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CYTOMEGALOVIRUS INFECTION IN IMMUNOCOMPROMISED HOSTS

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ABBREVIATIONS:

CMV	cytomegalovirus	HSCT	haematopoeitic stem cell transplantation:
GVHD	graft-versus-host disease	PTLD	post-transplant lymphoproliferative disorder

KEY WORDS:
cytomegalovirus, herpesvirus, immunosuppression, infectious mononucleosis, ganciclovir, foscarnet, cidofovir

INTRODUCTION

Cytomegalovirus (CMV) is a member of the Herpesvirus family. It contains double stranded DNA 0f 229 KB. CMV has worldwide distribution with more prevalence in developing countries due to poor hygiene. It is transmitted via prolonged intimate exposure, blood transfusion and sex. CMV is present in passenger leukocytes of blood. Genome of CMV has been detected in lymphocytes, granulocytes, hematopoietic precursors and monocytes but not in platelets and erythrocytes.

PATHOGENESIS

Pathogenesis of CMV infection is less well understood. It may initially infect neutrophils that spread the infection to fixed macrophages. Virus infected cells induce T- cell immune response causing mononucleosis. Virus replication causes large intranuclear inclusions and smaller cytoplasmic inclusions. Once infected, an individual probably carries virus for life. Most of the persons remain asymptomatic. Latent

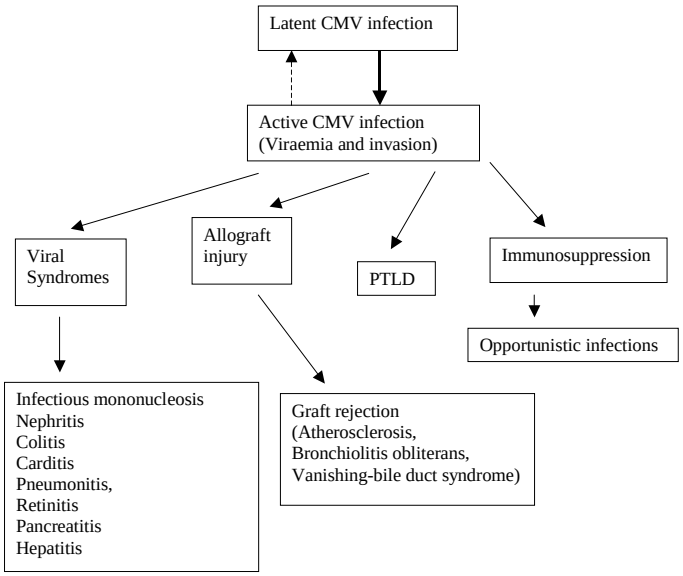

Figure 1 Clinical Features of CMV Infection

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infection is found in many tissues like blood, lungs, salivary glands and bowel. Reactivation of the virus occurs whenever T- cell immunity is suppressed.

CLINICAL FEATURES

Figure 1 describes clinical manifestations of CMV infection. CMV infection in an immunocompetent host is usually asymptomatic. It is the second most common cause of infectious mononucleosis. Unlike developed countries, majority of the persons are infected with CMV by the age of 5 years. Incubation period is 30 –50 days and illness generally lasts for 2 to 6 weeks. Clinical manifestations are fever (90 %), malaise (80 %), hepatosplenomegaly (40%), pharingitis (10%), lymphadenopathy (10 %), palatal petechiae (5%) and skin rash (5 %). Skin rashes are maculopapular and they increase dramatically with ampicillin or amoxicillin. CMV infection can cause hemolytic anaemia, thrombocytopenia, Guiller Barre syndrome, encephalitis, transverse myelitis or pneumonitis[1]. Rare patients of infectious mononucleosis have post-viral asthenia, recurrent fever, malaise, sweating and flushing for months.

CMV infection rate in neonates is 5 to 24 %. The predisposing factors for infection are: exposure to at least 50 ml of blood, birth weight < 1.2 kg and maternal CMV sero positivity[2]. The newborn acquires CMV through birth canal, breast milk, mother's secretion and due to perinatal transfusions. About 40 – 60 % infants of sero positive mothers become sero positive. A newborn has 90 % chance of normal development if the mother is infected many months before pregnancy. If she is infected during pregnancy, 25 % of the newborns have symptoms. Microcephaly, growth retardation and prematurity are seen with congenital CMV infections. Psychomotor, hearing, ocular, or dental abnormalities can manifest over next several years after birth [3].

CMV infection is very common after organ transplantation. There are various risk factors:

1. CMV status of the donor: 50–70 % of sero negative patients develop infection if transplant donor is seropositive, while only 10-20 % patients develop infection if donor is seronegative [4].
2. CMV seropositive patients are more likely to develop CMV infection if anti-lymphocyte globulin is given.
3. HLA mismatched, sero positive donor.
4. Type of transplantation: Kidney- 5-23 %, liver- 5-10 %, heart- 30-40 % and lung or heart-lung-53-75 %.
5. CMV is more common after allogeneic HSCT as compared to autologous HSCT.

CMV infection in an immunocompromised host presents with fever, leucopenia, hepatitis, pneumonitis, colitis, carditis, nephritis and retinitis. CMV pneumonia occurs in 15–20 % of HSCT recipients with mortality of 80 –90 %. Carditis is more common in heart transplantation; nephritis is more common in renal transplantation and so on. CMV infection leads to bacterial infection, graft rejection and post-transplant lymphoproliferative disorder (PTLD) [5]. Small, opaque, white granular necrosis, hemorrhage, oedema and vessel sheathing characterize retinal involvement. Meningoencephalitis is an uncommon presentation. CMV disease usually manifests between 1–4 months following transplantation. Now a days it manifests late due to (1) prophylactic/ pre-emptive treatment of CMV infection which prevents early manifestations (2) increase in unrelated / HLA mismatched/ T-cell purged bone marrow transplants causing prolonged T-cell dysfunction.

DIAGNOSIS

Infectious mononucleosis is considered in presence of lymphocytosis (>50% of T- cells) with >10 % activated lymphocytes.

Various tests are available for the diagnosis of CMV infection: (1) CMV antigen (pp65) assay (2) Demonstration of CMV by polymerase chain reaction (3) CMV culture (4) CMV antibody titre. CMV antigen assay and identification of CMV by polymerase chain reaction are more reliable than CMV culture [6].

IgM and IgG antibodies to antigens in CMV infected fibroblasts can be demonstrated by immunofluorescense or ELISA. Immunofluorescence can be false positive in Epstein bar virus infection [7]. IgM cytolytic antibody to CMV infected cells is not seen with EBV mononucleosis [8]. Circulating RA may give false positive CMV IgM tests. A four-fold rise in complement–fixing anti-CMV antibody titre is considered diagnostic. In most cases rise is at least 16–fold. Rise in antibody titre may take 1 month.

CMV antigen pp65 in leukocytes is detected by staining with monoclonal antibodies [9].

Abnormal liver functions (70 %), thrombocytopenia (70 %), antinuclear factor (20 %), cold agglutinins (20 %) and cryoglobulins (20 %) are also seen in CMV infection. Lung biopsy may be needed for the diagnosis of CMV pneumonia.

DIFFERENTIAL DIAGNOSIS

Any infection which causes infectious mononucleosis, resembles CMV infection. Epstein bar virus and CMV infection are the two most common viral infections causing infectious mononucleosis. Exudative tonsillitis is more common with Epstein bar virus infection.

PREVENTION

CMV infection is troublesome in immunocompromised patients and in low birth weight newborn babies, hence preventive measures are directed at these two groups. Various measures are helpful for prevention of CMV infection.

(1) Use of CMV negative blood products
CMV infection rate is reduced significantly (from 22 % to 1 %) with the use of CMV seronegative blood products as compared to unscreened blood [10].

(2) Use of WBC poor blood products
Leucodepletion can be achieved using washed RBCs, frozen RBCs in glycerol and filtration. White cell count of the blood component should be less than 1 x 10^6 after leucodepletion. Washed RBCs can not effectively deplete white cells and hence CMV infection rate as high as 11 % has been reported[11]. Frozen RBCs are not easily available and hence filtration is the only cost effective, easy and efficient method.

(3) Preference of CMV negative donor for transplantation of CMV IgG/IgM negative patient.

(4) Prophylactic use of anti-viral drugs
CMV prevention during blood transfusion

Leucocytes transmit CMV. CMV infection occurs with frequency of 0.14 to 10 % per unit of blood transfused. Removal of leucocytes effectively reduces CMV infection incidence.

Leucocyte depletion of blood products is currently indicated for [12]:

1. CMV negative transplant recipient with a sero-negative donor
2. CMV negative patients who are likely candidates for transplantation
3. Low birth weight neonates born to sero-negative mothers
4. CMV sero-negative pregnant women
5. Intrauterine transfusions
6. CMV negative HIV patients

Leucocyte depletion of blood products may be useful in following conditions:

1. CMV seronegative patients with Hodgkin's disease, Non-Hodgkin's lymphoma and hereditary / acquired immunodeficiency.
2. Patients of marrow transplantation on immunosuppression and /or suffering from chronic GVHD.

STRATEGY	DEFINITION	ADVANTAGE	DISADVANTAGE
Prophylaxis	Antiviral drugs are given to all patients	May reduce opportunistic infections and graft rejection rate	1. Unnecessary exposure to low risk patients 2. Risk of resistance development
Selective prophylaxis	Antiviral drugs are given to only high-risk patients	1. May reduce opportunistic infections and graft rejection rate 2. Exposure to less number of of patients	1. Need to classify high risk group 2. So called low risk group is prone to CMV
Pre-emptive therapy	Antiviral drugs are given when there is evidence of active CMV infection (CMV viral load, CMV antigenaemia)		1. Additional cost of repeated tests 2. Tests do not identify active infection always[20]

Table 1

Patients who are more than 2-year post-transplant without GVHD and off immunosuppression are still at risk of CMV but they hardly need blood transfusion.

3. CMV seronegative patients on immunosuppressive therapy and patients waiting for autologous HSCT.

CMV prophylaxis using anti-viral drugs

Table I describe salient features of three strategies commonly used. Advantage of pre-emptive therapy over selective prophylaxis is not proved in clinical comparative trials. Ganciclovir and Foscarnet are useful in immunocompromised patients. Ganciclovir is associated with pancytopenia while Foscarnet is associated with azotemia and electrolyte disturbances. Ganciclovir, 5 mg / kg BW, BID for 14 days followed by 5 mg/kg BW for 5-7 days /week for several weeks is useful in immunocompromised patients [13]. Valganciclovir is an oral prodrug of Ganciclovir with a tenfold greater bioavailability compared to oral Ganciclovir. Systemic Ganciclovir exposure achieved with Valganciclovir is comparable to that of intravenous Ganciclovir. Thus, Valganciclovir has the potential to replace intravenous drug treatment. Valgancyclovir is given in the dose of 900 mg daily once with food for three months. Foscarnet is given as 60 mg/kg/BID, I.V. for 2 weeks followed by 90 mg/kg BW once a day I.V. for 5 days per week for 2 weeks or more depending on the clinical condition [14]. Cidofovir is found to be useful where other drugs have failed [15].Cidofovir can cause nephrotoxicity, opthalmological toxicity and neutropenia. The risk for nephrotoxicity and opthalmic toxicity can be reduced by the use of concomtitant probenecid and prehydration. The dosage of Cidofovir is 1-5 mg/kg /week followed by maintenance every other week. CMV specific cytotoxic T lymphocytes are useful in controlling CMV infection [16]. Valacyclovir (2 gm every 6 hours orally for 90 days) has been shown to reduce incidence of CMV disease and graft rejection in seropositive as well as seronegative patients in renal transplant patients [17]. Use of acyclovir in HSCT patients reduces CMV related mortality [18]. Acyclovir is given as 500 mg/ M2 from –day 5 to + day 30 followed by oral acyclovir 800 mg /day for 6 months.

TREATMENT

Corticosteroids are useful for life threatening complications like thrombocytopenia, hemolysis, upper airway obstruction or CNS involvement. Usually 40 – 60 mg is given daily for 4 days and then tapered over 7 days. Gancyclovir improves 70 – 90 % of cases of retinitis and colitis, and <30 % of pneumonitis cases. Addition of hyperimmune globulin along with Gancyclovir improves response rate to 50 – 70 % in pneumonia. Dose of anti-viral drugs is similar to that in prophylaxis. Dose of Valgancyclovir for retinitis in HIV patients is higher i.e. 900 mg twice a day for 21 days followed by 900 mg once a day.

Medical termination of pregnancy is required for fresh CMV infection during 1st trimester to avoid complications in the newborn.

Resistance to Ganciclovir and Foscarnet is rare in HSCT but it is common in HIV patients. Resistance of CMV to Ganciclovir is related to mutations in the UL97 region of the viral genome and/or mutations in the viral DNA polymerase (UL 54 region). Resistance to Foscarnet and Cidofovir is associated with mutations in the viral DNA polymerase. Antiviral susceptibility of CMV strains containing DNA polymerase mutations is dependent on the region of the DNA polymerase where the mutations are located. Some DNA polymerase mutant viruses are cross-resistant to Ganciclovir, Foscarnet, and Cidofovir. The recognition that specific UL97 and UL54 mutations are associated with resistance to antiviral agents has led to the development of molecular methods for detection of mutant viruses [19]. Resistance may occur more frequently with suboptimal viral suppression and use of oral gancyclovir due to its low oral bioavailability.

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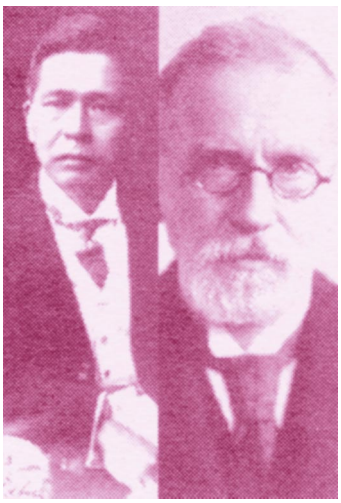

Development of Antibiotics

The first systemic antiseptic, Salvarsan, was introduced by Ehrlich and became widely used against spirochaetal infections, especially during the First World War. Ehrlich called this drug his 'magic bullet'. In 1935, Domagk discovered Prontosil, a drug that killed streptococci in mice; its active constitutent was soon afterwards found to be sulphanilamide. Thus, the first of the sulphonamides, were to be given orally or parenterally. Within a few years, numerous other sulphonamides were synthesized and were widely used in post surgical complications.

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