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# Cytomegalic Inclusion Virus Encephalitis in Patients with AIDS: CT, Clinical, and Pathologic Correlation

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The computed tomographic (CT) scans of 10 patients with acquired immunodeficiency syndrome who had central nervous system (CNS) involvement by cytomegalovirus (CMV) were retrospectively reviewed and correlated with clinical data and pathologic findings. Diagnosis was established in all 10 patients by autopsy, which showed the pathognomonic "owl's eye" intracellular inclusions of CMV. In six patients CMV caused an initial CNS infection that was directly responsible for the patient's progressive encephalopathy and death. In four patients CMV caused a superimposed nondominant CNS infection that had no clinical expression in two. Cortical atrophy and mild hydrocephalus ex vacuo were seen on CT in all 10 patients. Positive findings on CT that could be attributed to infection with CMV were present in only three of the 10 patients, and in these three symptomatic cases autopsy correlation revealed that CT underestimated the degree of CNS involvement. In the other three symptomatic patients, CT showed no parenchymal abnormalities, while autopsy demonstrated diffuse cerebral involvement. In the four patients whose CNS was secondarily involved by CMV, CT showed changes proven at autopsy to be related only to the dominant infection with *Toxoplasma gondii* and to postoperative hematomas. CT did not demonstrate any abnormalities at the sites of CMV involvement, which were found at autopsy in this latter group. It was concluded that CT is not very sensitive for the detection of CMV encephalitis.

Cytomegalovirus (CMV), a member of the herpesvirus family, exists in a latent form in a large percentage of the general adult population [1, 2]. When reactivated this virus most often causes a subclinical or mild infection resembling mononucleosis [1, 3]. Less often encountered is the disseminated form of the disease, which can be fatal and which usually occurs in those with known causes of immunosuppression [1-4]. Recently, severe infection with CMV has been reported in those with the acquired immunodeficiency syndrome (AIDS) [5]. Sites of CMV involvement have usually been outside the central nervous system (CNS), often in the respiratory, gastrointestinal or genitourinary tracts, hematopoietic system, or liver [1, 2, 4]. CMV meningoencephalitis, however, while quite uncommon, has been reported in immunocompromised hosts [3, 4, 6-8], including those with AIDS [5, 9-18], as well as in previously healthy adults [19-22].

While CMV encephalitis has been well described in the clinical and pathologic literature, it has not been reported frequently in the radiologic literature, either before or after the recognition of AIDS, despite radiologic articles on AIDS patients with CNS disease [23-28]. Recent experience at our institution [29] with 62 AIDS patients revealed that the CNS of 16% of these patients was affected by CMV. The paucity of radiologic literature on CNS CMV infections prompted us to review the CT scans in 10 patients with proven CMV encephalitis and correlate the CT findings with the clinical and pathologic material.

## Materials and Methods

The cranial CT scans and autopsy records of 10 patients with CNS CMV were retrospec-

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tively reviewed. Nine patients fit the criteria for AIDS established by the Centers for Disease Control. A presumptive diagnosis of AIDS was made in the other patient, a homosexual man with multiple opportunistic infections and an antibody-positive serum for the human T-cell lymphotropic virus, type III (HTLV-III). This man had been on long-term immunosuppressive therapy for dermatomyositis.

All patients had plain and contrast-enhanced studies performed on the GE 8800 and/or 9800 CT/T scanners. The contrast examinations were performed with a double-dose technique, either immediately and/or after a 1 h delay from the time of intravenous injection. This technique involved the use of 79.3 g of iodinated contrast material.

## Results

### Clinical

Patient ages ranged from 22 to 56 years (median age, 40 years). Of the nine patients with definite AIDS, six were homosexual men, two were Haitian men, and one was a Haitian woman. The other patient was a homosexual man.

In six patients CMV acted as the initial and dominant CNS infecting agent, directly accounting for their abnormal neurologic status and progressive clinical deterioration. In four patients CMV was not the primary source of CNS infection but was found secondarily infecting the brain. The coexistent CNS infections that were found in five patients were secondary to *Toxoplasma gondii* in four, the papovavirus (causing progressive multifocal leukoencephalopathy) in two, and a Gram-positive coccus in one.

In those six patients whose neurologic deterioration was directly caused by CMV encephalitis, CNS symptoms were noted for 8 days to 3 months before admission. They included fever in six, altered mental status in six, progressive confusion in six (leading to coma in three), impaired memory in four, dementia with an inability to care for self in four, and a new onset of seizures in two. A steadily progressive encephalopathy characterized the subsequent hospital course of these patients and resulted in death within 6 days to 8 weeks of hospital admission.

Although a diagnosis of subacute viral encephalitis was entertained in most of these patients, a specific diagnosis of CMV could not be established antemortem. Results of lumbar puncture, performed in three of the six patients, were non-specific. Cerebrospinal fluid (CSF) protein was mildly elevated in all three. Glucose and cell count were normal. Bacterial, mycobacterial, fungal, and viral isolate cultures had no growth. CSF cytology revealed nonspecific inflammatory cells in two patients. Complement-fixation blood titers for CMV did not correlate with disease activity. Autopsy established the final diagnosis by showing intranuclear inclusions pathognomonic of CMV in the brain of all six patients. CMV was also found in the spinal cord and spinal nerves in three patients and in the retina in two patients. There was evidence of disseminated CMV outside the CNS in every patient: CMV was seen in the lung in four, in the adrenals in three, in the gastrointestinal tract in one, in the lymph nodes in one, in the pancreas in one, and in the liver in one.

In the four patients whose CNS was secondarily involved by CMV, initial CNS symptoms were caused by *Toxoplasma*

encephalitis. These symptoms resolved on long-term medical therapy. Autopsy in two of these patients, whose deaths were not CNS-related, revealed inactive *Toxoplasma* lesions, adjacent to which there were very small and clinically insignificant foci of CMV. In the third patient autopsy showed that around a healing *Toxoplasma* lesion and a postbiopsy hematoma, there was extensive parenchymal and ventricular infection with a Gram-positive coccus, the latter believed to be the primary cause of the patient's death. Although not as prevalent, foci of CMV were also found in the same areas and were believed to have contributed secondarily to the patient's neurologic decline. In the fourth patient, superimposed infection with CMV was believed at autopsy to be the cause of the patient's final neurologic deterioration.

### Radiologic and Pathologic Findings

CT showed parenchymal or ventricular abnormalities directly related to CMV in only three patients, all of whom had symptomatic CMV encephalitis. The positive findings in the first patient consisted of diffuse subependymal enhancement, smooth and regular in outline, around the lateral ventricles (figs. 1A and 1B). This abnormal enhancement was best seen on the delayed double-dose scans, which showed denser and broader areas of contrast uptake. Autopsy confirmed these periventricular abnormalities, showing extensive destruction of the ependymal and subependymal regions (fig. 1C). Microscopy revealed enlarged cells resembling an owl's eye (an appearance caused by the distension of the nucleus by intranuclear viral inclusions and by its surrounding halo) in the ependymal cells and subependymal astrocytes of the lateral ventricles (fig. 1D) and in the adjacent white matter. These owl's-eye cells were also found in areas that had appeared normal on CT, including the thalamus, hippocampus, and occipital lobe. Disseminated microglial nodules, a few with intranuclear inclusions, were also seen. Inflammatory response was only slight.

In the second patient CT showed widespread white-matter disease associated with ventricular dilatation and cortical sulcal enlargement (fig. 2). At autopsy CMV was found diffusely throughout the brain and involved both white and gray matter. Intranuclear inclusions were seen in the oligodendroglia, neurons, and astrocytes. The areas of brain involvement by CMV were more extensive than expected from the abnormalities noted on CT.

A small enhancing cortical nodule was the only parenchymal change found in the third patient, despite the presence at autopsy of diffuse parenchymal and subependymal involvement of the brain by CMV. This patient's CT scan also showed ventricular dilatation and markedly enlarged low-density extraaxial spaces. The latter was found at autopsy to represent very dilated subarachnoid spaces, a reflection of the severe cortical atrophy caused by the CMV encephalitis.

In the three other patients with symptomatic CMV encephalitis, CT showed only changes of mild atrophy, while autopsy demonstrated diffuse involvement of the brain by CMV, with both white and gray matter affected.

In the four patients in whom CMV was not the primary



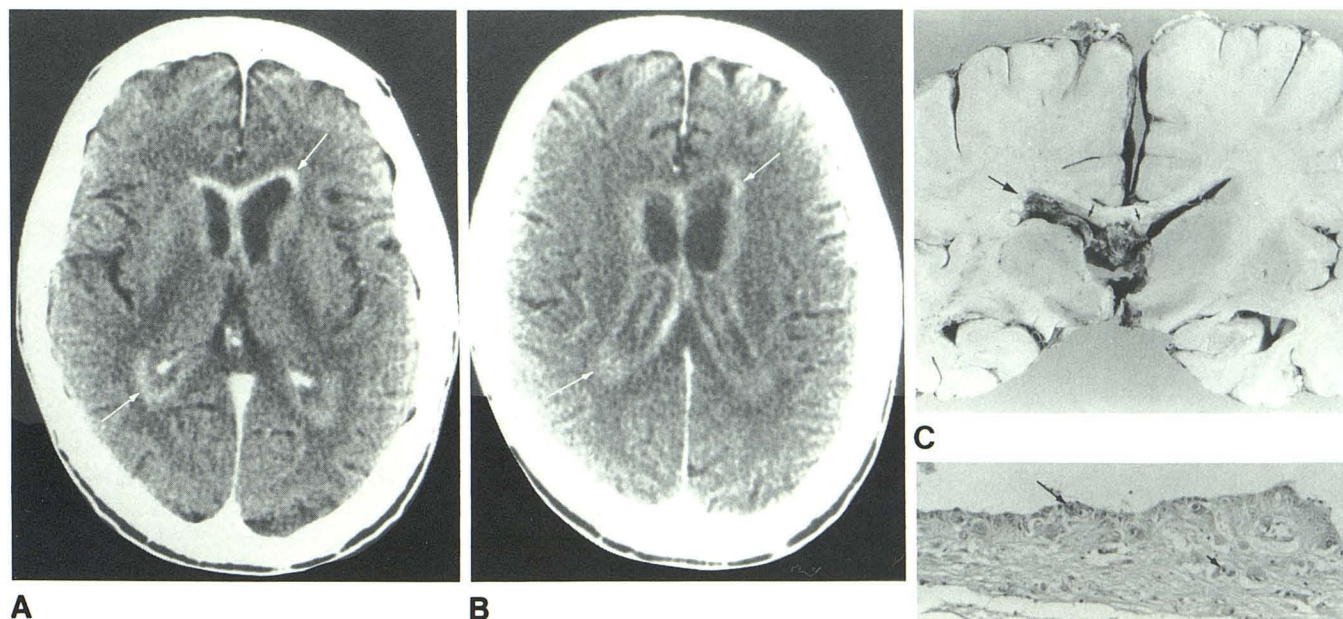


Fig. 1.—A and B, Initial double-dose-contrast axial CT scans 8 days before death. Marked, diffuse periventricular enhancement (arrows). C, Gross specimen, coronal section. Broadening and rounding of lateral ventricular angle and softening of subependymal white matter of cerebral hemispheres (long arrow) and corpus callosum (short arrows) with extension of necrotic exudative tissue into frontal horn. D, Microscopic section of lateral ventricles. Owl's-eye cells pathognomonic of CMV in ependymal cells (long arrow) and in subependymal astrocytes (short arrow). (H and E stain.)

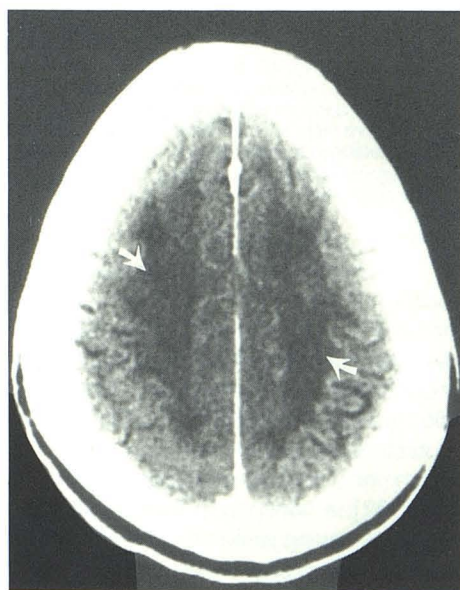


Fig. 2.—Delayed double-dose-contrast CT scan. Diffuse hypodensity of centrum semiovale bilaterally (arrows).

infection, CT findings were related only to the dominant CNS infection with *Toxoplasma gondii* and to postoperative hemorrhage. Figure 3 illustrates one of these cases. It shows that the CT appearance of the *Toxoplasma* lesions and the resolv-

ing hematoma remained essentially unchanged over a 6 month period of medical therapy. While autopsy confirmed the *Toxoplasma* lesions and the chronic hematoma, it also showed widespread changes of CMV in the frontal lobes, corpus callosum, hypothalamus, and ependyma of the lateral ventricles that were accounting for the patient's neurologic deterioration.

Common to all 10 patients in our series were the findings of diffuse enlargement of the cortical sulci and mild hydrocephalus ex vacuo, which were believed at autopsy to be related to CMV in the six patients with symptomatic CMV encephalitis.

In two recent patients with clinically suspected CMV encephalitis (not included in this series and not pathologically proven), magnetic resonance (MR) showed parenchymal abnormalities in the white matter around the ventricles and in the centrum semiovale that were not evident on plain and contrast-enhanced CT scans [30].

## Discussion

Affliction of the CNS and/or peripheral nervous system by CMV, while distinctly uncommon in comparison with other organ involvement, has been reported in both the immunologically normal and immunosuppressed adult [3-8, 8-22]. Conditions such as acute and chronic meningoencephalitis, cranial neuropathy, vasculitis, cerebral hemorrhage secondary to thrombocytopenia, subarachnoid hemorrhage, retinitis, myelitis, brachial plexus neuropathy, and peripheral neuropathy



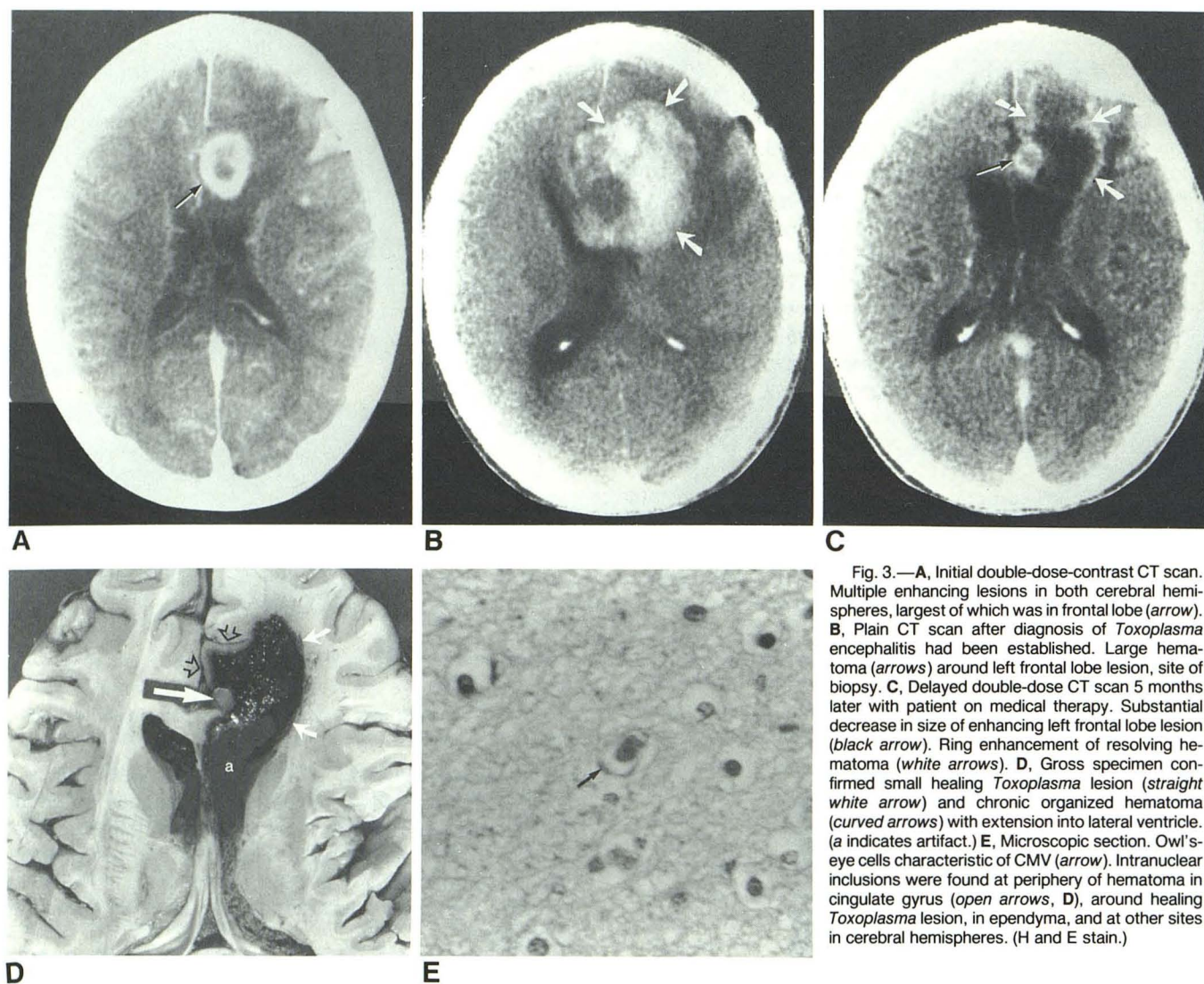


Fig. 3.—A, Initial double-dose-contrast CT scan. Multiple enhancing lesions in both cerebral hemispheres, largest of which was in frontal lobe (arrow). B, Plain CT scan after diagnosis of *Toxoplasma* encephalitis had been established. Large hematoma (arrows) around left frontal lobe lesion, site of biopsy. C, Delayed double-dose CT scan 5 months later with patient on medical therapy. Substantial decrease in size of enhancing left frontal lobe lesion (black arrow). Ring enhancement of resolving hematoma (white arrows). D, Gross specimen confirmed small healing *Toxoplasma* lesion (straight white arrow) and chronic organized hematoma (curved arrows) with extension into lateral ventricle. (a indicates artifact.) E, Microscopic section. Owl's-eye cells characteristic of CMV (arrow). Intranuclear inclusions were found at periphery of hematoma in cingulate gyrus (open arrows, D), around healing *Toxoplasma* lesion, in ependyma, and at other sites in cerebral hemispheres. (H and E stain.)

have all been attributed to CMV [3, 4, 6, 12, 14, 15, 19]. In AIDS patients who have progressive encephalopathy, often characterized by dementia, altered mental status, and psychiatric problems, CMV has been either postulated as or proven to be a cause of this abnormal neurologic state [5, 9, 11–14, 18]. When involving the brain, CMV has been seen to induce either a dominant or a superimposed infection [21, 25].

Because of the infrequent involvement of the CNS by CMV and the protean clinical manifestations that may occur after CNS infection, CNS involvement by CMV has been difficult to diagnose clinically [12, 14]. Laboratory studies, including CSF analysis and complement-fixation blood titers, have usually given nonspecific results [14]. Even at autopsy, owl's-eye cells characteristic of CMV have been difficult to identify [14]. Often the diagnosis of CMV encephalitis has rested on the nonspecific finding of diffuse microglial nodules [3, 7, 8, 12, 14].

Radiologic studies, infrequently described in CNS CMV, have usually been nondiagnostic as well because of the lack of positive or specific findings [6, 10–12, 14, 26, 28]. Generalized atrophy with cortical sulcal and ventricular dilatation has been the most commonly described CT abnormality [11, 12, 14, 25, 26, 28, 31, 32], a nonspecific finding also seen frequently in AIDS patients having diseases other than CMV encephalitis [6, 23, 29]. While some of these patients with atrophy seen on CT had pathologically proven CMV encephalitis [11, 12, 25], most were only suspected [12, 14, 26, 28, 31, 32].

CT abnormalities, other than atrophy, have included those secondary to parenchymal and subarachnoid involvement. Levy et al. [25] described an AIDS patient who had two ring-enhancing hemispheric lesions caused by *Toxoplasma gondii* and who later also developed two small ring-enhancing lesions in the cerebellum proven at autopsy to be caused by focal



CMV encephalitis. In the report of Snider et al. [12], marked hypodensity of the white matter bilaterally was seen in two AIDS patients with CMV encephalitis. Hawley et al. [10] reported an AIDS patient with CMV encephalitis whose CT scan just before death revealed subarachnoid hemorrhage but did not show changes of parenchymal necrosis secondary to CMV.

In the literature reported to date, there has been, to our knowledge, no large series of AIDS patients who have had CT scans and pathologically proven CMV encephalitis. In the 15 patients described by Burszty et al. [28] who had progressive encephalopathy and CT scans showing cortical atrophy, CMV was strongly suspected but the virus was not isolated. In the 18 patients reported by Snider et al. [12] (10 of whom showed cortical atrophy on CT), definite histologic evidence of CMV was found in four. Recently, the HTLV-III virus has been postulated as a cause of some of these cases of unexplained encephalopathy [16]. While autopsy results strongly suggest that in our six patients with symptomatic CMV encephalitis the atrophy was secondary to the CMV infection, the possibility that the HTLV-III virus may also have contributed to the atrophy cannot be excluded.

Other CT findings in our series included periventricular enhancement and diffuse white-matter hypodensities. These abnormalities were not unexpected considering our autopsy results and reports in the literature that show that CMV sometimes affects the ependymal and subependymal cells and adjacent astrocytes of the white matter [3, 10] and that demyelination of the white matter can occur [3, 12, 14]. The periventricular region is, of course, well known to be the site of predilection in infants with congenital CMV [10]. On the basis of this autopsy correlation, it would seem prudent to include CMV encephalitis in the differential diagnosis of AIDS patients with progressive encephalopathy whose CT scans show either subependymal enhancement or white-matter disease.

These CT findings, of course, are not specific. Periventricular enhancement has been seen in AIDS patients with lymphoma [23–25, 29] and cerebral toxoplasmosis [27] and in non-AIDS patients with various other tumors and infections. White-matter hypodensities have been observed in AIDS patients with PML [23, 24, 28, 29] and in non-AIDS patients with a variety of degenerative and vascular diseases. Despite their lack of specificity, these CT abnormalities do localize disease for possible biopsy.

Because of the frequent lack of positive CT findings in AIDS patients with CMV encephalitis, we recommend the use of MR when no discrete lesions are identified on CT. Our early experience with MR suggests that it can detect diffuse CNS lesions in AIDS patients that are not apparent on CT [30]. White-matter lesions are particularly well seen on MR and are evident at earlier stages of the disease than on CT.

As a result of our study, we conclude the following:

1. CMV should be recognized as one of the causes of encephalitis in patients with AIDS.
2. Typically, it causes a progressive encephalopathy, often characterized by dementia, and usually fatal.

3. CT is not a very sensitive imaging method in the detection of CMV encephalitis. Scans are usually noncontributory or when positive underestimate the degree of CNS involvement.

4. We suggest MR be used to aid in the early detection of this infection after initial CT has been performed.

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