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The Crux

BIMONTHLY FORUM FOR THE LABORATORIANS

CONTENTS

Editorial

Cytomegalovirus (CMV) (from *cyto-* 'cell' via Greek *κύτος kútos-* 'container' + μέγας mégas 'big, *megalo-*' + *-virus* via Latin *vīrus* 'poison') is a genus of viruses in the order *Herpesvirales*, in the family *Herpesviridae*, in the subfamily *Betaherpesvirinae*. Humans and monkeys serve as natural hosts. The 11 species in this genus include human betaherpesvirus 5 (HCMV, human cytomegalovirus, HHV-5), which is the species that infects humans. Diseases associated with HHV-5 include mononucleosis, and pneumonia. In the medical literature, most mentions of CMV without further specification refer implicitly to human CMV. Human CMV is the most studied of all cytomegaloviruses. Viruses in *Cytomegalovirus* are enveloped, with icosahedral, spherical to pleomorphic, and round geometries, and T=16 symmetry. The diameter is around 150–200 nm. Genomes are linear and nonsegmented, around 200 kb in length. Viral replication is nuclear and lysogenic. Entry into the host cell is achieved by attachment of the viral glycoproteins to host receptors, which mediates endocytosis. Replication follows the dsDNA bidirectional replication model. DNA templated transcription, with some alternative splicing mechanism is the method of transcription. Translation takes place by leaky scanning. The virus exits the host cell by nuclear egress, and budding. Humans and monkeys serve as the natural hosts. Transmission routes are dependent on coming into contact with bodily fluids (such as saliva, urine, and genital secretions) from an infected individual. "**DISEASE DIAGNOSIS**" segment details all you want to know about CMVs.

"**TROUBLE SHOOTING**" portion in this issue highlights all aspects of the TORCH SYNDROME, while **INTERPRETATION** section talks about various TORCH Investigations especially the sero-immunology related ones.

This is not all, please turn a few pages!

DISEASE DIAGNOSIS

CYTOMEGALOVIRUS

Background

Cytomegalovirus (CMV) is a double-stranded DNA virus and is a member of the Herpesviridae family. The other family members include herpes simplex virus type 1 (HSV-1 or HHV-1) and herpes simplex virus type 2 (HSV-2 or HHV-2), varicella zoster virus (VZV), human herpes virus (HHV)–6, HHV-7, and HHV-8. CMV shares many attributes with other herpes viruses, including genome, virion structure, and the ability to cause latent and persistent infections. CMV has the largest genome of the herpes viruses. Replication may be categorized into immediate early, delayed early, and late gene expression based on time of synthesis after infection. The DNA is replicated by rolling circles. Human CMV grows only in human cells and replicates best in human fibroblasts. At least 60% of the US population has been exposed to CMV, with a prevalence of more than 90% in high-risk groups (eg, male homosexuals). The prevailing age of infection varies worldwide. In developing countries, most infections are acquired during childhood, whereas, in developed countries, up to 50% of young adults are CMV seronegative. The incidence of CMV seropositivity rises with age and in a US-based study was reported to increase from 36% in children aged 6-11 years to 91% in individuals older than 80 years. Other factors associated with CMV seropositivity include ethnicity (77% in Mexican Americans and 71% in blacks), female sex, foreign-born status, and low socioeconomic status. CMV usually causes an asymptomatic infection; afterward, it remains latent throughout life and may reactivate. Infection is defined as isolation of CMV, its viral proteins, or its nucleic acid from any tissue sample or body fluid. In immunocompetent individuals, symptomatic disease usually manifests as a mononucleosis syndrome, which was first described in adults in 1965. Clinically significant CMV disease (reactivation of previously latent infection or newly acquired infection) frequently develops in patients immunocompromised by HIV infection, solid-organ transplantation, or bone marrow transplantation, as well as in those receiving high-dose steroids, tumor necrosis antagonists, or other immunosuppressing medications for conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Crohn disease, or psoriasis, among others. In patients coinfected with HIV, CMV infection leads to progression to AIDS and eventually death, even in those receiving highly active antiretroviral therapy (HAART). Symptomatic CMV disease in immunocompromised individuals can affect almost every organ of the body, resulting in fever of unknown origin, pneumonia, hepatitis, encephalitis, myelitis, colitis, uveitis, retinitis, and neuropathy. Individuals at an increased risk for CMV infection include individuals who attend or work at daycare centers, patients who undergo blood transfusions, persons who have multiple sex partners, and recipients of CMV mismatched organ or bone marrow transplants. CMV is transmitted from person to person via close contact with an individual who is excreting the virus. It can be spread through the placenta, blood transfusions, organ transplantation, and breast milk. It can also be spread through sexual transmission. Even in advanced countries, congenital CMV transmission from a mother with acute infection during pregnancy is a significant cause of neurological abnormalities and deafness in approximately 8000 newborns annually. Multiple genetically distinct strains of CMV exist. Differences in genotypes may be associated with differences in virulence. Infection with more than one strain of CMV is possible and has been observed in organ transplant recipients. Dual infection is a possible explanation for congenital CMV infection in children of CMV-seropositive mothers.

Pathophysiology

CMV is a lytic virus that causes a cytopathic effect in vitro and in vivo. The pathologic hallmark of CMV infection is an enlarged cell with viral inclusion bodies. Cells that exhibit cytomegaly are also seen in infections caused by other Betaherpesvirinae. The microscopic description given to these cells is most commonly an "owl's eye," depicted in the image below. Although considered diagnostic, such histological findings may be minimal or absent in infected organs.

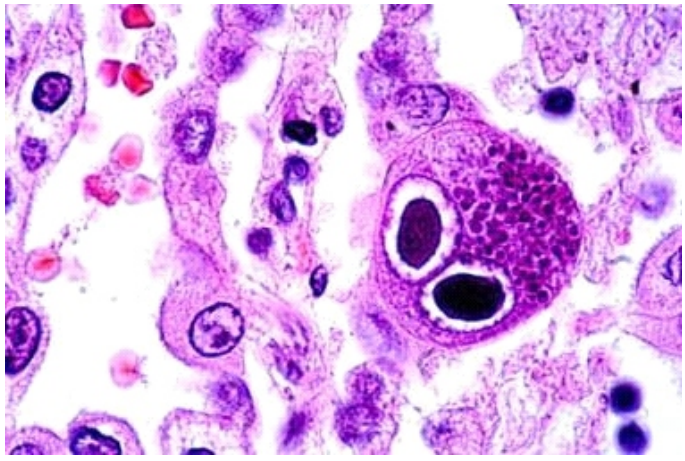


Fig: Hematoxylin-eosin–stained lung section showing typical owl-eye inclusions (480X).

When the host is infected, CMV DNA can be detected with polymerase chain reaction (PCR) in all the different cell lineages and organ systems in the body. Upon initial infection, CMV infects the epithelial cells of the salivary gland, resulting in a persistent infection and viral shedding. Infection of the genitourinary system leads to clinically inconsequential viruria. Despite ongoing viral replication in the kidney, renal dysfunction is rare except in renal transplant recipients, in whom CMV is associated with rare cases of glomerulopathy and possible graft rejection.

Immunology

Primary CMV infection is defined as infection in an individual who was previously CMV seronegative. In these patients, CMV immunoglobulin M (IgM) antibodies may be found as early as 4-7 weeks after initial infection and may persist as long as 16-20 weeks. Most neutralizing antibodies are directed against an envelope glycoprotein gB. Studies have shown that more than 50% of neutralizing activity in convalescent serum is attributable to glycoprotein gB. However, virion tegument proteins such as pp150, pp28, and pp65 evoke strong and durable antibody responses. CMV is an immunomodulatory virus and may aggravate underlying immune disorders (eg, SLE). The presence of CMV DNA in the blood and viruria are commonly found in healthy CMV seropositive women. Naturally acquired immunity to the virus does not seem to prevent reinfection or the duration of viral shedding. Cell-mediated immunity is considered the most important factor in controlling CMV infection. Patients deficient in cell-mediated immunity are at greatest risk for CMV disease. CMV-specific CD4 and CD8 lymphocytes play an important role in immune protection after primary infection or reactivation of latent disease. Studies of bone marrow transplant recipients have revealed that those who do not develop CMV-specific CD4 or CD8 cells are at higher risk for CMV pneumonitis.

Additionally, no cases of CMV pneumonia have been reported in allogeneic marrow transplant recipients receiving infusions of CMV-specific CD8 cells.

Primary cytomegalovirus infection and viremia

In most hosts, primary CMV infection is clinically silent. The presentation of symptomatic primary infection is addressed in Adult Cytomegalovirus Infection in the Immunocompetent Host. Primary CMV infection of the immunocompromised host carries the greatest risk for CMV disease. Viremia is diagnosed by isolation of CMV in culture (either via standard or shell vial culture; see Laboratory studies). CMV excretion in the saliva and urine is common in immunocompromised patients and is generally of little consequence. In contrast, viremia in organ transplant recipients identifies those at greatest risk for CMV disease. The sensitivity of CMV viremia as a marker for CMV pneumonia is 60%-70% in allogeneic marrow transplant recipients. Having no evidence of virus in the bloodstream has a high negative predictive value for CMV disease. Prophylactic or preemptive antiviral therapy against CMV disease in transplant recipients typically relies on the detection of CMV in the blood by shell vial cultures, CMV antigenemia, and PCR amplification.

Congenital cytomegalovirus disease

Congenital CMV infection is one of the TORCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and HSV), which carry a risk of significant symptomatic disease and developmental defects in newborns. The clinical syndrome of congenital cytomegalic inclusion disease includes jaundice, splenomegaly, thrombocytopenia, intrauterine growth retardation, microcephaly, and retinitis. The most common clinical findings of congenital CMV infection include petechiae (71%), jaundice (67%), microcephaly (53%), and small size for gestational age (50%). Common laboratory abnormalities include hyperbilirubinemia (81%), increased levels of hepatocellular enzymes (83%), thrombocytopenia (77%), and increased CSF protein levels (77%). Studies have shown that asymptomatic children with neurological findings are more likely to have CMV IgM antibody. Many cases of hearing loss in children may be caused by CMV infection. CMV excretion is common in children with congenital infection and may represent a reservoir for infection in other children and daycare workers. The CMV immune status of the woman is important in determining the risk of placental infection and subsequent symptomatic disease in the child or fetus. Symptomatic CMV congenital disease is less likely to occur in women with pre-existing immune responses to CMV than in CMV-naïve individuals. One in ten cases of acute CMV infection during pregnancy is estimated to result in congenital CMV disease.

Cytomegalovirus pneumonia

CMV pneumonia is defined as signs and symptoms of pulmonary disease in combination with detection of CMV in bronchoalveolar fluid or lung tissue. CMV detection should be performed via culture, histopathology, immunohistochemical analysis, or in situ hybridization, as CMV DNA PCR testing alone is too sensitive for diagnosing CMV pneumonia. Approximately 0%-6% of adults who present with CMV infection as a mononucleosis syndrome develop pneumonia. One study found that the incidence of CMV pneumonia in immunocompetent patients was 19%. In most cases, CMV pneumonia is found on chest radiography and is of no clinical significance, rapidly resolving with the disappearance of the primary infection. Life-threatening CMV pneumonia may develop in immunocompromised patients (see Adult Cytomegalovirus Infection in the Immunocompromised Host). The highest rate of CMV pneumonia, as well as the greatest severity, occurs among lung transplant recipients, who are at an overall 50% risk of developing CMV illness (infection or disease).

Cytomegalovirus hepatitis

CMV hepatitis is defined as elevated bilirubin and/or liver enzymes levels in combination with the detection of CMV in the absence of other causes for hepatitis. CMV may be detected via culture, histopathology, immunohistochemistry, or in situ hybridization. CMV PCR alone is not satisfactory for diagnosis, as a positive result may reflect transient viral shedding. The first described case of CMV hepatitis involved a child with chorioretinitis, hepatosplenomegaly, and cerebral calcifications. Hepatitis has been commonly observed in patients with primary CMV infection and mononucleosis. Levels of hepatocellular enzymes may be mildly and transiently increased, and, in rare cases, jaundice may develop. The prognosis of CMV hepatitis in immunocompetent hosts is typically favourable, but death has been reported in immunosuppressed patients. Histology typically reveals mononuclear cell infiltration of the portal areas but may also reveal granulomatous inflammation.

Cytomegalovirus gastritis and colitis

CMV GI disease is defined as the combination of symptoms of the upper and lower GI tract, mucosal lesions visible on endoscopy, and detection of CMV via culture, histopathology, immunohistochemistry, or in situ hybridization. CMV colitis was first described in 1985 in two homosexual men who presented with abdominal pain, diarrhea, and hematochezia. CMV PCR alone is insufficient for diagnosis, as a positive result may simply reflect transient viral shedding. CMV may infect the GI tract from the oral cavity through the colon. The typical manifestation of disease is ulcerative lesions. In the oral cavity, these may be indistinguishable from ulcers caused by HSV or aphthous ulceration. Gastritis may present as abdominal pain and even hematemesis, whereas colitis more frequently presents as a diarrheal illness. CMV disease of the GI tract is often shorter-lived than that of other organ systems because of the frequent sloughing of infected cells of the GI mucosa.

Cytomegalovirus CNS disease

CMV CNS disease is defined as CNS symptoms in combination with CMV detection in CSF (culture, PCR) or brain biopsy tissue (culture, histopathology, immunohistochemistry, in situ hybridization). The association between CMV and Guillain-Barré Syndrome involves 2 groups. Younger patients (typically < 35 y) present with sensory defects and facial palsy, antiganglioside (GM2) IgM response, and milder long-term sequelae. A second group includes women older than 50 years. These observations were made in France and thus may not be applicable to other populations due to different ages of primary CMV exposure.

Cytomegalovirus retinitis

CMV retinitis is one of the most common opportunistic infection in persons with AIDS, typically those with CD4 lymphocyte counts below 50 cells/μL. Although the number of cases has decreased with the use of HAART, new cases continue to be reported. Individuals with CMV retinitis typically exhibit a progressive decrease in visual acuity, which may progress to blindness if untreated. Unilateral and bilateral disease may exist. Long-term CMV treatment is necessary to prevent retinitis relapse. All lesions suspected to be CMV retinitis must be confirmed by an ophthalmologist. Immune reconstitution syndrome (IRIS) is reported in 16%-63% of HIV-infected patients with CMV retinitis following the

initiation of HAART. In one study, the median time to IRIS following HAART initiation was 43 weeks but has been reported as early as 4 weeks or as late as 4 years in some cases. CMV IRIS may manifest as painless floaters, blurred vision, photopia, decreased visual acuity, or ocular pain. Some patients may develop macular edema leading to vision loss or proliferative vitreoretinopathy, spontaneous vitreal hemorrhage, and retinal detachment.

Cytomegalovirus nephritis

CMV nephritis is defined as CMV detection in combination with a renal biopsy showing CMV-associated changes in the setting of renal failure. CMV PCR alone is inadequate for diagnosis. Of note, detection of CMV in the urine of a patient with renal failure does not meet diagnostic criteria for CMV nephritis. CMV viremia has been associated with acute glomerular injury.

Cytomegalovirus syndrome

In general, it is better to avoid this term in stem cell transplant recipients, as other viruses (eg, HHV-6) can also cause fever and bone marrow suppression. However, in solid organ transplant recipients, CMV syndrome is better defined: fever (>38°C) for at least 2 days within a 4-day period, CMV detection in blood, and either neutropenia or thrombocytopenia.

Graft versus host disease

CMV infection has been associated with acute graft verus host disease in bone marrow transplant recipients. Multiple genotypes (gB 1-4) of CMV exist, each with variations in the gene encoding envelope glycoprotein gB. The association of gB types with acute graft versus host disease and death related to myelosuppression has been examined. Taking into account disease type, donor-recipient HLA matching, donor CMV serostatus, and age, Torok-Storb et al (1997) found that gB3 and gB4 were linked to a higher degree of myelosuppression and death. Interestingly, no specific CMV genotypes were linked to worse outcome in solid organ transplant recipients, although mixed gB genotype infections were associated with higher viral loads and delayed viral clearance.

Frequency

International

Serologic surveys conducted worldwide demonstrate CMV to be a ubiquitous infection of humans. Depending on the population surveyed, CMV may be found in 40%-100% of people, depending on socioeconomic conditions. Infection earlier in life is typical in developing countries, whereas up to 50% of young adults are seronegative in many developed nations.

Mortality/Morbidity

CMV is seldom associated with mortality in non-immunocompromised hosts (< 1%). Substantial morbidity may occur in patients with a mononucleosis syndrome, as described in Adult Cytomegalovirus Infection in the Immunocompetent Host. In both solid organ and marrow transplant recipients, CMV causes substantial morbidity and mortality. For example, even with antiviral therapy, the mortality rate in allogeneic marrow transplant recipients with interstitial pneumonia varies from 15%-75%. CMV RNA can be detected in 15% of fetal tissues or placentae, indicating that CMV infection during pregnancy contributes to stillbirths.

Age

CMV prevalence increases with age. Age has also been found to be a risk factor for CMV disease in certain transplant populations.

Prognosis

The prognosis of CMV hepatitis is generally good. Most patients recover completely. Symptoms can persist, usually in the form of fatigue, for several months after primary infection. CMV pneumonia in marrow transplant recipients once carried a mortality rate higher than 85%. The use of ganciclovir plus high-dose immune globulin for the treatment of CMV pneumonia in allogeneic marrow transplant recipients has lowered the mortality rate to 30%-60%. Because patients who develop CMV disease are immunocompromised, their prognosis may be determined by their underlying disease. The need for mechanical ventilation is a poor prognostic sign.

Patient Education

For excellent patient education resources, visit eMedicineHealth's Infections Center. Also, see eMedicineHealth's patient education article Mononucleosis.

CLINICAL PRESENTATION

History

History varies depending on whether the host is immunocompetent or immunocompromised.

Adult cytomegalovirus infection in the immunocompetent host

Cytomegalovirus (CMV) can cause a wide spectrum of infection in immunocompetent hosts. Sites most often involved include the lung (severe community-acquired viral pneumonia), liver (transaminitis), spleen (splenomegaly), GI tract (colitis), CNS (encephalitis), hematologic system (cytopenias), and multisystem involvement (fever of unknown origin). Uncommon sites of CMV infections in immunocompetent individuals include the kidneys, adrenals, salivary glands, pancreas, and esophagus. In most cases, primary CMV infection is asymptomatic or produces mild flulike symptoms. Symptoms, when apparent, develop 9-60 days after primary infection. The lymph nodes and spleen may be enlarged, so CMV infection should be included in the differential diagnoses of infections that produce lymphadenopathy. Extreme fatigue may persist after normalization of laboratory values. CMV may produce a mononucleosis syndrome similar to that caused by Epstein-Barr virus (EBV), primary toxoplasmosis, or acute HIV seroconversion. In a large study of 494 patients with infectious mononucleosis, 79% of cases were due to EBV, and, in the 73 heterophile antibody–negative patients, approximately half of these were CMV positive (rising complement-fixing antibodies). In about a third of patients with CMV mononucleosis, a rash may also be present (macular, papular, maculopapular, rubelliform, morbilliform, or scarlatiniform). Both CMV and EBV may result in atypical lymphocytes in the blood. Other pertinent test results include negative findings on heterophil antibody studies, mildly or moderately elevated levels of aspartate aminotransferases, and evidence of subclinical hemolysis. Hepatitis and atypical lymphocytes usually disappear after 6 weeks. Despite its great sensitivity, the CMV IgM test is limited by a one-way cross-reaction of acute EBV infectious mononucleosis sera. False-positive reactions have resulted from the presence of rheumatoid factors. CMV infection should be suspected in patients with clinical mononucleosis or fever of unknown origin. Most cases have a paucity of physical examination findings. Some studies have shown that, as a

group, patients infected with CMV have less hepatomegaly, splenomegaly, and pharyngitis than those infected with EBV. Patients with CMV mononucleosis may be older, have a longer duration of fever, and have less cervical lymphadenopathy. However, such clinical findings are inadequate to differentiate between the two viruses. Transfusion of multiple blood units is a risk factor for CMV mononucleosis and has been implicated in postoperative fever or fever in patients following trauma. Traditionally, CMV antibody tests were performed using complement fixation and showed peak viral titers 4-7 weeks after infection. Multiple tests for CMV antibody are now available, some of which are sensitive enough to detect anti-CMV IgM antibody early in the course of the illness and during CMV reactivation. Reactivation of the virus is not uncommon, sometimes occurring with viremia and a positive IgM result in the presence of IgG antibody. This is usually observed during intercurrent infections or at times of patient stress. The clinical significance, time course, and natural history of reactivation in immunocompetent patients are not known for either virus.

In rare cases, CMV can cause community-acquired pneumonia in immunocompetent hosts and should be considered a possible etiology (along with influenza [human, swine, avian] and adenovirus) in cases of severe viral community-acquired pneumonia. Case reports describe prolonged fever, lack of cough or other respiratory symptoms, bilateral interstitial or patchy infiltrates on chest radiography, relative lymphopenia, atypical lymphocytes, and mild transaminitis. Of note, some patients had negative CMV IgM findings initially but subsequently developed elevated levels of both IgM and IgG, with resolution of the infiltrates over 6 weeks. There are varying degrees of hypoxemia. The prognosis of CMV pneumonia in immunocompetent hosts, even severe cases, is usually good, rarely requires a full course of antiviral treatment, and usually resolves during CMV induction therapy. Rarer manifestations of CMV infections in immunocompetent individuals include Guillain-Barré syndrome, meningoencephalitis, pericarditis, myocarditis, thrombocytopenia, and hemolytic anemia. Rubelliform or maculopapular rashes are observed with and without administration of ampicillin. GI ulceration may result from acute CMV infection in immunocompetent persons, although this finding is much more likely in immunocompromised individuals. CMV frequently reactivates in critically ill patients and may be linked to increased length of hospital and/or intensive care stay, duration of mechanical ventilation, morbidity, and mortality. However, an opposing retrospective study looking at the impact of CMV serostatus on outcomes in immunocompetent ICU patients found no association between CMV seropositivity, ICU mortality, in-hospital mortality, time to hospital discharge, duration of mechanical ventilation, or the need for renal replacement therapy. Further data are required to ascertain if CMV prophylaxis/treatment of critically ill seropositive patients leads to better clinical outcomes.

Adult cytomegalovirus infection in the immunocompromised host

CMV infection in transplant recipients may be primary or recurrent. Again, the former refers to CMV detection in an individual who was previously seronegative, while recurrent infection includes both reinfection and reactivation. Reinfection refers to detection of a CMV strain different from the one that caused the patient's original infection. Reactivation is defined as infection by the same CMV strain as was previously involved. A study by Kim et al examined CMV infections in patients after liver transplantation. The study determined that the occurrence of CMV disease, and not CMV infection, was a risk factor for mortality and graft failure in adult liver transplant recipients. CMV infection may cause direct or indirect effects. Direct effects include bone marrow suppression, pneumonia, myocarditis, GI disease, hepatitis, pancreatitis, nephritis, retinitis, and encephalitis, among others. The main indirect effects include acute and chronic graft rejection, accelerated atherosclerosis (heart transplants), secondary bacterial or fungal infections, EBV-associated post-transplant lymphoproliferative disease (PTLD), and decreased graft and patient survival. CMV infection may affect the same organ systems in HIV-positive patients with low CD4 counts as those in organ transplant recipients. Retinitis has been the major reported CMV disease in patients with HIV infection, followed by CNS involvement. Not surprisingly, CMV disease has been associated with decreased survival in transplant recipients. As an example, in a group of 187 lung transplant recipients in Sweden between 1990 and 2002, the 10-year survival rate was only 32% in patients with CMV disease, compared with 53% among those with asymptomatic CMV infection and 57% in those without CMV infection.

Organ transplantation and cytomegalovirus

CMV is an important pathogen isolated in organ transplant recipients, as primary CMV infection in an organ transplant recipient may be quite severe. CMV disease occurs with the highest frequency in donor-positive/recipient-negative transplant recipients. This relationship is true for all organ transplant recipients except those who receive bone marrow, in whom the highest incidence of CMV disease is in donor-negative/recipient-positive individuals. The reason for this is unknown but may be related to the level of immunosuppression observed in patients who have received marrow transplants compared with those who have received other transplants. Patients who have received marrow transplants undergo ablative chemotherapy and/or radiation. A period of neutropenia and a loss of specific antigen reactivity follow. All transplant recipients have a period of decreased CMV-specific cell-mediated immunity. The next step is unknown; however, patients at greatest risk for CMV disease develop viremia. The role viremia plays in the pathophysiology of CMV disease is unknown. Life-threatening CMV pneumonia may develop in immunocompromised patients, with the incidence varying based on the type of transplant received. Patients who receive marrow, lung, heart, heart-lung, liver, pancreas-kidney, and kidney transplants have different levels of immunosuppression. Those most at risk include bone-marrow transplant recipients and recipients of lung transplants. In patients who have received marrow transplants, CMV disease is most likely 30-60 days after transplant. Fatal CMV pneumonia is much less common in patients who have received solid organ transplants than in those who have received marrow transplants. Patients may initially present with an asymptomatic infiltrate on chest radiograph. The most common clinical presentation of CMV pneumonia is fever and shortness of breath, accompanied by an interstitial infiltrate. The differential diagnoses of CMV pneumonia in immunocompromised patients include Pneumocystis pneumonia, viral respiratory infections, pulmonary hemorrhage, drug toxicity, recurrent lymphoma, and other infections. CMV is frequently detected in the lungs of patients with HIV/AIDS but usually represents viral shedding and does not frequently cause clinically significant disease. CMV pneumonia is difficult to treat, even with the antivirals now available. The mortality rate among bone marrow transplant recipients with CMV pneumonia was approximately 85% prior to the introduction of ganciclovir and CMV-specific immune globulin. The addition of these drugs has decreased the CMV pneumonia mortality rate to 15%-75%. The mortality rate of CMV pneumonia in marrow transplants that requires mechanical ventilation is high, despite treatment with ganciclovir and immune globulin. Poor clinical outcomes are also observed in patients who are also infected with community respiratory viruses (eg, parainfluenza, influenza, respiratory syncytial virus) and those who have received allogeneic

marrow transplants. This suggests that the severity of CMV pneumonia is not exclusively secondary to viral characteristics. The use of immune globulin is based on studies of marrow transplant recipients, which noted improved survival rates in those with CMV pneumonia who received combination therapy (ganciclovir plus immune globulin). This has not been studied in patients with CMV pneumonia who have received solid organ transplants. Some experts believe that the mechanism of CMV pneumonia in patients who have received solid organ transplants may differ from that in marrow transplant recipients, making the addition of immune globulin unnecessary in the former. CMV pneumonia in marrow transplant recipients does not appear to involve a simple and direct viral cytopathic effect on pneumocytes. The addition of CMV-specific immune globulin has not been shown to affect the mortality and morbidity of CMV infection of other organ systems. Severe CMV disease is likely secondary to synergism between the virus and other factors, such as radiation, chemotherapy, conditioning regimens, a nonimmune inflammatory response, or other infections. The diagnosis of CMV pneumonia depends on recovering CMV from patients with a positive finding on chest radiograph and appropriate clinical signs. CMV may be isolated from the lung with bronchoalveolar lavage (BAL) or open lung biopsy. In support of the diagnosis, CMV antigen or inclusions are found with histological examination. CMV isolated from clinical samples in the absence of clinical symptoms may represent viral colonization or subclinical replication. In many cases, the detection of subclinical replication in transplant recipients warrants antiviral suppressive therapy. In patients infected with HIV, antiviral therapy is often not required in the absence of clinical apparent disease. Primary GI CMV disease in solid organ transplant recipients is difficult to treat and may relapse. The relapse rate was recently studied in solid organ transplant recipients following treatment for CMV infection at the Mayo clinic. The investigators found that extensive involvement of the GI tract was significantly associated with CMV relapse but that endoscopic resolution of GI disease did not necessarily translate into a reduced risk of CMV relapse.

Human immunodeficiency virus disease and cytomegalovirus

CMV is often isolated from patients who are co-infected with other bacterial, parasitic, and fungal pathogens. In fact, CMV may be found in the lungs of approximately 75% of individuals infected by both HIV and Pneumocystis. The of CMV infection in Pneumocystis pneumonia is unclear, and treatment of the latter usually leads to resolution of the pneumonia and hypoxemia, meaning that CMV treatment is not typically warranted in most cases. For unknown reasons, CMV pneumonia without a co-infecting pathogen is uncommon. In patients with HIV infection, CMV involves the entire GI tract. In the upper GI tract, CMV has been isolated from esophageal ulcers, gastric ulcers, and duodenal ulcers. Patients with upper GI tract esophageal disease can present with painful dysphagia. Patients with CMV disease of the lower GI tract may present with diarrhea (colitis). CMV colitis frequently affects only the right colon, necessitating full colonoscopy and multiple biopsies for accurate diagnosis. Diagnosis of CMV GI disease depends on a biopsy specimen demonstrating the typical CMV intranuclear inclusions. Recovery of CMV in tissue culture may be helpful but is difficult to interpret because of CMV shedding. CMV may be isolated from many different sites and is not necessarily associated with disease, reinforcing the need for histopathologic examination. Retinitis is the most common manifestation of CMV disease in patients who are HIV positive. It occurs most commonly in patients with CD4 counts below 50 cells/µL, with rates of up to 40% in this population. Affected patients report decreased visual acuity, floaters, and loss of visual fields on one side. In many cases, it progresses to bilateral involvement that may be accompanied by systemic CMV disease. Ophthalmologic examination shows yellow-white areas with perivascular exudates. Hemorrhage is present and is often referred to as having a "cottage cheese and ketchup" appearance. Lesions may appear at the periphery of the fundus, but they progress centrally. Ganciclovir has been used to treat CMV retinitis. Unfortunately, it only slows the progression of the disease. Many clinicians switch to foscarnet after ganciclovir fails. Ganciclovir implants have emerged as an important therapy in the management of CMV retinitis. The optimal treatment consists of ganciclovir implants in the vitreous, accompanied by systemic ganciclovir therapy. Oral ganciclovir may be used for prophylaxis of CMV retinitis but should not be used for treatment. The incidence of CMV retinitis has dropped since the widespread use of highly active antiretroviral therapy. During reconstitution of the immune response in patients who are HIV positive and on antiviral therapy, retinitis may worsen for a period. If severe inflammation is present, corticosteroid treatment may be necessary. In patients who are HIV positive, CMV may cause disease in the peripheral and central nervous system.

Physical

Most patients with CMV infection exhibit few clinical findings on physical examination. Primary CMV infection may be a cause of fever of unknown origin. Symptoms, when apparent, develop 9-60 days after primary infection. Pharyngitis may be present. Examination of the lungs may reveal fine crackles. The lymph nodes and spleen may be enlarged, so CMV should be included in the differential diagnoses of infections that produce lymphadenopathy. Many physicians believe that CMV mononucleosis is less associated with pharyngitis and cervical adenopathy than EBV infectious mononucleosis. A recent study in young children questioned the accuracy of this clinical pearl. The study found that cervical adenopathy was more common in patients infected with EBV than in patients infected with CMV (83% versus 75%). Although statistically significant, relying on this sign for the differentiation between CMV and EBV mononucleosis is difficult.

Complications

Despite long treatment courses with valganciclovir and documented clearance of CMV viremia, CMV relapse remains common among solid organ transplant recipients. A better understanding of the epidemiology of CMV infection among solid organ transplant recipients and risk factors for disease relapse is warranted.

Differential Diagnoses

- Autoimmune Hepatitis
- Early Symptomatic HIV Infection
- Enteroviruses
- Fever of Unknown Origin (FUO)
- HIV Infection and AIDS
- Human Herpesvirus 6 (HHV-6) Infection
- Epstein-Barr Virus (EBV) Infectious Mononucleosis (Mono)
- Toxoplasmosis
- Viral Hepatitis

WORKUP

Laboratory Studies

Cytomegalovirus (CMV) has been detected via culture (human fibroblast), serologies, antigen assays, PCR, and cytopathology. The IgM level is elevated in patients with recent CMV infection, or there is a 4-

fold increase in IgG titers. False-positive CMV IgM results may be seen in patients with EBV or HHV-6 infections, as well as in patients with increased rheumatoid factor levels. Some tests are sensitive enough to detect anti-CMV IgM antibody early in the course of the illness (CMV early [nuclear] antigen, CMV viral capsid antigen) and during CMV reactivation. As with EBV infection, observing reactivation of the virus with a positive IgM result in the presence of IgG antibody is not uncommon. This is most commonly observed during intercurrent infection in immunocompromised patients. An anti-CMV immediate early antigen monoclonal antibody assay is available. This reacts with an early protein and can detect CMV infection 3 hours into the infection. Intense coarse granular intranuclear inclusion staining is noted. No other nuclear staining or cytoplasmic staining is visualized. In the transplant population, antigen assays or PCR is used (sometimes in conjunction with cytopathology) for diagnosis and treatment determinations, with the choice of test varying among institutions.

Antigen testing

Antigenemia is defined as the detection of the CMV pp65 antigen in leukocytes. The pp65 assay is used to detect messenger matrix proteins on the CMV virus, with either immunofluorescence assay or messenger RNA amplification. These proteins are typically expressed only during viral replication. Antigen tests are often the basis for institution of antiviral therapy in transplant recipients and may allow for the detection of subclinical disease in high-risk patients. The assay is sensitive and specific yields results quickly. Antigen assays cannot be used in patients with leukopenia, as these tests detect antigen within neutrophils. In immunocompromised patients, low or moderate CMV antigenemia may indicate reactivation or infection. It has been reported that the pp65 antigen assay and quantitative CMV PCR (COBAS Amplicor Monitor Test; see Quantitative polymerase chain reaction) yield similar effectiveness in diagnosing and monitoring patients with active CMV infection.

Qualitative polymerase chain reaction

Qualitative PCR is used to detect CMV in blood and tissue samples. PCR depends on the multiplication of primers specific for a portion of a CMV gene. The primers usually bind to the area of virus that codes for early antigen. Qualitative PCR is extremely sensitive, but, because CMV DNA can be detected in patients with or without active disease, the clinical utility of qualitative PCR is limited. Serial PCR may be more helpful clinically. It yields a positive result before the antigenemia test in transplant recipients with viremia. Results are typically negative in patients without CMV viremia. In transplant recipients, a negative CMV PCR result goes against reactivation, but not infection. Commercially available qualitative PCR testing can be performed using the NucliSens CMV Test, a nucleic acid sequence-based amplification assay (NASBA, Organon Teknika Corporation, Durham, North Carolina).

Quantitative polymerase chain reaction

Quantitative PCR has been used to detect plasma CMV. The advantage of quantitative PCR over regular PCR is unknown. Ideally, quantitative PCR is as sensitive as qualitative PCR and provides an estimate of the number of CMV genomes present in plasma. A study of newborns compared real-time PCR assays of liquid-saliva and dried-saliva specimens with rapid culture of saliva specimens obtained at birth. Both PCR assays showed high sensitivity and specificity for detecting CMV infection. A study of more than 3400 blood specimens from organ transplant recipients tested with CMV PCR and pp65 antigenemia found that quantitative real-time PCR for CMV DNA could be used in lieu of antigenemia for monitoring CMV infection and determining when to initiate preemptive treatment. In theory, the CMV viral load would indicate whether therapy is necessary because patients whose viral load is below a certain cutoff would not develop CMV disease. However, the level of viremia necessary for CMV disease to occur may vary depending on host factors and the type of organ transplant, and this may need to be determined empirically. For example, in CMV retinitis, the viral load has a poor positive predictive value, meaning its clinical utility is limited. A detectable CMV viral load at the time of CMV retinitis diagnosis was shown in one study to correlate with increased mortality (P = 0.007). CMV involvement of the GI tract also has a poor correlation with CMV viremia. Commercially available quantitative PCR assays include the COBAS Amplicor CMV Monitor test (Roche Diagnostics, Indianapolis, IN) and various laboratory-developed PCR assays. The COBAS Amplicor CMV Monitor test measures viremia in the range of 600-100,000 copies/mL. In the quest to standardize viral load testing for CMV, the FDA approved marketing in July 2012 of a fully automated assay, the COBAS AmpliPrep/COBAS TaqMan CMV test (CAP/CTM CMV test, Roche Molecular Diagnostics, Pleasanton, CA), which uses an international standard to quantitate plasma CMV load. This assay is available in Europe, but not yet in the United States. It measures viremia in a range of 150-10,000,000 copies/mL. Because viral loads are not comparable among different assays, it is important to use the same test and same sample type (whole blood or plasma) when monitoring patients over time.

Shell vial assay

The shell vial assay is performed by adding the clinical specimen to a vial that contains a permissive cell line for CMV. The shell vials are centrifuged at a low speed and placed in an incubator. After 24 and 48 hours, the tissue culture medium is removed and the cells are stained using a fluorescein-labeled anti-CMV antibody. The cells are read using a fluorescent microscope. Alternatively, the cells are stained with an antibody against CMV, followed by a fluorescein-labeled anti–immune globulin. This test has been found to be as sensitive as traditional tissue culture.

Cytopathology

Intracellular inclusions surrounded by a clear halo may be demonstrated with various stains (Giemsa, Wright, hematoxylin-eosin, Papanicolaou). This gives the appearance of an "owl's eye" (see Pathophysiology).

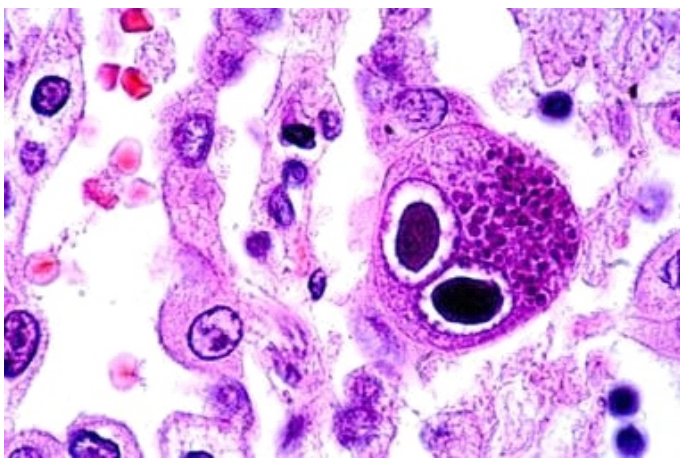


Fig: Hematoxylin-eosin–stained lung section showing typical owl-eye inclusions (480X).

Imaging Studies

The diagnosis of CMV pneumonia can be suggested by chest radiography findings, but these findings cannot be used to differentiate

between other common causes of pneumonia in immunocompromised hosts. A chest radiograph finding consistent with pneumonia and a BAL result that is CMV positive is a common method for diagnosis. CT scan is more sensitive for the identification of infiltrate. It has been valuable in patients who present with hypoxia and no infiltrate visible on chest roentgenography.

Other Tests

Cytomegalovirus resistance testing

CMV infection continues to pose a major problem in transplant recipients, and antiviral resistance is encountered in all forms of transplantation. In solid-organ transplant recipients, ganciclovir resistance is found mainly among donor-positive, recipient-negative lung, kidney, and kidney/pancreas transplant recipients. Among stem cell transplant recipients, resistance primarily affects the donor-negative, recipient-positive group. Other risk factors include T-cell depletion, more than 3 months of antiviral therapy, very high viral loads, recurrent episodes of CMV disease, increased levels of immunosuppression, and suboptimal antiviral drug concentrations due to noncompliance or decreased absorption. Resistance to foscarnet and cidofovir has also been reported in solid-organ and stem cell transplant recipients. Resistance typically takes weeks to months to develop. In fact, among patients with HIV infection, a 10% ganciclovir resistance rate has been reported at 3 months. Resistance should be suspected in patients who initially respond to CMV therapy but who subsequently develop an increasing viral load despite drug compliance. It should also be considered in patients who are clinically deteriorating. Only two CMV resistance genes have been reported to date: UL-97 and UL-54. UL-97 (a phosphotransferase gene), encodes ganciclovir resistance, while UL-54 (viral DNA polymerase) mutations confer resistance to ganciclovir, foscarnet, and cidofovir. In approximately 90% of patients, ganciclovir resistance initially results from UL-97 mutations. To date, proven ganciclovir resistance mutations in UL-97 are found only in codons 460, 520, and 590-607. Mutations in codons 696-850 mediate foscarnet resistance, and mutations in these sites do not usually mediate cross-resistance to the other anti-CMV drugs. If a patient develops resistance while taking cidofovir, it is caused by a UL-54 mutation, which will encode cross-resistance to ganciclovir. Specialized assays can be used to test resistance. The most widely used of these is a genotypic assay using fluid samples (eg, CSF, blood) that contain CMV DNA or samples with cultures positive for CMV. Genotype assay results can be performed and results received in a matter of days. Unfortunately, the assay is expensive and may pick up irrelevant mutations. Hence, familiarity in interpreting the results is key. Other resistance assays include those used to measure viral load via antigenemia or quantitative DNA, as well as a phenotypic plaque reduction assay. The former is not well standardized, and interpretation may vary from one institution to the next. In addition, in certain CMV diseases (eg, retinitis), viral load testing yields a low positive predictive value. The plaque reduction assay takes at least 1 month to complete, is poorly standardized, and is not routinely performed in the laboratory.

Histologic Findings

The hallmark of CMV infection is the finding of intranuclear inclusions consistent with herpesvirus infection. CMV infection may be confirmed using in situ hybridization or direct or indirect staining of intranuclear inclusions using CMV-specific antibodies linked to an indicator system (eg, horseradish peroxidase, fluorescein).

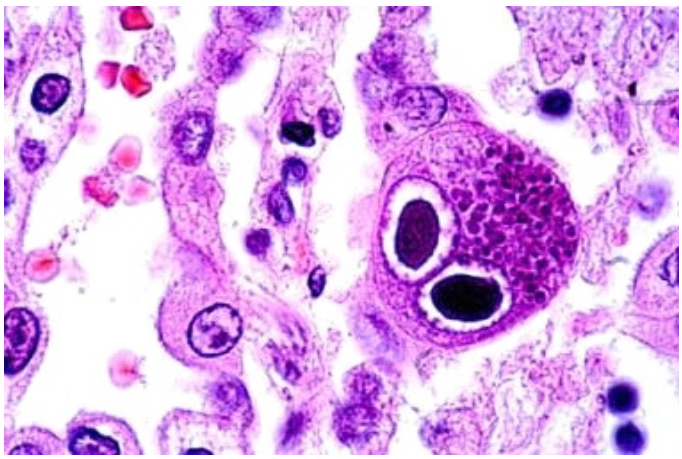


Fig: Hematoxylin-eosin–stained lung section showing typical owl-eye inclusions (480X).

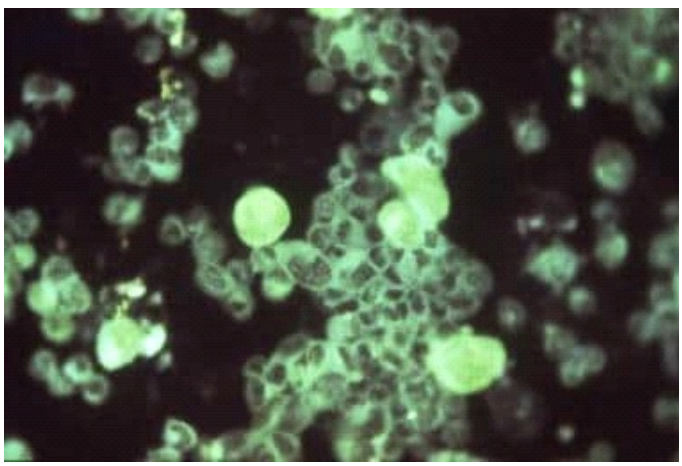


Fig: Here, using immunofluorescent technique, a specimen of human embryonic lung (25X) reveals the presence of cytomegalovirus.

Management

Healthy people who are infected with CMV but who have no symptoms usually do not require medical treatment. Antiviral treatment is used for immunocompromised individuals who have eye infections or life-threatening illnesses due to CMV. The drug of choice for prevention of CMV disease in solid-organ transplant patients is valganciclovir. Other than CMV retinitis, however, ganciclovir remains the mainstay of treatment, at least initially. Second-line treatments include foscarnet, cidofovir, or maribavir. Currently, there is no vaccine to prevent CMV infection.

INTERPRETATION

TORCH investigations.

There are 2 Types of Antibodies which we need to test for. IgG and IgM.

IgM Antibodies:

- Appear immediately after an infection, usually persist for 10-12 weeks.
- MAY PERSIST for 1-2 YEARS. Every IgM + doesn't mean a recent infection.
- IgM + does NOT mean fetal infection. Further workup is needed.

IgG Antibodies:

- IgG Antibodies appear after around 2 weeks, start falling after 2 months but Persist LIFELONG.

Interpretation:

No exposure to infection: IgM, IgG Negative

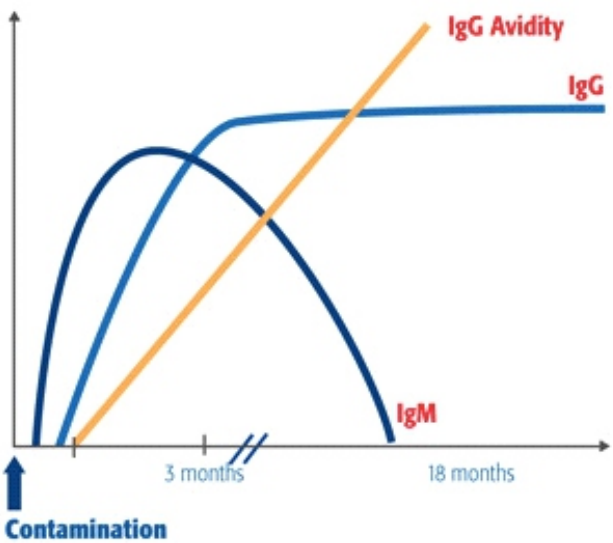
Acute infection: IgM, IgG Positive

Past infection: IgM Negative, IgG Positive

So is this enough to diagnose TORCH infections?

We have another weapon in our arsenal of tests.

IgG Avidity:



Measures the binding AFFINITY of the IgG Antibody after infection.

The affinity increases over time.

A recent infection: LOW AVIDITY

A Past infection: HIGH AVIDITY since the antibodies have been around for some time. They have developed a strong affinity i.e avidity. Avidity, in most cases but not all, shifts from low to high after about 5 months. If the avidity is high, this suggests infection occurred at least 5 months before testing.

Let's look at a few clinical cases.

CASE 1: 25 year old Woman with a history of 2 prior abortions is advised a TORCH test. She is currently 8 weeks pregnant.

The Results are as follows:

1. Rubella IgG, IgM -ve
2. CMV IgG, IgM -ve
3. Toxo IgG IgM : +ve

What is to be done next?

If acute infection is suspected, repeat testing is recommended within 2 to 3 weeks. A 4-fold rise in IgG antibody titres between tests indicates a recent infection

Then, A Toxo IgG Avidity is advised.

Results:

Avidity is LOW

This means that the Infection is more recent.

Spiramycin is the treatment of choice.

USG is advised for fetal anomalies

Amniocentesis is advised in the 2nd TMP to detect fetal infection

Regular monitoring by USG

There are 10-20% chances of infection of fetus

Out of these infections approximately half can be severe.

Serologic screening in pregnant women should be done only if they are at risk for primary Toxoplasma gondii infection.

Toxoplasma gondii infection should be suspected and screening should be offered to pregnant women with ultrasound findings consistent with possible TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes, and other) infection, including but not limited to intracranial calcification, microcephaly, hydrocephalus, ascites, hepatosplenomegaly, or severe intrauterine growth restriction.

CASE 2: 26 year old female with a history of recurrent abortions

Toxo IgG, IgM Positive.

Can Toxoplasmosis be responsible for recurrent abortions?

No, it cannot. It can only cause sporadic infections.

The reason being that after an episode of Toxoplasmosis, the woman becomes immune. She is unlikely to be infected unless she has comorbidities and is immunocompromised.

CASE 3: 32 Year old 8 weeks pregnant

Rubella IgG +, IgM -: She is protected from infection and is at no risk for Rubella Infection. Reassure the patient.

On the other hand, if the IgG is negative, we must educate the woman on the signs and symptoms of rubella.

Clinical symptoms appear after the incubation phase of 13-20 days, and are characterized by lymphadenopathy, maculopapular rash and fever.

In some cases, there is arthralgia (30% of adults), encephalitis (1 case out of 10 000) with good prognosis and thrombocytopenia. After a primary infection, adults have long-term immunity, but sometimes, it is possible to have a new infection. The incidence of this type of re-infection during pregnancy is not known.

It is important to determine the immune status of women of childbearing age, preferably before pregnancy, to vaccinate those who are seronegative.

If no determination has been performed prior to conception, it should be carried out as soon as pregnancy is confirmed to ensure monitoring of women who are not immune

CASE 4: 30 Year old with 12 weeks gestation

CMV IgG +, IgM +

Interpretation:

Primary infection or a reactivation of a latent infection

Perform CMV IgG Avidity:

High: Reactivation

Low: Primary Infection

TAKE AWAY MESSAGES:

- Women with past Toxoplasmosis or Rubella are unlikely to have a recurrent infection.
- Reinfection\recurrences are more likely with CMV and HSV
- TORCH infections are don't cause recurrent ABORTIONS. They can explain sporadic events.
- Vaccination against Rubella is important. If Rubella status is not clear. Administer vaccine and wait for 1-2 months before planning.
- Testing of TORCH should be in a reference lab with us of IgG Avidity.
- Maternal infection doesn't always mean a fetal infection.
- Further testing with USG, Amniocentesis in the 2nd TMP is important
- If Toxo IgG,M is +, Advise repeat testing in 2-3 weeks.
- Then perform Avidity. If avidity is low, this could mean a recent infection. This still needs to be confirmed with USG and amniocentesis in the 2nd TMP.
- A Toxo IgG + result with a IgM -ve does not warrant treatment.
- A Rubella IgG Positive with IgM -ve is not at risk of Rubella.
- For Rubella: Carry out an IgM assay in the following cases:
- possible contact with the disease, if clinical symptoms suggest primary infection, seroconversion or if raised IgG levels are observed during systematic checks.
- If USG shows signs of TORCH infection, Diagnostic tests are important in First TMP.

TROUBLESHOOTING

TORCH Syndrome

What is TORCH syndrome?

Many women think that TORCH syndrome is a single health disorder. However, according to health experts, TORCH syndrome is a group of different infectious diseases. They can cause serious problems and harm the health of a fetus.

TORCH diseases in pregnancy

Developing TORCH infection in pregnancy is dangerous for your unborn baby. It spreads rapidly through your blood to the baby. At this level, the immune system of your baby is not strong enough to fight the infection so he/she develops the infection as well. Moreover, if the infection or disease remains in your baby's blood, he or she might not develop vital organs properly. There are the risks of numerous health problems as well. For instance, jaundice or hearing problems. TORCH diseases in pregnancy increase the risk of stillbirth and miscarriage as well.

Among the diseases that are associated with TORCH syndrome are:

Toxoplasmosis

Caused by parasites, toxoplasmosis is a rare condition. It happens when parasite enters your body through the mouth. You can get this parasite from eating uncooked meat. The infection transfers into your unborn baby as well, which might result in brain damage, excess fluid in the brain, seizures, inflammation in certain parts of the eyes, and delays in the ability to use muscles.

Rubella

Rubella or German measles is caused by a virus and is a contagious disease. Pregnant women, who have rubella, develop a sore throat, rash, along with low-grade fever. Moreover, if you are pregnant and get rubella (especially in your first trimester), you need to visit your doctor as your unborn baby might get it as well.

Cytomegalovirus (CMV)

It is an infection in the herpes virus group and affects around 50% of adults by the time they are 30. Although there is no cure for it, it gets better on its own very quickly and it does not cause serious problems. However, the case is different for pregnant women; if they develop the condition, CMV may pass on to their baby. Cytomegalovirus is also one of the common viral infections that affect newborn babies.

If a baby is born with congenital CMV, it may get sick or encounter the following chronic issues:

- jaundice
- small birth size
- hearing loss
- vision loss
- mental disability
- muscle weakness
- Lung problems
- seizures

Herpes Simplex virus

Herpes is one of the very common chronic infections. There are two types of herpes, i.e. HSV-1, which causes blisters around your mouth. It can pass on to your genitals as well. HSV-2 is an STD that leads to genital herpes. It causes blisters and opens sores which are painful. This infection can also contribute to oral herpes. Herpes simplex can affect your baby when he or she is in the uterus, which is rare. Moreover, babies often get the infection during delivery. The risk of infection increases in babies when mothers get the first outbreak of herpes while they are pregnant. at the start of pregnancy. This is because pregnant women shed excess virus particles for a long time. However, the risks of herpes infection in your baby increase if you get herpes later in your pregnancy. So, you should consult with the doctor about this situation. With suitable precautions, you can reduce the risk of infection to some extent.

TORCH test before pregnancy

TORCH screen is done to detect whether you have an infectious disease (covered by screening) or had one in the past. This test is also necessary to find out if you are immune to infectious diseases such as rubella. Many health experts recommend TORCH tests before conception for the healthy development of a fetus and safe pregnancy. Furthermore, the results of a TORCH test are termed positive and negative. A negative test result is considered normal unless it is for a disease that you should be vaccinated against. This indicates that there are no antibodies in your body. And, there is no recent or past infection in your body. On the other hand, a positive test result indicates that IgG or IgM antibodies are found. These antibodies can be a sign of one or more infections that are covered in your TORCH test. These can also suggest that you have been vaccinated for a disease before. Your doctor will further elaborate if your test results are positive and recommend the best treatment.

TORCH infections treatment

The treatment or management of TORCH diseases differs and is based on the symptoms.

Treatment of TORCH infections during pregnancy

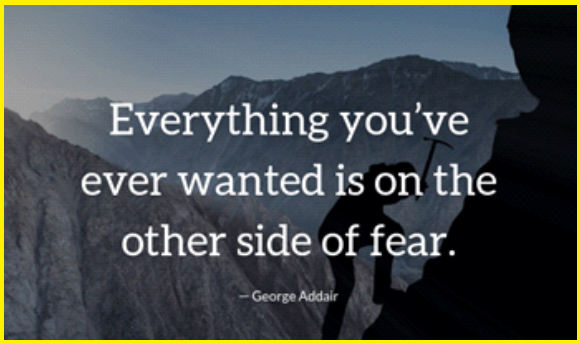
- To treat toxoplasmosis, your doctor may suggest sulfadiazine and pyrimethamine.
- The treatment of cytomegalovirus is done according to the patient's symptoms, such as fever or fatigue.
- In the case of Herpes Simplex virus, your doctor might suggest cesarean delivery if active lesions are found.
- Pregnant women who develop Rubella can treat it by resting and mild analgesics.
- If the mother has developed chicken pox in her life, then it is not a major concern. However, if a pregnant mother has never had chicken pox, its risk increases during pregnancy. You can protect your baby from congenital varicella syndrome by avoiding people who have chicken pox.
- Health experts do not recommend getting vaccinated against varicella infection while you are pregnant.

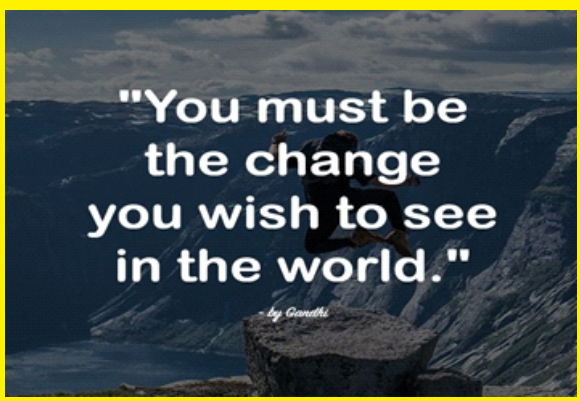
TORCH infection treatment before pregnancy

TORCH infection treatment is less stressful before pregnancy. However, you need to eliminate TORCH infection from your body to promote the healthy development of the fetus. Health experts recommend TORCH tests before you conceive. These tests help with disease or infection detection. In case of positive results, your doctor might suggest the treatment on the basis of your symptoms. Although negative results are not a significant concern, your doctor may suggest precautionary steps for a safe pregnancy. TORCH infections can lead to critical health conditions and affect the health of your unborn baby. It is highly recommended to discuss TORCH syndrome with your doctor before your pregnancy to avoid unwanted outcomes.

BOUQUET

Wisdom Whispers





In Lighter Vein

Why is an 'A' or 'B' better than a 'C' or 'D'?
Aren't all letters equal in the eyes of GOD?

"What a school day!!! The computers broke down...
And We had to Read!"

"Just Think Of It As If You Are Reading a Long Text Message"

Brain Teasers

1. **Which is the most ideal time to test for TORCH infections in a pregnant woman?**
   A. First prenatal visit
   B. Second prenatal visit
   C. Just before delivery
   D. After delivery

2. **What is the species name of Toxoplasma as related to TORCH infections?**
   A. Pylori
   B. Gondii
   C. Simmplex
   D. Zoster

3. **How many Herpes viruses routinely infect human being?**
   A. 2
   B. 4
   C. 6
   D. 8

4. **Kaposi's sarcoma is related to**
   A. Toxoplasma
   B. Rubella
   C. Herpes virus 8
   D. Cytomegalovirus

ANSWER: 1: A, 2: B, 3: D, 4: C

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