CMV Infection in Malignancy

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Human Cytomegalovirus
Virion Structure

- envelope
- glycoproteins
- tegument
- capsid
- DNA core

200 nm
CMV comes from the Greek language: "cyto," "cell," and "megalo," "large" → is the largest known virus to infect human beings.


Alphaherpesvirinae (including HSV 1 and 2 and varicella), Gammaherpesvirinae (including Epstein-Barr virus).

All herpesviruses share a characteristic ability to remain latent within the body over long periods.

At least 60% of the US population has been exposed to CMV, with a prevalence of more than 90% in high-risk groups (e.g., male homosexuals).

In developing countries, most infections are acquired during childhood, whereas, in developed countries, up to 50% of young adults are CMV seronegative.

Serologic surveys conducted worldwide demonstrate CMV to be a ubiquitous infection of humans, CMV may be found in 40%-100% of people, depending on socioeconomic conditions.

The Incidence of CMV Reactivation in Hematologic Malignancies

Australian investigators reported that the rate of CMV reactivation over a 5-year period at a single referral center:

- Alemtuzumab (50%)
- HyperCVAD (9.7%)
- Denileukin diftitox (6.1%)
- Autologous stem-cell transplantation (4.2%)
- Fludarabine-containing regimens (4.6%)
- Rituximab (2.6%)
- Other standard-dose chemotherapy regimens (<1%)

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**CMV Infection versus Disease**

- **Infection:**
  - Definition: detection of virus via culture techniques or changes in serology.
  - Criteria:
    1. Seroconversion with appearance of anti-CMV IgM antibodies
    2. Fourfold increase in preexisting anti-CMV IgG titers.
    3. Detection of CMV DNA-emia by molecular techniques.
    4. Isolation of virus by culture of throat, buffy coat or urine.

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**CMV Infection versus Disease**

- **Disease:** requires clinical signs and symptoms, including fever, leukopenia or organ involvement:
  - Hepatitis
  - Pneumonitis
  - Pancreatitis
  - Colitis
  - Meningoencephalitis
  - Myocarditis (rare)
**Pathogenesis of CMV Infection**

- CMV is a large complex virus that has 20 times the genetic material of HIV, with DNA sequences encoding more than 100 proteins.
- The infection occurs due to impairment of T-cell immunity.
- Cytomegalic cells: pathognomonic.

**Pathogenesis of CMV Reactivation in Hematologic Malignancies**

- Lymphopenia
- T-cell depletion

**Pathogenesis of CMV Infection**

- Lytically replicating virus disrupts the cytoskeleton
- Cytoplasmic + intranuclear inclusions + multinucleus
- Massive cell enlargement
Pathogenesis of CMV Infection

Important features in pathogenesis

- Ability of the virus to destroy host cells
- Ability to infect wide range of cells and tissues
- Ability to evade and interfere with host defense mechanisms
- Ability to persist indefinitely in the host

Impaired organ function results from combination of lytic infection of cells and vascular compromise.

Dissemination is due to infection of WBC and vascular endothelial cells.

A small proportion of circulating monocytes in seropositive persons harbor latent CMV.
CMV infection of blood vessel endothelial cells (EC) in humans is a major cause of atherosclerosis. Cells that were infected with CMV could create renin that contributes to high blood pressure.

After infection, the virus remains latent in the body for the rest of the person's life. Some develop infectious mononucleosis/glandular fever-like syndrome. Most healthy people who are infected by HCMV after birth have no symptoms.

**Progression of Infection CMV**

- Most healthy people who are infected by HCMV after birth have no symptoms.
- Some develop infectious mononucleosis/glandular fever-like syndrome.
- After infection, the virus remains latent in the body for the rest of the person’s life.
- Cells that were infected with CMV could create renin that contributes to high blood pressure.
- CMV infection of blood vessel endothelial cells (EC) in humans is a major cause of atherosclerosis.

**CMV Infection in Immunocompetent Patients**

The primary infection presents as mononucleosis-like syndrome which soon resolves.

- **Signs & symptoms**
  - Fever
  - Lethargy
  - Myalgia
  - Headache
  - Mild hepatitis

- **Complications**
  - Rash
  - Granulomatous hepatitis
  - Guillain-Barre Syndrome
  - Meningoencephalitis
  - Myocarditis
  - Pneumonia
  - Hemolytic anemia
  - Thrombocytopenia

Most of them asymptomatic for life.

**Cancer Therapeutics**

Cytomegalovirus (CMV) infection has devastating effects on cancer patient survival.

- **Immune Evasion**
  - Reactivation
  - Dormant Infection

**Cancer Treatment**
CMV seropositivity remains associated with a poorer outcome, mainly in highly immunosuppressed patients.

Primary CMV infection in patients with weakened immune systems can lead to serious disease

A more common problem is reactivation of the latent virus

Severe, prolonged mononucleosis-like syndromes, leukopenia, pneumonitis, cholecystitis, fulminant liver failure, cytomegalovirus retinitis, colitis, death

Complications: bacterial, fungal & parasitic superinfections, increased risk of graft rejection

Direct
- Gastrointestinal disease
- CMV pneumonia
- Retinitis
- Encephalitis

Indirect
- CMV also exhibits an immunosuppressive effect, which can lead to an increased susceptibility to invasive bacterial and fungal disease
CMV Infections in Tumor/Malignancy Patients

- **CMV disease manifestations** include pneumonia, enteritis, encephalitis, retinitis, hepatitis, cholangitis, cystitis, nephritis, sinusitis and marrow suppression.
- **T-cell function is paramount** in the control of CMV, and T-cell depleting agents (e.g., alemtuzumab) and aggressive chemotherapy (e.g., hyper-CVAD, and acute leukemia induction) appear to increase the risk of CMV infection and disease.

CMV Infections in Acute Leukemia Patients

- An early prospective surveillance study from the University of Maryland Cancer Center reported an **incidence** of CMV infection in patients with acute leukemia that ranged from **32% to 58%**.
- CMV-associated **death** occurred in **8/130 patients** studied.
- CMV disease in these studies was associated with the use of high-dose cytarabine, fludarabine, or high-dose cyclophosphamide, and increased patient age.

CMV Infections in Patients who Receive Alemtuzumab

- Nguyen et al reported CMV viremia in **5/34 (15%)** patients who receive Alemtuzumab. Viremia developed a median of 28 days after starting therapy, and all patients experienced fever, but none of these patients developed CMV disease.
- A similar incidence of CMV infection was reported for patients with lymphoid malignancies who were treated with alemtuzumab and rituximab. CMV antigenemia occurred among **13/48 (27%)** patients. Nine patients received anti-CMV therapy, and no patient died as a consequence of this infection.
The most frequently used tests for the diagnosis of CMV infection:

- Detection of antigen (the pp65 antigenemia assay)
- DNA (highly sensitive and provide viral load measurements)
- mRNA (not quantitative but appears to work well in preemptive treatment strategies)

**Viral Load**

- **Definition**: number of CMV particles as determined by quantitative DNA-PCR.
- All patients with CMV DNA levels \( \geq 500 \) copies/ug of total DNA in peripheral blood had clinical evidence of disease, although some with lower viral burdens may be asymptomatic.

The diagnosis of CMV gastrointestinal disease and pneumonia:

- Rapid cultures
- Direct fluorescent antibody tests
- DNA hybridization
- Cytology
But, PCR is not accepted as definitive proof of CMV pneumonia or gastrointestinal disease by current internationally accepted diagnostic criteria.

Due to its high sensitivity, the negative predictive value of PCR is high, so it can be used to rule out disease.

There are presently no data on what level of CMV DNA in bronchoalveolar lavage (BAL) fluid or tissue correlates best with CMV disease.

Prophylaxis of infection or early preemptive intervention remains the foundation of effective CMV infection management for seropositive patients.

Both of these approaches have significantly lowered the risk of early mortality from CMV disease, but CMV disease continues to impact patient survival.

Two possible reasons for this lack of overall success is the occurrence of late cytomegalovirus infection and disease, and inadequate CMV prophylaxis for patients with latent CMV infection.

CMV Infections in Tumor/Malignancy Patients

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CMV Infections in Tumor/Malignancy Patients

1) **Antivirals**: Ganciclovir, Valganciclovir, Foscarnet, or cidofovir as alternatives.
2) **Supportive treatment**: Antihistamines, antipyretics, drying agents (calamine).
3) **Cytomegalovirus Immune Globulin Intravenous (Human) (CMV-IGIV)**: immunoglobulin G (IgG) containing a standardized amount of antibody to Cytomegalovirus (CMV), used for the prophylaxis of cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas, and heart.

Management of CMV Infections in Tumor/Malignancy Patients
CMV disease should be treated with antiviral agents such as ganciclovir or foscarnet.

Induction doses for at least 2 weeks (preferably 3 weeks, if tolerated)
Followed by maintenance dosing for another 3-4 weeks
Treatment should be continued until resolution of symptoms and negativation of the viral load
Continued maintenance or close virologic monitoring is recommended and additional treatment courses may be necessary.

Antiviral treatment for CMV infection should continue until
Confirmation of negative test results for CMV pp65 antigenemia is received
Or the patient recovers from severe lymphocytopenia

- **Ganciclovir**
  - An acyclic guanosine analog
  - Requires triphosphorylation for activation
  - Monophosphorylation is catalyzed by a phosphotransferase in CMV and by thymidine kinase in HSV cells
  - **M.O.A.**: same as acyclovir
  - **Uses**: CMV, HSV, VZV, and EBV
  - **Side Effect**: myelosuppression
**Valganciclovir**
- Monovalyl ester prodrug of gancyclovir
- Metabolized by intestinal and hepatic esterases when administered orally
- **M.O.A.**: same as gancyclovir
- **Uses**: CMV
- **Side Effect**: myelosuppression

**Foscarnet**
- An inorganic pyrophosphate
- Inhibits viral DNA polymerase, RNA polymerase, and HIV reverse transcriptase
- Does not have to be phosphorylated
- **Uses**: HSV, VZV, CMV, EBV, HHV-6, HBV, and HIV
- Resistance due to mutations in DNA polymerase gene
- **Side Effects**: hypo- or hypercalcemia and phosphotemia

**Treatment (Induction)**

**First line:**
- ganciclovir powder for injection, 500 mg in vial
- **Adults**: 5 mg/kg i.v twice a day for 14-21 days

**Second line:**
- foscarnet solution for injection, 24 mg/ml 250 ml, 500 ml
- **Adults**: retinitis; 90 mg/kg i.v daily for 14-21 days for CMV
- **Adults**: CMV oesophagitis; 90 mg/kg i.v twice a day for 14-21 days
Treatment (Maintenance)

First Line:
ganciclovir, capsules, 250 mg
Adults: 1 g orally three times a day

Second Line:
ganciclovir, powder for injection, 500 mg in vial
Adults: 5 mg/kg i.v daily

Third Line:
foscarnet, solution for injection, 24 mg/ml 250 ml, 500 ml
Adults: 90 mg/kg i.v daily

ALTERNATIVE TREATMENT

Valganciclovir 900mg b.i.d po
Cidofovir 5mg/kg weekly

A Case Report

Glioma patients are often treated with corticosteroids for prolonged periods to reduce intracranial swelling.

Temozolomide (TMZ) is the standard therapeutic agent used to treat patients with malignant glioma.

Treatment with TMZ in combination with steroids is believed to cause immunosuppression and subsequent CMV reactivation due to lymphocytopenia.

Cause CMV pneumonia, colitis, and transverse myelitis.
A Case Report

A glioblastoma patient who developed severe lymphocytopenia, continuous fever and hepatitis following surgery and radiotherapy with concomitant TMZ and steroid treatment.

After recovering from CMV reactivation, the patient continued maintenance therapy with TMZ for eight cycles under careful monitoring for CMV reactivation.

A Case Report

Physicians should be aware of the possibility for CMV reactivation when the ALC or CD4+ T-lymphocyte count of a patient treated with concurrent TMZ and steroids decreases to approximately 500 lymphocytes/μL.

Prophylaxis

Not recommended, because:

- Cost concerns
- Inconvenience
- The potential for development of resistance
**Prophylaxis**

- **Ganciclovir**
  - Prolonged neutropenia is the most important adverse outcome of ganciclovir prophylaxis.

- **Valganciclovir**
  - No randomized clinical trials on valganciclovir prophylaxis.

- **Foscarnet**
  - Foscarnet prophylaxis, which is associated with dose-dependent renal toxicity and electrolyte abnormalities, has not been studied in a randomized fashion.

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**NCCN Clinical Practice Guidelines in Oncology, v. 2.2009**

- Consider all patients receiving alemtuzumab to be at high risk for CMV disease.
- Intravenous ganciclovir or foscarnet or oral valganciclovir prophylaxis is recommended for 2 months after alemtuzumab administration.
- Until the CD4 count is 100 cells/mL or greater.

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**Prevention of CMV Infections in Tumor/Malignancy Patients**

1. Simple hand washing with soap and water is effective in removing the virus from the hands.
2. All preschool-age children should be considered potential sources of infection.
3. Avoid contact with body fluids from young children and careful hand washing.
4. Educating women before getting pregnant.
5. Vaccination.
7. Prophylactic antiviral treatment and passive immunization to prevent CMV disease after transplantation.
The spectrum of viral infections for patients with hematological malignancy is expanding and diagnosis has increased because of new molecular diagnostic techniques. Well-designed prospective studies are needed to better clarify the spectrum of viral infection, risk factors for disease, and define effective prevention and treatment strategies. Clinical management guidelines for patients receiving conventional T-cell-depleting therapy with agents like alemtuzumab will need to be developed if the maximum benefit from these agents is to be achieved.