Nonpulmonary Manifestations of Cytomegalovirus Infection in Immunocompromised Patients

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INTRODUCTION

Cytomegalovirus (CMV) infection is acquired throughout life. By age 50 years, ~50% of the population in a developed country is seropositive for CMV. The clinical impact of infection differs by time of acquisition. Beyond the neonatal period, infection in the healthy patient is asymptomatic in ~90% of cases. When clinical illness occurs, it is usually manifested as an infectious mononucleosis-like syndrome, with atypical lymphocytosis but no heterophil antibody.

Although primary infection with CMV is usually benign, the virus remains latent within the host thereafter, as do all other herpesviruses. Under conditions of immune compromise, especially impairment of cell-mediated immunity, latent virus may reactivate to produce a variety of clinical syndromes, including chorioretinitis, esophagitis, colitis, pneumonia, encephalitis, and adenitis (9, 10). Primary CMV infection is also severe in immunocompromised patients.

CMV infections have been noted in many types of immune compromised patients but are most notable in organ transplant recipients and in patients with AIDS. For example, autopsy and clinical studies indicate that 90% of patients with AIDS develop active CMV infection during their illness, and up to 25% may experience life- or sight-threatening infections due to this virus (10).

CHORIORETINITIS

Ocular disease due to CMV occurs only in patients with severe immunodeficiency and is especially common in patients with AIDS. Clinical evidence of CMV retinitis occurs in at least 5 to 10% of AIDS patients, and autopsy series have revealed that CMV retinitis is present in up to 30% of patients (3). Retinitis is occasionally the presenting manifestation of AIDS but is more commonly present months to years after the diagnosis of AIDS has been established. Retinitis usually begins unilaterally, but progression to bilateral involvement is common. Systemic CMV infection is also frequently present, and viscera may be simultaneously diseased. Retinitis in the peripheral regions of the retina may be asymptomatic. The presence of "floaters," unilateral loss of visual field, or decreased visual acuity is the usual presenting complaint. Ophthalmologic examination typically reveals large, creamy to yellowish white granular areas with perivascular exudates and hemorrhages (referred to as "cottage cheese and cat's foot") (Fig. 1). The abnormalities may be found initially at the periphery of the fundus, but if left untreated, the lesions often progress to involve the macula and the optic disk. In some patients, the initial lesion is in or near the macula. Histologic examination reveals coagulation necrosis and microvascular abnormalities.

Differentials suspected CMV retinitis lesions from cotton wool spots is essential. Cotton wool spots are small, fluffy white lesions with indistinct margins that are not associated with exudates or hemorrhages. They are common in AIDS patients but are asymptomatic. These lesions do not progress and often undergo spontaneous regression.

The differential diagnosis of retinal lesions in patients with AIDS may be complex, and if there is any uncertainty, a diagnosis of such lesions should be made with an ophthalmologist's assistance.

Diagnosis of CMV retinitis is based on characteristic retinal changes and may be supported by culture of the virus from blood, urine, semen, or other samples, since the infection is often generalized. Virologic confirmation is not mandatory, however, and biopsy of the retina itself is rarely performed. Retinal detachment is a frequent complication of CMV retinitis, even with antiviral therapy (15).
GASTROINTESTINAL INFECTION

Colitis

CMV colitis occurs in at least 5 to 10% of patients with AIDS. Diarrhea, abdominal pain, weight loss, anorexia, and fever are frequently present. The differential diagnosis includes infection due to other gastrointestinal pathogens, including Mycobacterium avium complex and Cryptosporidium, Giardia, Entamoeba, Shigella, Salmonella, and Campylobacter spp., as well as Clostridium difficile toxic colitis, although the prominence of abdominal pain may suggest the possibility of diverticulitis, intraabdominal abscess, or mesenteric ischemia. Colonoscopy reveals diffuse mucosal ulcerations that are nondiagnostic (Fig. 2). Biopsy reveals vasculitis, neutrophilic infiltration, and nonspecific inflammation. The presence of CMV inclusions and/or CMV antigen and/or a positive culture of biopsy tissue helps substantiate the diagnosis, especially when the pathogens listed above are not detected by routine smears (including acid-fast smears), cultures, examinations for ova and parasites, or C. difficile toxin assay. Colonic perforation or hemorrhage, as well as peritonitis, may occur as a complication. Colitis due to CMV may improve with ganciclovir therapy or with careful supportive measures (9). In severe CMV gastrointestinal infection, the dosage of ganciclovir should be 5 mg/kg of body weight twice daily for 14 to 21 days (depending on clinical response). Maintenance therapy is usually not necessary, although relapse or recurrences may occur.

Esophagitis

Clinically evident esophagitis in patients with AIDS is most commonly due to either Candida albicans or herpes simplex virus, but CMV may also cause esophagitis. The most common symptom of CMV esophagitis is odynophagia (pain on swallowing), which is present in almost 90% of patients. Dysphagia (difficulty in swallowing) is present in approximately one-third of patients. Ulcerations with characteristic viral inclusions are present in the esophagus of virtually all patients with CMV esophagitis. Thrush is commonly present simultaneously with CMV esophagitis. Failure to respond to treatment for thrush is an instant clue to the presence of CMV esophagitis (7). Patients with esophagitis who do not have Candida albicans or herpes simplex virus detected by endoscopy with microscopy and culture and who do have CMV detected by these methods may benefit from treatment with ganciclovir.

Gastritis

CMV gastritis may also occur and may be signified by severe, continuous epigastric pain. Gastric ulcers may be seen on radiographs or gastroscopy. The diagnosis is made by biopsy, using the same techniques described above for colitis and esophagitis.

Hepatitis

Histologic evidence of CMV hepatitis is seen in one-third to one-half of patients with AIDS who have evidence of CMV infection in other organs. The clinical impact of hepatitis is usually minimal; alkaline phosphatase levels are elevated, but bilirubin levels are rarely increased. It has been suggested that CMV might contribute to the pathophysiology of AIDS-associated sclerosing cholangitis and papillary stenosis by inducing ulceration and subsequent fibrotic strictureting (7).

CENTRAL NERVOUS SYSTEM DISEASE

Subacute encephalitis caused by CMV probably occurs in patients with AIDS, but this syndrome more commonly results from neural invasion by human immunodeficiency virus (18). Fever, altered mental states, personality changes, difficulty in concentrating, headaches, confusion, and somnolence are frequent symptoms. The diagnosis can be documented by cultures of cerebral spinal fluid but may require brain biopsy, with evidence of periventricular necrosis, giant cells, intranuclear and intracytoplasmic inclusions, and isolation or other identification of the virus, e.g., the presence of antigen or nucleic acid. Administration of ganciclovir should be considered in patients who have CMV encephalitis, but no data on ganciclovir’s efficacy are available.

Recently, a syndrome of progressive polyradiculopathy in patients with AIDS has been described (23). Symptoms are notable for acute urinary retention and progressive flaccid paralysis in days to weeks, leading to being bedridden.
Sacral sensory loss with paresthesias and diffuse bilateral leg pain occurs. Cerebrospinal fluid is notable for the presence of a polymorphonuclear leukocytosis, and cultures are positive for CMV. Early recognition and treatment with ganciclovir may minimize progression of the disease.

DIAGNOSIS OF CMV INFECTION

The diagnosis of CMV infection can be substantiated by isolation of virus or seroconversion. A diagnosis of CMV disease is much more difficult to establish. For example, patients may excrete the virus in urine, semen, or cervical secretions for years following its acquisition. Thus, a positive culture from these sites does not, by itself, prove that CMV is the cause of the patient’s current symptoms. Although recovery of the virus from the blood is suggestive of active disease due to CMV, patients may be asymptomatic even when viremic.

The presence of characteristic CMV inclusions in samples from intestinal or esophageal biopsies as well as in brain, liver, and adrenal tissues indicates end organ pathology and is the most definitive evidence that the virus is contributing to or responsible for disease. If no other pathogen is identified, CMV is probably responsible for the disease. However, the detection of viral inclusions is not a sine qua non for proving disease, because inclusions can be rare and therefore may be missed because of sampling error.

In the absence of inclusions, the presence of CMV antigen or in situ nucleic acid may help to define tissue invasion. In such cases a positive CMV culture can further substantiate the probability of CMV disease. However, culture may no longer be the gold standard of diagnosis. There appear to be instances in which detection of CMV antigen or CMV DNA or both in tissue represents a true positive, despite a negative culture.

Cytology and Histology

The microscopic hallmark of CMV infection is the large (cytomegalic) 25- to 35-μm cell containing a large, central, basophilic intranuclear inclusion. The inclusion is referred to as “owl’s eye” because it is separated from the nuclear membrane by a halo. These inclusions are seen well with Papanicolaou or hematoxylin-eosin stain (Fig. 3). Clusters of small intracytoplasmic inclusion may also be seen in CMV-infected cells. These inclusions are best seen with Wright-Giemsa stain.

Cytologic and histologic observations are not sensitive measures of CMV infection. For example, cytologic examination of urine is one-third to one-fourth as sensitive as viral culture. Histologic examination of a small piece of tissue obtained, e.g., by transbronchoscopic lung biopsy is prone to sampling errors and to false-negative results.

Nucleic Acid Hybridization and Polymerase Chain Reaction

The use of DNA-DNA hybridization to detect CMV in clinical samples directly was first described by Chou and Merigan (8) and by Myerson et al. (26). Chou and Merigan ultracentrifuged urine, immobilized the sample on nitrocellulose filters, and hybridized it with a 32P-labeled, cloned probe prepared by digestion of CMV AD-169 with the restriction enzyme EcoRI. Although the test could be performed in 24 h, it was somewhat insensitive: 14 (25%) of 48 culture-positive samples were negative. Virtually all samples with titers of <500 CFU/ml were negative. No false-positive results were reported.

Investigators in other laboratories have reported improved sensitivity of nucleic acid hybridization of urine samples (up to 92%) but have also reported occasional positive results (3 to 12%) in specimens that were culture negative (Table 1) (4,
TABLE 1. Detection of CMV by DNA-DNA hybridization

<table>
<thead>
<tr>
<th>Type of specimen</th>
<th>Reference</th>
<th>No. of positive results</th>
<th>Sensitivity (%)</th>
<th>No. of false-positives/total no. of samples (%)</th>
<th>NPV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>32</td>
<td>34</td>
<td>48</td>
<td>71</td>
<td>80.3</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>22</td>
<td>24</td>
<td>92</td>
<td>3/26</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>47</td>
<td>51</td>
<td>92</td>
<td>1/29</td>
</tr>
<tr>
<td>Buffy coat cells</td>
<td>32</td>
<td>13</td>
<td>14</td>
<td>93</td>
<td>21/52</td>
</tr>
</tbody>
</table>

* NPV, negative predictive value.

32). Positive hybridization assays of culture-negative specimens occurred more often with buffy coat cells (32). On the basis of additional clinical and laboratory data, Spector et al. suggested that the cultures for their patients were false negative rather than that the hybridization assays were false positive (32).

The polymerase chain reaction technique has been successfully applied to the diagnosis of CMV infection in blood and lungs (28). This technique may in some instances be overly sensitive; i.e., it may detect nonreplicating virus that does not cause end organ damage.

Isolation of Virus

The yield of CMV from urine is increased two- to threefold by processing several specimens. Although infectivity can be well preserved for up to 7 days by storing specimens at 4°C, the virus is rapidly destroyed by freezing and thawing. Specimens should therefore be kept refrigerated, and they should be packed in wet ice for transport.

Urine specimens being cultured for CMV can be inoculated directly into cell culture medium. Some authorities have recommended that specimens be diluted to a strength of 1:2 or 1:3.3 (22). Alternatively, specimens may be centrifuged, and the supernatant urine as well as the sediment resuspended in a small volume of urine can each be used as an inoculum. Since CMV grows only in human diploid fibroblast cell cultures, specimens for isolation must be inoculated into a cell line such as WI-38, MA-184, or Flow 2000. Cultures must be maintained for up to 6 weeks, since the characteristic cytopathic effect develops very slowly when titers are low.

In 1972, Anderson and Michaels (1) described the use of fluorescent-antibody staining of cell cultures to permit detection of CMV antigen prior to the development of cytopathic effect. The average time for detection of a positive culture by such staining was 3 days, and the technique was 86% as sensitive as conventional culture.

Recently, investigators at the Mayo Clinic and elsewhere have reported excellent correlation between an overnight cell culture method (shell vial assay), using fluorescent antibodies, and the standard culture procedure (16). In the rapid method, specimens are inoculated by centrifugation at 700 × g in 1-dram (3.7-ml) vials containing a coverslip seeded with MRC-5 cells. After overnight culture, the coverslip cells are stained by the indirect immunofluorescence technique with a monoclonal antibody to an immediate-early CMV antigen.

In a later report, Gleaves et al. found that this test was not only rapid but also more sensitive than the standard tube culture (17). Of 555 urine specimens, 109 were positive for CMV in the shell vial assay versus 77 in the standard tube cell culture assay. Gleaves et al. speculate that the greater sensitivity of the shell vial cultures may stem from the fact that the urine is too toxic to permit the development of the viral cytopathogenic effects but still permits expression of early antigen. The same group also processed 56 lung tissue specimens in a similar manner; 8 were positive in the shell vials, and 7 were positive in the conventional tubes.

The success of the shell vial centrifugation method depends on centrifugation as well as on the types of cells and monoclonal antibodies used. Centrifugation of the clinical specimen increases contact between the cells of the specimen and those of the tissue culture, but it may also increase toxicity. For this reason, some laboratories precentrifuge specimens and then use the supernatant fluid as the inoculum in the centrifugation-inoculation step. When human fetal fibroblasts rather than MRC-5 cells are used, not only the toxicity but also the sensitivity of the centrifugation culture may be decreased (17). The monoclonal antibody used in this procedure should be directed against either immediate-early antigen or a combination of immediate-early and early antigens. For critical samples, e.g., from biopsies or blood, laboratories that use this procedure should continue to perform standard cell culture as well.

Serology

Seroconversion, i.e., the development of CMV antibody in an individual whose serum was antibody negative before or early in the course of infection, usually indicates primary CMV infection. However, levels of complement-fixing (CF) antibodies fluctuated in individuals monitored for 18 months, vaccinating at least once between significant (≥1:8) and undetectable (<1:4) levels (34). Therefore, apparent seroconversion may not really reflect primary infection. Whether this degree of vacillation of antibody level occurs in individuals whose antibodies are measured by another test (e.g., immunofluorescence, indirect hemagglutination, or enzyme-linked immunosorbent assay) is unknown.

Vacillation of titers of CF antibody also complicates the interpretation of a fourfold antibody rise. Up to 16-fold increases in CF antibody are seen when healthy individuals are followed longitudinally (34). Again, it is not known whether such vacillation occurs with antibody types other than CF.

Since CF antibody determinations may miss 10 to 25% of those patients who are antibody positive by other assays (27), latex agglutination, indirect hemagglutination and immunofluorescent-antibody tests are more suitable for antibody screening. The latter test should be done by an anticomplement immunofluorescence procedure because CMV infection induces Fc receptors on the surface of cells, an event leading to a binding of immunoglobulin G (IgG) molecules. Therefore, if serum is being tested for the presence of IgG antibody to CMV by immunofluorescent antibody, IgG may be bound to the cells nonspecifically. When fluorescein-labeled anti-IgG is then added as the detection reagent, it is bound to the IgG on the surface of the cell and gives rise to a false-positive result.

This problem can be avoided by using an anticomplement immunofluorescence procedure (25). In this method, complement is added after the patient’s serum is added. A fluorescein-tagged anticomplement antibody is then added. Complement is bound, and fluorescence is detected only when a true CMV antigen-antibody reaction occurs; fluores-
ence is not detected when there is nonspecific binding of IgG by CMV-induced Fc receptors. The rate of false-positive results in the standard immunofluorescent-antibody test for CMV antibody is as high as 32%. The rate with the anticomplement immunofluorescence procedure is 1.7% (25). Methods such as indirect hemagglutination and enzyme-linked immunofluorescence antibody are not plagued by false-positive results caused by the presence of Fc receptors (14).

Despite the pitfalls described here, seroconversion is usually an excellent marker for primary CMV infection. Although the incubation period for CMV infection may be 3 to 4 weeks, acutely ill patients experiencing a first infection are usually seronegative when they first present. High titers of IgG antibody then develop in 1 to 2 weeks.

Since the processing of acute- and convalescent-phase sera does not provide a rapid diagnosis, considerable effort has been expended to develop a reliable assay for IgM antibody to CMV. The presence of CMV-specific IgM antibody may be helpful in indicating recent or active infection, especially when seroconversion has already occurred by the time the first blood specimen is obtained.

Figure 4 shows the typical course of development of IgM antibody during primary CMV infection. In primary CMV infection, IgM antibody generally develops and then disappears over a period of 6 to 9 months. It would be unusual for this antibody to be absent in an immunocompetent patient suspected of having acute primary CMV infection, especially after a week or more of illness.

In certain types of immunocompromised patients, the ability to mount an IgM response may be impaired by the disease itself or by the treatment for that disease; therefore, titers of IgM antibody may be falsely negative during active infection. In homosexual men, IgM antibody is so prevalent (>90% in our study) that it is far less useful as a positive diagnostic test, but its absence would also argue against acute primary infection (24). The high prevalence of IgM antibody in the sera of homosexual men is presumably a result of reactivation of CMV, although repeated exposure to different strains of the virus may account for its presence in some individuals (13). Theoretically, CMV-specific IgM antibody should be useful for identifying infants with congenital CMV infection. Unfortunately, this test is neither sensitive nor specific in infants (33) and therefore is not as useful as a urine culture obtained at birth or within the first 2 to 3 weeks of life.

![Graph showing CMV serology: antibody response to CMV infection.](image)

**FIG. 4.** CMV serology: antibody response to CMV infection. Time course of the development of CMV-specific IgG and IgM antibodies. Reprinted with permission of Syntex Laboratories, Inc.

### CMV Antigen Detection

Recently, detection of CMV antigen in peripheral blood has provided a rapid and accurate means of detecting CMV viremia. When monoclonal antibody directed against the immediate-early antigen of CMV was used, an immunofluorescence assay of peripheral blood was positive in all patients whose blood was culture positive (30). This assay has the advantage of being completed within hours and appears to be both sensitive and specific.

**TABLE 2. Clinical relapse of CMV retinitis in patients with AIDS**

<table>
<thead>
<tr>
<th>Maintenance ganciclovir</th>
<th>No. of patients relapsing at last follow-up</th>
<th>Days to relapse</th>
<th>Mean Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>20</td>
<td>12/20 (75)</td>
<td>41 47</td>
</tr>
<tr>
<td>Low dose (10–15 mg/kg/wk)</td>
<td>9</td>
<td>5/9 (55)</td>
<td>51 47</td>
</tr>
<tr>
<td>High dose (25–35 mg/kg/wk)</td>
<td>32</td>
<td>13/32 (41)</td>
<td>128 105</td>
</tr>
</tbody>
</table>

* From reference 11, with permission of the publisher.

* Kaplan-Meier estimate.

**TREATMENT OF CMV RETINITIS**

CMV retinitis in AIDS patients is progressive and generally leads to blindness if untreated (21). Ganciclovir stabilizes or improves retinitis and vision in 75 to 85% of AIDS patients with the disease; the degree of improvement depends on the degree to which disease involves the macula (5). If the macula is already destroyed at the onset of therapy, no improvement of vision in that eye should be expected, and if the contralateral eye is not involved, there may be no reason to initiate therapy with ganciclovir. On the other hand, if the macula is edematous secondary to active inflammation nearby, therapy may be expected to markedly improve vision. If the retinal lesions are peripheral, the patient should be monitored very carefully, with at least weekly ophthalmologic examinations, or treatment may be initiated to prevent progression.

Eighty-seven percent of patients with severe CMV infections treated with ganciclovir had a complete virologic response (conversions of culture from positive or negative or a reduction in CMV titer of >100-fold) in urine, and 83% showed such a response in blood culture. The median time until response was 8 days for both blood and urine cultures (5).

Initial induction treatment with ganciclovir consists of 10 mg/kg given in two divided doses for 14 days. After this point, the patient is reassessed, and if retinitis has stabilized or improved, the patient is placed on maintenance ganciclovir at a dose of 30 to 35 mg/kg per week, given in single daily doses of 5 to 6 mg/kg for 5 to 7 days per week. Maintenance ganciclovir is effective in prolonging the time until relapse (Table 2).

Early in the AIDS epidemic, a diagnosis of CMV retinitis was considered a preterminal event, with patients generally surviving less than 6 weeks after the diagnosis. In a recent series by Jabs et al. (20), however, the median survival time after diagnosis ranged from 6 months for all patients to close to 1 year for those who responded to ganciclovir therapy.

Therapy is often complicated by severe neutropenia, which requires temporary discontinuation or dosage modifi-
TABLE 3. Comparison of neutropenia and thrombocytopenia in patients with AIDS versus those with other causes of immunodeficiencya

<table>
<thead>
<tr>
<th>Hematologic parameter</th>
<th>AIDS (%)</th>
<th>Other (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadir of absolute neutrophil countb</td>
<td>&lt; 500</td>
<td>16.2</td>
</tr>
<tr>
<td></td>
<td>&lt; 500 to &lt;1,000</td>
<td>24.3</td>
</tr>
<tr>
<td></td>
<td>≥1,000</td>
<td>59.5</td>
</tr>
<tr>
<td>Nadir of platelet count</td>
<td>&lt; 20,000</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>20,000 to 50,000</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>&gt; 50,000</td>
<td>86.0</td>
</tr>
</tbody>
</table>

a From reference 11, with permission of the publisher. There were 462 patients on whom adequate hematologic data were available to calculate neutropenia; there were 470 patients who were evaluated for thrombocytopenia.
b Counts are number of cells per microliter. Absolute neutrophil count (percentage of neutrophils x leukocytes) + (percentage of bands x leukocytes).

... of ganciclovir in 25% of patients and complete discontinuation in 10% (11) (Table 3). Neutropenia is generally reversible if the drug is discontinued. Granulocyte colony-stimulating factor may provide adjunctive therapy for patients on ganciclovir who are experiencing such severe neutropenia. Other side effects include thrombocytopenia, central nervous system effects, gastrointestinal and liver function abnormalities, and local phlebitis. These are all generally reversible if the drug is discontinued. Zidovudine has overlapping hematologic toxicity with ganciclovir, making it difficult or impossible to administer zidovudine to patients requiring therapy with ganciclovir (19); however, didanosine does not cause significant bone marrow toxicity and is apparently usable in patients receiving ganciclovir. In one study, 82% of patients receiving the combination of zidovudine and ganciclovir experienced life-threatening hematologic toxicity (19). Retinal detachment commonly occurs (10 to 15%) in patients on therapy with ganciclovir (15), but this is probably due to the underlying retinal disease rather than the drug. Ganciclovir is excreted by renal mechanisms and has a half-life of 3 h. Dosage must be adjusted when renal function is impaired.

Relapse or progression of retinitis while the patient is on maintenance therapy ultimately occurs in many cases but may respond to reinduction and higher maintenance doses, as it did in all cases in the series reported by Jabs et al. (20). However, in some cases, relapse may be due to viral resistance to ganciclovir. Resistant CMV isolates may occur in up to 10% of patients on ganciclovir therapy for more than 3 months (12).

Another modality of treatment with ganciclovir that has potential utility is intravitreal administration of the drug. Advantages include the absence of systemic toxicity, no need for intravenous access, and the ability to administer zidovudine simultaneously. Disadvantages include lack of treatment of systemic infection, which is often symptomatic; local complications such as retinal detachment, vitreal bleeding, or endophthalmitis; and the requirement of special skill to administer the drug. Cantrill et al. (6) used intravitreal injections to treat 10 patients who were unable or unwilling to receive intravenous ganciclovir. Vision improved or remained stable after induction (six injections over 2 to 3 weeks) in all but one treated eye, and treatment was well tolerated. Relapse occurred during maintenance (one injection per week) in 20% of infected eyes, but all of these responded to repeat induction. Further studies are under way to explore this modality.

Phosphonoformate (foscarnet) has been approved recently for treatment of CMV retinitis (13). It appears to have an initial efficacy similar to that of ganciclovir. The recommended dosage for maintenance is 60 to 90 mg/kg/day but an optimal maintenance regimen has yet to be determined. Its bone marrow toxicity is not as severe as that of ganciclovir, but it is nephrotoxic. It appears that CMV isolates resistant to ganciclovir maintain susceptibility to foscarnet, and clinical improvement was noted when patients harboring ganciclovir-resistant isolates were switched to foscarnet (21). Studies are under way to determine the comparative safety and efficacy of this agent and to develop an effective dosing regimen.

TREATMENT OF GASTROINTESTINAL INFECTION

Subjective impressions and anecdotes suggest that gastrointestinal CMV infection is responsive to ganciclovir. However, in bone marrow transplant recipients no statistically significant impact on clinical parameters was seen when ganciclovir was compared with placebo. In part, the failure to show an impact was because of a high rate of clinical improvement in the placebo recipients due to general supportive therapy (29). This study did indicate an impressive antiviral effect due to ganciclovir. A similar study in AIDS patients again showed an impressive antiviral effect, but the impact on clinical features was only minimally greater than supportive therapy (9).

FUTURE DIRECTIONS

Efforts are already under way to identify those immunocompromised patients who are at high risk of developing active CMV disease. These individuals would become candidates for suppression of their CMV infection prior to the development of clinical disease. Such suppression might be achieved with acyclovir, which is not effective in the therapy of CMV infection but may be effective in prophylaxis at a time when there is presumably a lower titer of virus in the patient. Other modalities for prevention include the use of ganciclovir in parenteral or, more conveniently, oral form if the latter can be shown to achieve effective antiviral levels in tissues and secretions. An additional possibility is the use of CMV immune globulin to enhance host antiviral activity. For these prophylactic regimens to be useful, it will be necessary to monitor patients by culture or direct detection procedures and to initiate prophylaxis when evidence of active infection is present. An example of such a strategy would be to screen all human immunodeficiency virus antibody-positive patients for CMV viruria. Once their CD4 lymphocyte count dips below 50/mm³, those individuals who are viruric would receive one of the above prophylactic antiviral agents in an effort to prevent the need to treat active CMV retinitis or other end organ disease. An effort such as this would require extreme cooperation between virology laboratories and physicians involved in the care of immunocompromised patients.

REFERENCES


