Cytomegalovirus Pneumonia: Community-Acquired Pneumonia in Immunocompetent Hosts

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HISTORY

In 1881, Ribbert noted large cells in kidney cells of a stillborn, which he later described as "protozoan-like" in 1904. These large cells had eccentric nuclei surrounded by a clear halo. Ribbert did not appreciate the significance of his findings until he read the report by Gesionek and Kiolemenoglou published in the same year, describing similar structures in the lungs, liver, and kidney of an 8-month-old fetus. In Ribbert's laboratory in 1907, Lowenstein found these protozoan-like large cells in the parotid glands of infants. Lowenstein was the first to appreciate that these large inclusions were in the nucleus. In 1911, Pettavel described similar inclusions in the thyroid gland of a premature infant. Later, in 1921, Goode, Pasteur, and Talbot reported a case of a 6-week-old infant with intranuclear eosinophilic inclusions similar to those previously described and were the first to use the term "cytomegalia." They did not believe that the large inclusion bodies in the nucleus represented protozoa. In 1925, von Glahn and Pappenheimer described the first adult case of cytomegalovirus (CMV) infection in a male who had an amebic liver abscess; inclusion bodies were found in the lungs and in the intestines. They concluded that the inclusions in this case were similar to those seen in other herpes virus infections. In 1934, Chaudry was the first to definitively link intracellular inclusion bodies with specific viral infections. In 1950, Wyatt

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and colleagues reported that inclusions (CMV) were always present in renal tubules and reasoned that inclusions might be present in urine specimens. They also coined the term, ''generalized cytomegalic inclusion disease,'' which was first described by Wolbach in 1932. Wyatt was the first to diagnose cytomegalic inclusion disease (CID) antemortem in an infant. In the early 1950s, Mercer and Margileth also showed that CID could be diagnosed by demonstrating inclusion cells in voided urine. Electron microscopy was first used by Minder in 1953 to visualize intracellular inclusions of CMV in the pancreas.[1–5]

In the history of CMV, 1905 to 1954 represented the "period of cytopathology," later followed by the "virological period." Until Enders was able to culture human cells, isolation of human CMV was not possible because human CMV cannot be cultured in nonhuman cell lines. In the late 1950s, Enders and his colleagues developed tissue culture techniques to isolate poliovirus. In 1954, Smith isolated mouse CMV in cell culture and human CMV was cultured in human cell lines Boston and Bethesda. In 1965, Clemola and Kariainen first described CMV (heterophile-negative) infectious mononucleosis in adults. The isolation and identification of CMV led the way to more sophisticated diagnostic methods. Widespread organ transplantation increased interest in CMV because it was the most important pathogen isolated in these immunosuppressed patients. In cases of human immunodeficiency virus (HIV) infection, retinitis, acalculous cholecystitis, esophagitis, colitis, or encephalitis, CMV is an important infection most commonly presenting as a prolonged febrile response, which is a hallmark of CMV infection. Not unexpectedly, CMV has been reported as a cause of fever of unknown origin in children and adults. CMV continues to be an important infection in immunocompetent hosts, for example, CMV infectious mononucleosis and postperfusion syndrome. In other compromised hosts (eg, patients with systemic lupus erythematosus [SLE]) and those on immunosuppressive drugs (eg, patients with Crohn's disease), CMV not uncommonly presents as CMV infectious mononucleosis, fever of unknown origin (FUO), or severe community-acquired pneumonia (CAP).[1,4,5]

In 1968, Carlstrom and colleagues[6] first reported a case of CMV CAPin their series of CMV infection of immunocompetent hosts. One of the patients was a 26-year-old woman who developed CMV CAP. In 1970, Sterner and colleagues[7] reported the case of a 27-year-old woman with CMV postperfusion syndrome who later developed CMV CAP. In 1972, Klemola and colleagues[8] reported 2 more cases of CMV CAP in immunocompetent adults. Klemola's report was the first to describe in detail the features of CMV CAP in immunocompetent adults. He reported that prolonged fever was the predominant presenting sign of CMV CAP. His 2 patients with CMV CAP, a 35-year-old woman and a 60-year-old woman, had no cough or respiratory symptoms but did have prolonged fevers and bilateral basilar patchy/interstitial infiltrates on chest radiograph (CXR). The CMV infiltrates resolved slowly over 6 weeks. He noted that the diagnostic clues to CMV CAP were relative lymphopenia, atypical lymphocytes, and mildly elevated serum transaminases. Typically, initial CMV IgM titers were negative in his patients, but later they developed elevated CMV IgM/IgG titers. CMV viruria was present in both of his cases.

MICROBIOLOGY

CMV DNA viruses are of the murine and human variety. CMVs are DNA viruses with an icosahedral capsid with 162 capsomers, and the viral particles have a diameter of 120 to 200 nm. The capsid is surrounded by a phospholipid-rich envelope.

CMVs are members of the Herpesviridae family, which consists of 8 human herpes viruses (HHVs). The family Herpesviridae includes herpes simplex virus type 1 (HSV-1

or HHV-1) and type 2 (HSV-2 or HHV-2), varicella-zoster virus (HHV-3), Epstein-Barr virus (EBV, HHV-4), and CMV (formerly known as HHV-5). Also there are human herpes viruses HHV-6, HHV-7, and HHV-8. The family of Herpesviridae is divided into 3 subfamilies, representing the HSVs (Alphaherpesvirinae), CMVs (Betaherpesvirinae), and the lymphocryptoviruses (Gammaherpesvirinae). Human CMV (HHV-5), one of the Betaherpesvirinae CMVs, has distinctive characteristics; it (1) has DNA molecular weight of 150×10^6; (2) grows only in human cells and has a narrow host range, that is, humans; (3) grows best in human fibroblasts; (4) has a relatively slow reproductive cycle (>24 hours); and (5) has distinctive inclusion bodies contained in the nuclei and cytoplasm. Infected host cells are enlarged cytomegalia with nuclear and cyto-plasmic inclusions. CMV has a predilection for salivary glands but is not present in parotid or submandibular glands or sublingual glands. After the kidneys, the lungs are the most common sites of infection in acquired-CMV infection.[1,4,5]

Morphologically, CMV resembles other herpes viruses, particularly HSV, with important cytopathic differences. Although cellular penetration of HSV and CMV takes place rapidly, the intracellular replication of CMV is much slower (approximately 4 days) compared with that of HSV (approximately 8 hours). The reason for the slow intracellular replication of CMV is not well understood. Although both HSV and CMV produce intranuclear inclusions, only CMV produces cytoplasmic inclusions (dense bodies). Because only CMV produces perinuclear cytoplasmic inclusions, cytopatho-logic diagnosis is possible. Cytopathologic changes in host tissue indicates active infection, not inactive or latent infection.[1,4,5,9,10]

EPIDEMIOLOGY

Typical bacterial causes of CAP may be differentiated from the atypical CAPs by the presence or absence of extrapulmonary findings. Patients presenting with CAP without extrapulmonary findings have infection caused by typical bacterial CAP path-ogens (ie, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrha-lis*). Patients presenting with CAP with extrapulmonary findings have atypical CAP that may be caused by zoonotic or nonzoonotic atypical pathogens. The most common causes of nonzoonotic atypical CAP are legionnaires disease, *Mycoplasma pneumo-niae*, or *Chlamydophila (Chlamydia) pneumoniae.* Aside from the usual zoonotic and nonzoonotic atypical pathogens causing CAP, there are other viral pathogens that not infrequently present in atypical CAP, such as CMV, adenovirus, influenza (human, avian, swine), and *Pneumocystis (carinii) jiroveci* (PCP). PCP and CMVs are recognized pathogens in compromised hosts, for example, those who undergo transplants and those on immunosuppressive drugs or steroids. However, CMV, influenza (human, avian, swine), and adenovirus are the 3 most common causes of severe viral CAP in immunocompetent adults.

CLINICAL PRESENTATION

In immunocompromised hosts and in those who are on immunosuppressive drugs, the clinical presentation of CMV CAP has been well described. CMV is present in the lungs in approximately 75% of patients with HIV and PCP. The presence of CMV in lung biopsy specimens of HIV-infected patients with PCP does not indicate a causal role in the patients' clinical presentation of severe CAP. In such patients, if PCP is treated, CAP resolves without specific anti-CMV therapy.

CMV CAP in immunocompetent hosts is an uncommon but is being recognized more frequently, particularly when presenting as severe viral CAP. As with other CAP pathogens, the severity of presentation of CMV CAP in normal hosts varies.

Certainly, many mild and moderately severe cases of CMV CAP go undetected because they are easily missed as "mild flu" or are ascribed to "a respiratory virus." CMV in normal hosts is most likely to be recognized when presenting as severe viral CAP.[1,6–8,11–13]

Severe CAP implies that the patient is sufficiently ill with CAP to require hospitalization and, often, ventilatory support. Patients presenting with severe CAP may be approached clinically by the degree of hypoxemia and the appearance and distribution of infiltrates on the CXR. Severe CAP may also be mimicked by noninfectious disorders presenting with severe hypoxemia, hypotension, and infiltrates on the CXR. The most common noninfectious disorders mimicking severe CAP are pulmonary embolus, congestive heart failure, pulmonary drug reactions, pulmonary hemorrhage, collagen vascular diseases (eg, SLE pneumonitis, sarcoidosis), and clinical decompensation in patients with preexisting severe interstitial lung disease. These mimics of severe CAP can usually be eliminated from further clinical consideration on the basis of history, physical examination, and routine nonspecific laboratory features, which point to the diagnosis. If the noninfectious mimics of severe CAP are eliminated, the clinician should then consider patients with focal/segmental pulmonary infiltrates (ie, bacterial CAPs) versus patients with either minimal/no infiltrates or bilateral symmetric interstitial infiltrates (ie, PCP/viral CAPs).[14–17]

The 2 most common bacterial pathogens that cause severe CAP are *S pneumoniae* and *Legionella* (legionnaires disease), which present with focal segmental or lobar infiltrates on CXR. The differential diagnosis of patients who present without focal/lobar infiltrates on CXR with hypoxemia with either minimal or no infiltrates or bilateral symmetric interstitial infiltrates on CXR includes HIV-infected patients with PCP, immunosuppressed patients, or patients with viral pneumonias, such as, influenza (human, avian, swine); severe acute respiratory syndrome (SARS); hantavirus pulmonary syndrome (HPS); or CMV. The viral CAPs, presenting as severe CMV infection, initially present with minimal or no pulmonary infiltrates on CXR but are accompanied by various degrees of hypoxemia. The degree of hypoxemia is related to the degree of oxygen diffusion defect caused by interstitial pathogens. The severity of viral CAP in normal hosts is directly related to the degree and duration of hypoxemia. The magnitude of the oxygen diffusion defect caused by viral involvement of the lung interstitium in severe viral CAPs is best assessed by the alveolar-arterial (A-a) gradient. Patients presenting with severe viral CAP typically have increased A-a gradients of more than 35. The CXR appearance of CMV CAP is not distinctive (**Fig. 1**).[11,12,14] The CXR is most helpful in excluding other pathogens or disorders in the differential diagnosis, that is, either focal infiltrates due to typical/atypical bacterial CAP pathogens or disorders that may mimic severe CAP. Typically, severe CMV CAP presents with no infiltrates, rapidly followed by bilateral patchy interstitial infiltrates most prominent in both lung bases. In immunocompetent patients presenting with otherwise unexplained severe CAP, with minimal or no infiltrates or bilateral symmetric interstitial infiltrates and hypoxemia with an increased A-a gradient. CMV should be included in the differential diagnosis when there are other clinical features of CMV that suggest CMV versus other causes of severe viral CAP. The associated features obtained from history, physical examination, and nonspecific laboratory tests can limit differential diagnostic possibilities and should prompt specific CMV diagnostic testing (**Table 1**).[1,3,8,14]

DIFFERENTIAL DIAGNOSIS

CMV is an immunomodulatory virus that may cause or perturbate immune disorders, such as SLE.[1,13,18] Not uncommonly, in patients with SLE, CMV presents with flare and CAP. SLE pneumonitis, per se, does not usually present as CAP with severe
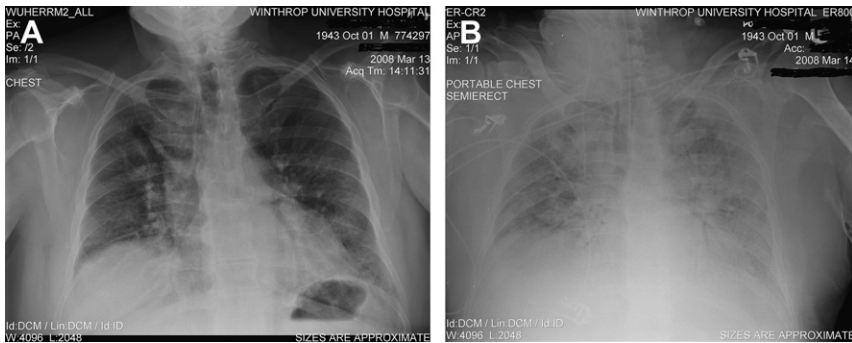
Fig. 1. CMV CAP on chest X-rays (*A*, *B*).

hypoxemia.[13] The clinical problem is to recognize that pulmonary infiltrates in a patient with SLE during flare may represent CAP, not SLE pneumonitis. Pneumonitis is characterized by migratory pulmonary infiltrates with or without pleural effusions.[11] SLE is a multisystem disorder that affects nearly all organs except the liver. If a patient with SLE flare has increased serum transaminases, CMV should be suspected as the cause of the SLE flare.[13,14,17,19] CMV characteristically involves the liver, which is manifested by mild elevations of the serum transaminases. SLE patients with flare and increased serum transaminases do not have lupoid hepatitis (autoimmune hepatitis) and should be viewed as having CMV-precipitated SLE flare until proved

Table 1
CMV spectrum of infection: preferred organ involvement in immunocompetent patients

Common Sites of CMV Involvement	Clinical Features	Uncommon Sites of CMV Involvement	Clinical Features
Lung	Severe CAP	Kidney	CMV viruria
Liver	Increased serum transaminases (AST/ALT)	Adrenals	Adrenalitis
Spleen	Splenomegaly	Salivary glands	Sialitis
Gastrointestinal tract	Segmental/pancolitis Colitis	Pancreas	Pancreatitis
Central nervous system	Encephalitis[a]	Esophagus	Esophageal ulcers Esophagitis
Hematologic	Leukopenia Relative lymphopenia Atypical lymphocytes Thrombocytopenia Aplastic anemia Increased procoagulant activity	—	—
Multisystem involvement	FUO	—	—

Abbreviations: AST/ALT, aspartate aminotransferase/alanine aminotransferase; FUO, fever of unknown origin.
[a] May present as the sole manifestation of CMV infection.

otherwise. CMV not only can induce the SLE flare but also may infect lung interstitium and present as severe viral CAP in patients with SLE. SLE pneumonitis, per se, is not accompanied by severe hypoxemia or a high A-a gradient.[13,14] With SLE flare, the presence of severe hypoxemia and increased A-a gradient and mildly increased serum transaminases (aspartate aminotransferase/alanine aminotransferase) should suggest superimposed CMV. Untreated SLE patients have impaired humoral immunity with impaired B lymphocyte function. Patients with SLE who are on immunosuppressive therapy, in addition, have impaired cell-mediated immunity (CMI) and T-lymphocyte function. In patients with SLE, CMV further intensifies the degree of immunosuppression, ie, impaired CMI.

DIAGNOSIS
Clinical

Clinically in normal hosts, the differential diagnosis of severe viral CAP may be due to a wide variety of viruses. It is usually possible, based on epidemiologic and clinical features, to eliminate some viral causes presenting as severe CAP, such as avian influenza (H5N1), SARS, and HPS. Other viral causes of severe CAP include human influenza, swine influenza (H1N1), adenovirus, and CMV. The most common differential diagnostic problem with severe viral CAP is to clinically differentiate influenza, adenovirus, and CMV. Severe human influenza A infection has characteristic clinical presentation in adults. Unlike CMV and adenovirus, human influenza has a seasonal distribution. Swine influenza (H1N1) should also be considered as a cause of severe viral CAP.[14,18,20–22]

Adenovirus is a great masquerader and may mimic viral and bacterial infections. It is usually relatively straightforward to differentiate influenza from adenoviral CAP. It is not the CXR appearance or degree of hypoxemia that permits clinical differentiation between influenza and adenoviral CAP. Rather, the associated clinical features may suggest the correct diagnosis. The clinical features that suggest adenoviral CAP include lobar infiltrates, conjunctival suffusion, leukopenia, relative lymphopenia, and thrombocytopenia. CMV CAP has, in common with seasonal human influenza and swine influenza (H1N1), otherwise unexplained relative lymphopenia or thrombocytopenia.[14] However, increased serum transaminases, nearly always a feature of CMV, may also occur in influenza, swine influenza (H1N1), or adenoviral infection.[23–25] The presence of atypical lymphocytes argues against the diagnosis of influenza (human, avian, swine) and, to a lesser extent, adenoviral infection, in a patient with viral CAP should suggest CMV CAP (**Table 2**).[14,25]

Patients presenting with severe viral CAP and a negative recent travel or zoonotic contact history with otherwise unexplained leukopenia, relative lymphopenia, thrombocytopenia, atypical lymphocytes with mildly increased serum transaminases should suggest CMV CAP and prompt specific diagnostic testing to confirm or rule out CMV.[1,3,14,25,26]

Although CMV is an uncommon but important cause of severe viral CAP, it is not a cause of late ventilator-associated pneumonia (VAP). In late-onset VAP, unlike in HSV-1, CMV does not present as otherwise unexplained hypoxemia after 1 to 2 weeks in ventilated patients. HSV-1 late-onset VAP often presents as "failure to wean." HSV-1 reactivation occurs secondary to reactivation of HSV-1 from the trauma of intubation/ventilation. Whereas CMV reactivation in blood lymphocytes is detected by CMV antigen, a positive CMV polymerase chain reaction (PCR) is common in septic/ventilated patients without clinical CMV infection.[27–35] Late-onset VAP caused by CMV occurs very rarely.[31,36–38]

Table 2
Differential diagnosis of severe viral CAP in adults

	Influenza	Adenovirus	CMV
Symptoms			
Onset	Acute	Acute	Subacute/acute
Myalgias	+	±	±
Neck/back myalgias	+	–	–
Signs			
Fever	+	+	+
Dry cough	+	±	±
Conjunctival suffusion	±	±	–
Blood-tinged sputum	±	–	–
Laboratory tests			
Leukocytosis	±	–	±
Leukopenia	±	+	±
Relative lymphopenia	+	+	±
Atypical lymphocytes	–	±	+
Thrombocytopenia	+	+	±
Mildly elevated cold agglutinin titers	±	±	±
Mildly elevated serum transaminases (AST/ALT)	±	±	+
Severe hypoxemia (A-a gradient >35)	±	±	±
Chest radiograph			
No/minimal infiltrates (early, <48 h)	+	+	+
Bilateral/patchy infiltrates (later, >48 h)	+	±	±
Focal segmental/lobar infiltrates	–[a]	+	–
Diagnostic tests			
DFA for respiratory viruses	+	+	–
↑ Adenoviral IgM titers	–	+	–
↑ CMV IgM titers	–	–	+[b]
Positive CMV PCR	–	–	±
Diagnostic cytopathology			
BAL	–	–	+
TBB	–	+	+

Abbreviations: AST/ALT, aspartate aminotransferase/alanine aminotransferase; BAL, bronchoal-veolar lavage; DFA, direct fluorescent antibody; IgM, immunoglobulin M; PCR, polymerase chain reaction; TBB, transbronchial biopsy; ↑, increase.
[a] Only with simultaneous bacterial CAP (*S aureus*).
[b] May be falsely positive with rheumatoid factors (RFs) in acute Epstein-Barr virus infectious mononucleosis.
Adapted from Cunha BA. Pneumonia essentials. 3rd edition. Sudbury (MA): Jones and Bartlett; 2010; with permission.

Laboratory Tests

CMV may be diagnosed by isolating the virus from body fluids, such as respiratory secretions and urine; multiple specimens may be needed to demonstrate CMV viruria. CMV cultured from body fluids or biopsy specimens suggests infection, but

after primary CMV infection, some patients become long-term shedders of the virus into the urine. Care must be taken in interpreting the clinical significance of CMV viruria. However, if a patient has an infection compatible with CMV and other pathogens are not isolated, CMV cultured from the urine may have a diagnostic significance. In immunocompetent older children and sometimes adults, CMV viruria may occur after CMV infection. CMV viruria indicates infection in immunocompetent individuals but is uncommon in nonimmunosuppressed hosts. In contrast, viremia is associated with immunocompetent and immunosuppressed adults. CMV viremia may be demonstrated in buffy coat specimens by CMV culture.[1,4,5,9,10]

Viral isolation
Human fibroblast cultures should be observed twice a week for CMV cytopathic effect (CPE). CMV CPEs resemble that of HSV in the first 1 to 2 days. Because CMV CPE changes occur slowly, CMV cultures should be maintained for 3 weeks before being reported as negative. CMV monoclonal antibodies are used to detect CMV in cell cultures approximately 2 days before CPE changes become apparent.[5,9,10,14]

Serologic tests
Serologic testing is the most common method used to demonstrate current or past CMV infection. The diagnosis of recent CMV infection depends on demonstrating either a single elevated CMV IgM titer or a 4-fold increase in CMV IgG titers. Care must be taken in interpreting a single elevated CMV IgM titer because there may be falsely elevated IgM titers in patients with elevated rheumatoid factors (RFs), EBV, or HHV-6 infection. False-positive CMV IgM test results may occur in patients with EBV or HHV-6 infectious mononucleosis because such individuals may produce heterotypic IgM antibodies. RF is an IgM antibody that reacts with IgG. IgM RF forms a complex with CMV IgG. The CMV IgG binds to CMV antigen together with nonviral RF IgM, resulting in false-positive results. False-negative results may occur if there is competitive inhibition of the binding of RF IgM to CMV antigen. For this reason, separate IgM and IgG titers should be ordered to minimize the incidence of false-positive and false-negative CMV IgM results. If there is any discrepancy between CMV IgM titers and the clinical presentation (ie, false-positive/negative tests), RF, EBV VCA IgM, and HHV-6 IgM titers should be obtained.[1,4,5]

CMV antigen assays
CMV semiquantitative antigenemia assay is a sensitive/specific and rapid method to detect CMV activation in lymphocytes. More important than an isolated elevated level are serial increases in CMV antigen titers. In general, a low-titer positive antigenemia indicates asymptomatic infection. Usually with CMV reactivation infection, CMV antigen titers are higher or increase over time. However, in immunosuppressed patients, such as transplant patients, even low or modest CMV antigenemia may indicate reactivation/infection.[5,9,10,18,22]

CMV PCR
CMV PCR is very sensitive and indicates reactivation of CMV in lymphocytes. The main difficulty in using CMV PCR is that it does not distinguish between asymptomatic or latent infection and active infection. Because PCR is so sensitive, serial qualitative PCR, as with semiquantitative CMV antigen levels, may be more clinically useful. As with CMV antigenemia, very high levels or increasing levels suggest active/impending CMV infection. Particularly in immunocompromised hosts, eg, transplants a negative CMV PCR argues strongly against reactivation but not CMV infection. Importantly, in immunocompetent hosts with primary CMV CAP, CMV PCR is usually negative.[4,5,10,18]

CMV cytopathology

Because CMV produces characteristic large cells (cytomegalic cells) with intranuclear basophilic inclusions and cytoplasmic eosinophilic inclusions, active CMV infection can be diagnosed by demonstrating characteristic CMV intracellular inclusions with hematoxylin-eosin, Giemsa, Wright, or Papanicolaou stains in tissue specimens. CMV intranuclear inclusions are surrounded by a clear halo giving them the typical appearance of an ''owl's eye,'' but dense granular cytoplasmic inclusions, although not present in all cells, are diagnostic of CMV active infection (**Table 3**).[1,4,5,14]

THERAPY

CMV, like other herpes viruses, is characterized by its latency, ability to evade host defenses/survive indefinitely, and by its ability to be reactivated resulting in subclinical or clinical infection. CMV reactivation is a function of the host's CMI. CMV is a major problem in compromised hosts with impaired CMI and in those on steroids or immunosuppressive therapy that facilitates the reactivation of CMV. In immunocompetent hosts, most CMV infections are mild-to-moderately severe. However, in some cases, CMV infection in normal hosts may be severe. Excluding HIV with PCP, CMV CAP in compromised hosts, particularly in organ transplants, is usually severe and may be fatal. Anti-CMV therapy may be lifesaving in such cases. CMV is an uncommon cause of severe viral CAP in immunocompetent adults. Severe CMV CAP is treated with CMV antivirals. Often, in normal hosts, CMV CAP resolves during CMV therapy (induction).[18,22]

Table 3
Cytopathologic effects of CMV, HSV, and adenoviral pneumonias

Cytopathologic Findings	CMV[a]	HSV[b]	Adenovirus
Cytopathic effects	+	+	+
Intranuclear inclusions	Early	Late	
Intracytoplasmic inclusions	Late	–	Early (multiple, small) Late (large dense)
Cytomegalia (enlarged infected cell size)	+++	++	+
Intranuclear Inclusions			
Ground glass appearance	–	+	–
Prominent perinuclear halo	+	–	+ (Late)
Kidney bean–shaped nucleus (nuclear molding)	–[e,f]	+[e]	–
Multinucleated giant cells (syncytia)	–	+	–
Eosinophilic intranuclear inclusions	–[c]	+	+[d] (Early)
Nucleolus (basophilic) accessory body	+	–	–
Smudged nucleus	–	–	+
Intracytoplasmic Inclusions			
Dense (basophilic) granular inclusions	+[f]	–	–

[a] CAP.
[b] CAP or Late-onset VAP.
[c] May be eosinophilic early.
[d] Small.
[e] Gomori methenamine silver stain (GMS).
[f] GMS positive and periodic acid-Schiff stain positive.
 Adapted from Cunha BA. Pneumonia essentials. 3rd edition. Sudbury (MA): Jones and Bartlett; 2010; with permission.

Although acyclovir is active against other herpes viruses, it is ineffective against CMV. The mainstay of anti-CMV therapy is ganciclovir 5 mg/kg (intravenous) every 12 hours for the duration of infection. The oral equivalent of parenteral ganciclovir is valganciclovir. Valganciclovir is metabolized to ganciclovir in vivo and is as effective as parenteral ganciclovir. Oral valganciclovir may be used to complete therapy after the initial ganciclovir therapy or may be used for the entire duration of therapy. The dosage of oral valganciclovir for induction therapy is 900 mg (by mouth) every 12 hours for 21 days. In immunocompetent hosts, a complete course of therapy with ganciclovir/valganciclovir is usually not necessary because patients usually improve after 1 to 2 weeks of therapy. In such patients, anti-CMV therapy is often continued for an additional week to prevent potential relapse. Foscarnet is alternative CMV therapy, but is administered intravenously and is nephrotoxic.[1,2,4,5,14,18,22]

The decision to treat CMV CAP is based on severity, that is, the degree of hypoxemia. Treatment of CMV CAP in organ transplants is obligatory but not so in patients with HIV. In patients with HIV, CAP may be caused by the usual typical CAP pathogens or *Mycobacterium tuberculosis*. CAP in patients with HIV may also be caused by an atypical CAP pathogen, for example, legionnaires disease. However, the most common CAP in patients with HIV with mild/moderately decreased CD4 cell counts is PCP. Even though patients with HIV are, by definition, immunosuppressed with various degrees of impaired CMI, CMV is an "innocent bystander" and not a pathogen in such patients. In patients with HIV with PCP CAP, CMV is present in lung tissue in 75% of such patients as an "innocent bystander" and is not responsible for the hypoxemia due to PCP. As PCP is treated in patients with HIV, hypoxemia gradually resolves and CMV does not reactivate but remains an "innocent bystander". For this reason, in HIV patients with PCP CAP, CMV is not treated.[14,25]

COMPLICATIONS AND PROGNOSIS

In patients with organ transplants, CMV CAP may be fatal. The severity of CMV CAP in such patients is related to the degree of impaired CMI. In immunocompetent hosts, even with severe CMV CAP, the prognosis is good. Most mild or moderately severe cases resolve before the diagnosis of CMV CAP is confirmed. In organ transplants with severe CMV CAP, CMV therapy with ganciclovir/valacyclovir is essential.[14,32] CMV CAP in immunocompetent hosts, even if severe, rarely requires a full course of anti-CMV therapy.

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