciclovir, foscarnet and cidofovir are the most commonly used antivirotics and new agents against CMV like the anti-sense oligonuleotides appear promising.

Epidemiology:

CMV is the major cause of infectious mononucleosis in the general population and an important pathogen in immunocompromised hosts, including patients with AIDS, neonates and transplant recipients. The risk of exposure to CMV increases with age and serologic evidence of prior infection can be detected.(7) The incidence of CMV infection among patients with advanced HIV disease is high (2) and CMV is a major cause of morbidity and mortality in this group.(8) CMV infects both vertically and horizontally; by either routes during primary infection, reinfection or reactivation. CMV is frequently shed in saliva, semen and cervicovaginal secretions in the absence of symptoms, allowing infected individuals to transmit to the community.(9)

The current incidence of CMV disease in HIV patients is approximately 3-5 patients-years in the United States (10) and between 1 and 3.5 patient-years in France.(11) Moreover, the incidence of relapse in patients with previous history of CMV disease has also decreased dramatically.(12) CMV infection is more prevalent in populations at risk for HIV infection, approximately 75% of injection drug users and greater than 90% of homosexual men who are infected with HIV have detectable levels of IgG antibodies to CMV.(13) In addition high prevalence rates of CMV IgM antibody in longstanding CMV-seropositive homosexual men suggest that this group is frequently re-exposed to different exogenous strains of CMV.(14) Despite the high prevalence of CMV antibody in HIV infection, the clinical manifestations of CMV disease do not generally present until the CD4 count drops below 100 CD4 cells/mm^3.(15)

Clinical manifestations of CMV in patients with AIDS

Chorioretinitis

Chorioretinitis most commonly occurs in patients with CD4 lymphocyte counts below 50 cells/mm^3 and accounts for 80% to 90% of CMV disease in patients with AIDS.(16) Patients may present with symptoms of blurred vision, a scotoma or dark area covering part of the visual field, light flashes or floaters. However, a significant percentage of infected patients are often asymptomatic despite the presence of extensive or vision threatening CMV retinitis. In a study, fewer than 50% of AIDS patients with CMV retinitis had visual symptoms.(17) Untreated, CMV retinitis leads to the progressive disease that spreads through out the entire retina causing total retinal destruction and blindness. CMV retinopathy is an index disease for AIDS; only approximately 2% of patients with AIDS have CMV retinopathy as the first and only manifestation of the syndrome.(18)

The widespread introduction of HAART in the developed world has resulted in a dramatic decline both in incidence of opportunistic infections and in death rates from AIDS.(10) The incidence of CMV disease has decreased in line with other AIDS-defining diagnosis. The poor prognosis previously associated with the development of CMV retinitis has improved dramatically following the introduction of HAART.(5) In a study of eleven patients at the Royal Free Hospital who started HAART following CMV retinitis showed survival times of up to 5 years (median 43.5 months).(19) In comparison, the median survival time following CMV retinitis at the same hospital before the introduction of HAART was 7.8 months. In addition, the risk of disease progression is reduced markedly by successful HAART, although this effect may be delayed for up to 6 months in some individuals.(20)

Gastrointestinal infection:

Gastrointestinal involvement of CMV may present as either involvement of the upper and/or lower gastrointestinal tract. CMV colitis occurs in 5 – 10% of patients with AIDS and is often difficult to distinguish from other infections of the lower gastrointestinal tract.(21) Diarrhea, abdominal pain, fever, weight loss and anorexia are frequently present. Extensive gastrointestinal hemorrhage and perforation can also occur. The radiographic manifestation of CMV colitis is nonspecific and may mimic the findings of other inflammatory bowel conditions, including ulcerative colitis. (22)

Esophagitis in patients with AIDS is most commonly due to either *Candida albicans* or Herpes simplex virus, but may also be caused by CMV.(23) Patients with CMV esophagitis often have pain on swallowing in association with large distal ulceration. CMV gastritis may also occur and may be signified by severe, continuous epigastric pain. CMV hepatitis is seen in one-third to one-half of patients with AIDS who have evidence of CMV infection in other organs.(3) Pancreatitis in HIV-infected patients is noted to be increasing in frequency. CMV has been found to be the most common viral agent associated with this condition.(24) The presentation is similar to other forms of pancreatitis, i.e., abdominal pain, nausea, vomiting, cachexia, abdominal tenderness and hypoactive bowel sounds. However, some of these patients may have only mild increase in amylase and a marked increase in lipase.(25)

Pneumonitis

CMV causes a syndrome of intestinal pneumonia in patients with AIDS. Patients often complain of gradually worsening shortness of breath, dyspnea on exertion and a dry, nonproductive cough. CMV frequently can be isolated from the pulmonary secretions or lung tissue obtained during bronchoscopy of patients with advanced HIV disease, but only rarely in CMV pneumonia in AIDS patients. Many patients with pulmonary disease in whom CMV has been isolated are infected with other pathogens, especially *Pneumocystis carinii*.(3) Murray et al. studied a large group of AIDS patients with active symptomatic pneumonitis. 17% were found to have CMV by culture.(26) Two-third of these, however had coexistence of *Pneumocystis carinii* pneumonia (PCP) and only 4% had CMV as sole pulmonary pathogen.(27)

Central nervous system infection

CMV disease in the central nervous system has been found in 25% of persons with HIV infection, which was detected during autopsy.(28) A distinct neurologic syndrome caused by CMV in patients with AIDS is a syndrome of myeloradiculopathy characterized by lower extremity pain and weakness, spasticity, areflexia, urinary retention and hypoaesthesia.(29) Subacute encephalitis in conjunction with isolation of CMV from brain tissue or CSF has been reported. Clinical manifestations of CMV encephalitis in patients with AIDS are comparable to subacute encephalitis from other pathogens. Personality changes, difficulty in concentration, headaches and somnolence are frequently present.(30) Polyradiculoneuritis due to CMV has been recently identified as a progressive polyradiculoneuropathy associated with distinct cerebrospinal fluid abnormalities, including a predominantly polymorphonuclear pleocytosis and hypoglycorrhachia.(29)

Diagnostic methods for CMV disease

Diagnostic methods for CMV infection and CMV-associated disease include isolation of the virus by culture, histology of biopsies, serological methods, measurement of pp65 antigen in leukocytes and detection of viral DNA using molecular methods, particularly the PCR.(31) Detection of antigen pp65 in peripheral blood polymorphonuclear leukocytes and PCR (32) are useful in predicting development of CMV disease up to several months prior to clinical disease. Quantitative plasma CMV DNA has high sensitivity (89%) and good specificity (75%) for predicting development of CMV disease; pp65 antigenemia uses monoclonal antibodies against a lower-matrix phosphoprotein (pp65) of the CMV.(33) The PCR test has detected CMV DNA a median of 46 days before the onset of disease; this is earlier than 34 days median time for antigenemia test and a median of 1 day for CMV blood cultures. Multivariate analysis shows that the PCR method is superior to other tests (odds ratio: CMV PCR 10.0, antigenemia test 4.4 and CMV cultures 4.3).(34) In one study, the results of culturing CMV from plasma and urine was compared with that of determining the plasma PCR in 99 patients and it was found that the plasma PCR was superior to culture for identification of AIDS patients at risk for CMV disease, and that quantitation of plasma DNA further identified high-risk persons.(35) Branched DNA signal amplification for CMV viral load is being developed. Earlier results show that it can quantify CMV very accurately, but lacks sensitivity in the lower range.(36)

The Enzyme Linked Immunosorbent Assay (ELISA) is the most commonly available serologic test for measuring antibody to CMV. This recombinant antigen micro titer ELISA is more sensitive than a viral antigen micro titer ELISA and was able to detect the presence of CMV- specific IgM in response to CMV disease, before the detection of viral proteins by the pp65 antigenemia assay in some patients.(37) Serum IgM to CMV infection can be revealed by a variety of different tests, but the most widely used is the ELISA.(38)

Diagnosis of CMV retinitis is usually based on its distinct clinical appearance of retinal necrosis. This most commonly manifests as a whitish opacification of the retina with exudates and variable amounts of hemorrhage. The appearance of this lesion may vary depending upon the localization and rate of disease progression.(39) The presence of positive blood cultures for CMV is neither necessary nor sufficient to make a diagnosis of CMV retinitis. In a study, although all 24 patients had positive urine cultures for CMV at the time of diagnosis of CMV retinitis, only 15 out of 24 (63%) had positive blood cultures.(15) The diagnosis of CMV esophagitis is made from the histopathological evidence of CMV with an inflammatory response in the appropriate clinical setting. The presence of extensive, large, shallow mucosal ulcers in the distal esophagus is the classical sign of the disease.(40) The radiographic manifestation of CMV colitis is nonspecific and may mimic the findings of other inflammatory bowel conditions, including ulcerative colitis.(22) Evaluation in this group of patients should also include flexible sigmoidoscopy or colonoscopy with biopsy and culture. Although CMV involvement of the liver and biliary tract is often noted only at autopsy, hepatitis proven clinically to be secondary to CMV is rare in persons with HIV infection.(16) Diagnosis of CMV pneumonitis should be made by histological identification of multinucleated CMV inclusion bodies in lung tissues. CMV neurological diseases are diagnosed based on the pathological findings such as typical inclusion bodies, or by immunohistochemical or

in situ hybridization techniques. It is noteworthy that a recent autopsy study showed that 42% of patients with CMV retinitis had CMV encephalitis, with the prevalence of encephalitis increasing to 75% if the retinitis was adjacent to or involved the optic nerve. And 91% of those with CMV encephalitis had CMV retinitis.(41) Therefore, an ophthalmologic evaluation is indicated in AIDS patients with CMV encephalitis and may be of diagnostic value in AIDS patients with neurological symptoms. PCR appears to be more useful than clinical and neuroradiologic findings for documenting CMV infection of the CNS in patients with AIDS.(42)

Treatment and Prevention

Antiviral drugs

In the management of CMV disease, four different strategies can be distinguised. Besides antiviral treatment of manifested disease, these include prophylactic, suppressive and pre-emptive treatment which are aimed to prevention of disease. In prophylaxis, treatment is started in the absence of detectable virus or disease, which is aimed at prevention of CMV infection or reactivation in patients at risk of subsequently developing disease.(1) Currently available treatment options for CMV infections include the CMV DNA polymerase-inhibitors ganciclovir, foscarnet and cidofovir.(43) Although these antiviral agents potently inhibit CMV replication, they exhibit toxicity (nephrotoxicity, myelotoxicity, neurotoxicity, hepatotoxicity, teratogenity) and require intravenous administration to obtain therapeutic drug levels, both of which limit their use for long term treatment.(1)

Ganciclovir (Cytovene, DHPG) is a nucleoside analog, which inhibits herpes virus DNA polymerase. Its action depends on phosphorylation in CMV-infected cells. Most strains of CMV resistant to ganciclovir are unable to phosphorylate ganciclovir. The drug is virustatic against CMV. Thus, when treatment of disease is stopped, viral spread and progression of disease characteristically recur.(44) In uncontrolled trails, treatment with ganciclovir resulted in the improvement or stabilization of CMV retinitis in 80-90% of patients.(45) Foscarnet (Foscavir, trisodium phosphonoformate) is a pyrophosphate analogue with in vitro activity against all human herpes viruses as well as HIV.(46) Unlike ganciclovir, foscarnet does not require intracellular phosphorylation to inhibit viral DNA polymerase and therefore, retains activity against most ganciclovir-resistant strains of CMV.(47) Cidofovir (Vistide, HPMPC) is a nucleotide analogue with a prolonged intracellular half life and potent activity against a broad spectrum of herpes viruses including CMV.(48) As a nulceotide, cidofovir does not require virus-mediated activation by phosphorylation and therefore retains activity against many ganciclovir-resistant CMV clinical isolates that are resistant because of mutations in the kinase that phosphorylates ganciclovir.

A promising new agent for the treatment of CMV disease is valganciclovir (VGCV), a prodrug of GCV, and administered orally. It is as potent as intravenous GCV in induction therapy for newly diagnosed retinitis. The safety and efficacy of VGCV compared with GCV was assessed in a trial of HIV patients newly diagnosed with CMV retinitis.(49) Maribavir (Benzimidavir) is an innovative, orally bioavailable benzimidazole compound for the treatment of CMV disease (GlaxoSmithKline, Uxbridge, Middlesex, U.K.) Its mechanism of action is not fully understood; the fact that it is not phosphorylated in cells and does not inhibit DNA polymerase indicates a novel mechanism of action. It appears to interfere with DNA synthesis by blocking a virus-specific process on new viral target. This product, tested in a phase II trial for the treatment of CMV retinitis in HIV infected patients, was shown to cause a dose-dependent decrease in viral titres in semen and urine of HIV patients.(50)

Immunotherapy

CMV infections can be controlled by the CD8+ cytotoxic lymphocytes. Clinical studies of treatment with CMV-specific CD8+ cytotoxic lymphocyte clones, derived from seropositive donors and expanded in vitro have been initiated.(51) Humoral immunity plays a minor, though important, role in prevention or modulating the CMV disease. The neutralizing antibodies are targeted against envelope glycoproteins. They do not fully protect against infection, but they seem to aid in viral clearance and reduce dissemination of the virus.(52) Passive immune prophylaxis using either intravenous immunoglobulins or CMV-specific hyperimmune serum seems to reduce the severity of disease, but it seems to be inferior to antiviral treatment strategies.(53)

Vaccines

Optimal prevention of CMV disease would be vaccination. However, until today, no effective vaccine has been developed. Vaccination with the Towne strain reduced the severity of disease without affecting the infection rate. An alternative approach is the use of subunit, recombinant or DNA vaccines. Studies evaluating these strategies are currently ongoing.(54)

New approaches in treating CMV disease

Several new antiviral agents are currently under clinical development, including lobucavir, adefovir-dipivoxil and antisense oligonucleotides.(55) Recently a new category of antiviral – an "antisense" molecule - was

approved for intravitreal treatment of refactory CMV retinitis. The drug, known as fomivirsen (Vitravene), is thought to bind to a strand of viral DNA and prevent the production of messenger RNA. It was efficacious in retinitis that had failed to respond to standard parenteral therapy. Like ganciclovir implants, it is rarely used today because of the current success of systemic anti-CMV medications.(56) ISIS-2922 is a phosphorothioate anti-sense nucleotide complementary to CMV messenger RNA-encoding regulatory proteins. It is given only as an intravitreal injection once a week for 2-3 doses for induction and then every 2 weeks for maintenance. It has had apparent efficacy in patients intolerant of or unresponsive to intravenous ganciclovir or foscarnet, but can cause uveitis and a dose related retinal toxicity.(57) The benzimidazole riboside compounds, 1263W94 (5,6-dichloro-2(isopropylamino)-1-b -L-ribofuranosyl-1H-benzimidzole) and BDCRB (5,6-dichloro-2-bromo-1-b -D-ribofuranosyl-1H-benzimidazole) are new class of potent inhibitors for controlling CMV replication. 1263W94 inhibits the accumulation of linear and high molecular weight CMV DNA and is being tested in HIV-positive patients.(58)

Lobucavir is a new nucleoside analog with broad-spectrum in vitro activity against CMV and other herpes viruses, as well as HIV and hepatitis B viruses. Its oral bioavailability is 30-40%.(59) BDCRB blocks a step necessary for packaging unit lengths of CMV DNA into the nucleoside. Neither of these drugs depend on the inhibition of the viral DNA polymerase, which makes them attractive alternative agents for drug-resistant strains. It is now known that successful HAART can restore immune response to a variety of pathogens, including CMV. A study of patients with asymptomatic CMV viraemia at the time of initiation of HAART showed that all patients became CMV PCR negative following HAART.(60)

The present status of progress in medicine allows treating successfully an increasing number of HIV patients with CMV disease. Therefore prevention and therapy of CMV infection will deserve special attention. The development of new antiviral drugs seems very promising, thus preventing the CMV disease, which is one among the major opportunistic infections causing death in the HIV-infected population.

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