# Severe Cytomegalovirus Infection in Immunocompetent Patients

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Severe cytomegalovirus (CMV) infection is rare in previously healthy immunocompetent individuals; to our knowledge, only thirty-four such cases have been reported in the worldwide literature. Multiorgan involvement was associated with a high mortality rate among these patients. Disease that clinically involves only the liver or lungs could be fatal; in contrast, none of the patients with isolated central nervous system infection died. Although few patients were treated with specific antiviral therapy, five of six patients with severe infection recovered after receiving therapy with ganciclovir or foscarnet. The rarity of severe CMV disease in immunocompetent patients probably precludes the performance of a clinical trial to evaluate the efficacy of specific antiviral therapy. However, the historically poor prognosis in the absence of such therapy suggests that rapid diagnosis of CMV disease and early instigation of specific treatment may be important.

Cytomegalovirus (CMV) infection is common throughout the world; 40%–100% of adults in different populations become infected by the fourth decade of life [1, 2]. Although primary infection in immunocompetent persons is normally subclinical, a mononucleosis-like syndrome that is characterized by malaise, protracted fever, mild liver-function abnormalities, and lymphocytosis with atypical lymphocytes occurs in ~10% of immunocompetent adults [3, 4]. This syndrome is generally mild and self-limiting, but rarely patients may develop a fulminant infection that manifests with multiple organ involvement and marked constitutional symptoms.

Serious CMV infection occurs more frequently in immunocompromised patients and is a common cause of death among these patients [3, 5]. Studies of immunosuppressed transplant recipients have reported widespread CMV disease in ≤10% of these patients; subsequent mortality is high [6, 7]. Untreated single-organ involvement can also be fatal: studies in the mid-1980s showed that CMV pneumonia occurred in 15%–20% of transplant recipients and patients with AIDS and was associated with a mortality rate of 85% [6, 8].

Because we recently treated an immunocompetent patient with CMV infection and multiorgan dysfunction, we reviewed the literature on severe CMV disease in previously healthy immunocompetent adults to assess the natural history of this condition and its response to specific antiviral therapy.

## Methods

A literature search was performed with use of MEDLINE for the years 1966–1995 and Embase for the years 1980–1995;

the following keywords were used: *cytomegalovirus, cmv, cytomegalic, disseminated, generalized/generalised,* and *fatal.* Both English-language literature and non-English-language literature was reviewed; citations within the retrieved papers were followed up. For inclusion in table 1, patients had to have had severe infection that was considered potentially life-threatening (including all published cases of symptomatic pneumonia or hepatitis) and no underlying illness or previous chemotherapy that may have produced immunosuppression [48]. Cases of postinfection complications such as Guillain-Barré syndrome were not incorporated into the table. A further search of the two data bases was performed to retrieve papers reporting the use of ganciclovir or foscarnet in immunocompetent individuals.

## Severe CMV Disease in Immunocompetent Patients

We identified 34 cases of severe CMV infection in previously healthy individuals (table 1). Three of the patients were pregnant women; this finding suggests that pregnancy-associated immunosuppression [49] had predisposed them to infection. No other immune dysfunction was reported, although only simple blood film analysis was done in the majority of cases. It is possible that a subtle immunologic defect may be recognized in such patients in the future; however, at present there is no evidence for the validity of this hypothesis.

The cases could be divided into those in which multiple or non-CNS organs were involved and those in which the CNS was the only apparent site of disease. The outcome was much poorer for the former group: only nine of 24 patients survived. Nine patients in this group received treatment with corticosteroids for the CMV infection, and two of these nine patients survived. While the small number of patients makes definitive comment on the value of corticosteroid therapy difficult, clinical deterioration was reported after the initiation of this therapy in one case (case 11), and clinical improvement occurred following its withdrawal in another (case 21). In addition, it has

**Table 1.** Features of 34 cases of severe cytomegalovirus infection reported in the worldwide literature.

| Case no. [reference] | Age (y)/ sex | Site of involvement | Method of diagnosis* | Length of hospital stay (d) | Antiviral therapy (post-admission day on which therapy was initiated) | Immunosuppressive therapy[†] | Outcome |
|---|---|---|---|---|---|---|---|
| 1 [9] | 62/M | Liver, stomach, peripheral nervous system, retina | Serology, cultures | 49 (?) | Ganciclovir (21?) | No | Survived |
| 2 [10] | 63/F | Bone marrow, liver | Serology | 25 | Ganciclovir (5) | Yes | Survived |
| 3 [11] | 32/F | Lungs, liver | Serology, culture | 14 (?) | Ganciclovir (3) | No | Survived |
| 4 [12] | 40/F | Brain, muscle, skin | Culture, serology, histology, IFA | 154 | Ganciclovir (149) | NA | Died |
| 5 [13] | 40/F | Lungs, liver | Serology, culture, IH | 35 (?) | Ganciclovir (13) | No | Survived |
| 6 [14] | 35/M | Colon, liver, retina | Histology, IH, serology | NA | Foscarnet (NA) | No | Survived |
| 7 [15] | 21/F | Pancreas, lungs, brain | Histology | 28 | None | No | Died |
| 8 [16] | 34/M | Lungs | Serology | 35 | None | No | Survived |
| 9 [17] | 78/F | Brain, liver | Serology | 100 | Acyclovir (59, 93) | No | Died |
| 10 [18] | 26/F | Liver, brain | Serology | 3 | None | No | Died[§] |
| 11 [19] | 43/M | Liver, adrenal glands, bone marrow | Serology | 14 | Acyclovir (7) | Yes | Died |
| 12 [20] | 45/F | Retina | Serology, culture | 42 | None | No | Survived |
| 13 [21] | 28/F | Lungs, heart | Histology, serology, IFA | 5 | None | No | Died[§] |
| 14 [22] | 33/M | Liver | Serology | 32 | None | No | Died |
| 15 [23] | 38/M | Liver | Histology | 14 | None | Yes | Died |
| 16 [24] | 39/F | Liver, spleen, brain | Histology | 150 | None | Yes | Died |
| 17 [25] | 14/M | Liver, heart | Serology, culture | 35 | None | No | Died |
| 18 [26] | 43/F | Heart, liver, adrenal glands, brain | Serology, histology | 210 | None | Yes | Died |
| 19 [27] | 73/M | Lungs, liver | Histology | 58 | None | Yes | Died |
| 20 [28] | 37/F | Brain, heart, lungs | Serology | 35 | None | No | Survived[§] |
| 21 [29] | 63/F | Lungs, rectum, liver | Histology | 38 | None | Yes | Died |
| 22 [30] | 18/M | Colon | Histology | 143 | None | Yes | Survived |
| 23 [31] | 19/F | Liver | Culture, histology | 540 | None | Yes | Died |
| 24 [32] | 10/M | Liver, lungs | Histology | 20 | None | No | Died |
| 25 [33] | 60/F | Brain | Serology | 360 (?) | None | Yes | Survived |
| 26 [34] | 32/M | Brain | ISH | 40 (?) | Acyclovir (12), ganciclovir (25) | No | Survived |
| 27 [35] | 32/M | Spinal cord | Serology | 40 (?) | None | Yes | Survived |
| 28 [17] | 53/M | Brain | Serology | 60 | Vidarabine (10) | No | Survived |
| 29 [36] | 18/F | Brain | Serology | 21[‖] | None | Yes | Survived |
| 30 [37] | 35/M | Brain | Serology | 7 (?)** | None | No | Survived |
| 31 [38] | 52/M | Brain | Culture | 64 | Vidarabine (50) | No | Survived |
| 32 [38] | 20/F | Brain | Culture | 20 | Vidarabine (10) | Yes | Survived |
| 33 [39] | 31/M | Brain, meninges | Culture, serology | 28 | None | Yes | Survived |
| 34 [40] | 39/M | Brain | Serology | 12 | None | No | Survived |

NOTE.   The prognosis for the 10 patients with isolated CMV encephalitis was excellent (cases 25–34), in contrast to the prognosis for those with multiorgan or non-CNS infection (only nine survived). (Four additional cases of CNS infection were not included because of insufficient detail [41].) ? = exact value not stated; NA = not available.

* Cultures = virus recovered from urine, CSF, blood, or tissue; serology = titer of antibodies to CMV that changed during the illness or was significant; histology = presence of typical cytomegalic inclusion bodies in tissue sample; IFA = positive immunofluorescence or IH = immunohistochemistry for the detection of CMV antigen in tissue sections or bronchoalveolar lavage specimens; ISH = positive in situ hybridization signal in CSF cells.

[†] Corticosteroids given during CMV infection.

[‡] This patient also had intravascular hemolysis. There have also been six reports of CMV-induced thrombocytopenia in immunocompetent adults [42–47].

[§] Patients were pregnant.

[‖] Six months later, patient remained disabled and dysphasic.

** A similar episode of CMV encephalitis occurred 5 months after this first episode.

previously been proposed that the use of corticosteroids for the treatment of ulcerative colitis exacerbates CMV colitis [50].

In contrast, the prognosis for 10 patients with isolated CMV encephalitis was excellent; all of these patients survived (although case 29 still had neurological deficits 6 months after the episode). The diagnoses were made mostly on the basis of viral culture and serology, not definitively at autopsy. The use of corticosteroids was not a predictor of poor outcome for these patients. Treatment of four patients with the antiviral drugs vidarabine or ganciclovir was reported to improve their condition. The uniform survival of patients with encephalitis, whether treated or not, makes it difficult to comment on the efficacy of this therapy. Vidarabine, used for three patients, has been reported to lack efficacy in the treatment of CMV infection [51].

## Treatment of Severe CMV Infection

In both the United States and the United Kingdom, ganciclovir and foscarnet are recommended for the treatment of serious CMV infections in immunocompromised patients [52, 53]. In contrast, there are no recommendations for treatment of severe CMV disease in immunocompetent patients. Indeed, these sources actively discourage the use of antivirals: "The manufacturer warns that ganciclovir should *not* be used in immunocompetent persons since the drug is highly toxic and there currently are insufficient data to establish safety and efficacy in such patients" [52]. The safety and efficacy of foscarnet in nonimmunocompromised patients is similarly described as having "not been established" [52]. Two recent major reviews on the use of ganciclovir and foscarnet in the treatment of CMV disease did not address the role of these drugs in immunocompetent individuals [54, 55].

The major toxic effect of ganciclovir is myelosuppression, which results in cytopenia; this condition is particularly severe when other myelotoxic drugs such as zidovudine are being coadministered [53, 56]. Since immunocompetent patients rarely need to receive such drugs, it is likely that ganciclovir will be less toxic in these patients. Both ganciclovir and foscarnet may also cause renal impairment. Regular monitoring of the serum creatinine level allows withdrawal of the drug as necessary and recovery of renal function [52, 53].

Despite these warnings, we were able to find seven reports of immunocompetent patients with severe CMV disease who had received either ganciclovir or foscarnet (table 1). In addition, because these drugs are perceived as being effective in immunocompromised patients, it is likely that they have been used more frequently in immunocompetent patients but without being reported.

The use of antiviral drugs in only six of 24 patients with multiorgan involvement or non-CNS disease due to CMV may reflect both the recent development of these drugs and the lack of an antemortem diagnosis in some cases. Five of six patients who received either ganciclovir or foscarnet survived, whereas

only four of 18 who did not receive specific therapy survived. In case 4, the diagnosis of CMV disease was made only days before the patient died after a long illness; thus, this patient may have received ganciclovir therapy too late. The two patients treated with acyclovir, an antiviral agent with poor activity against CMV [51], both died.

It is difficult to separate the effects of improved clinical care from the use of antivirals in the increased survival of the more recent cases of CMV disease. The paucity of immunocompetent individuals with severe CMV infection is likely to preclude the setting up of a clinical trial to evaluate the efficacy of specific antiviral therapy. However, the successful outcome following early instigation of specific therapy in cases 1, 2, 3, 5, and 6 and the historically poor outcome of severe CMV disease in immunocompetent adults suggests that such treatment may be of benefit.

## Early Diagnosis of CMV Infection

Some patients had long hospital stays during which their CMV infection was not diagnosed before they died. A definitive diagnosis of CMV infection is based on the histological identification of cytomegalic inclusion bodies, but this procedure can be done only after biopsy or at autopsy. Since biopsy is rarely an early investigation for these patients, it would not result in the early treatment with antivirals which may be associated with improved survival. Although viral culture can be performed in order to reach a diagnosis, it is also a slow procedure. Recent studies indicate that PCR may be a sensitive and specific assay for the early diagnosis of CMV infection, since this technique has detected CMV in both immunocompetent [57] and immunocompromised [58] patients before specific IgM was detectable. It is likely that PCR assay of plasma or leukocytes [58, 59] will become the most important early investigation for these patients.

## Conclusions

We identified 34 cases of severe CMV infection in immunocompetent individuals by reviewing the worldwide literature. Fifteen of these patients died, and most of them had multiorgan involvement; this finding illustrates that CMV can cause severe, multiorgan infection in immunocompetent individuals. We hope that this review will stimulate the early diagnosis of this infection, the reporting of more of these rare cases, and the formulation of guidelines for treatment.

In the absence of a multicenter trial, more-extensive reporting of the management of cases of severe CMV infection may supply the safety data that are currently missing. In the meantime, in light of the effectiveness of ganciclovir therapy and the historically poor prognosis of widespread CMV disease, this infection should be included in the differential diagnosis for immunocompetent patients with severe viral infec-

tions, and the institution of specific therapy for CMV infection should be considered.

## Acknowledgments

The authors thank T. Merigan, K. N. Ward, and J. Kurtz for comments during the preparation of this paper.

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