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Magnetic resonance brain imaging lacks sensitivity for AIDS associated cytomegalovirus encephalitis

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Six patients are presented who died with active cytomegalovirus (CMV) encephalitis in whom brain MR scans within 25 days of death failed to reveal distinctive findings suggesting the diagnosis of CMV encephalitis. While MR scanning is crucial to evulation of AIDS patients developing neurologic complications, it is not sensitive to the presence of CMV encephalitis even when it is quite severe. The diagnosis of CMV encephalitis during life rests on characteristic clinical findings supported by typical laboratory measures including the presence of CMV DNA in cerebrospinal fluid as detected by polymerase chain reaction.

Keywords: viral encephalitis; magnetic resonance imaging; cytomegalovirus; encephalitis diagnosis

Introduction

Cytomegalovirus (CMV) has become a major opportunistic pathogen in human immunodeficiency virus (HIV) infection. Prior infection with CMV has occurred in approximately 60% of the adult population and over 90% of male homosexuals (Drew *et al*, 1981; Ho, 1990). As HIV infection advances to severe immunodeficiency marked by CD4 lymphocyte counts below 100 cell per mm^3, complications of CMV including retinitis, esophagitis, gastroenteritis, and pneumonitis are clinically recognized. Encephalitis is described as a rare manifestation in most clinical series (Gallant *et al*, 1992), yet CMV infection can be demonstrated using immunocytochemical or nucleic acid detection in roughly a third of HIV brains at autopsy (Wiley and Nelson, 1988; Achim *et al*, 1994). These observations suggest that CMV encephalitis is often not recognized during life.

Neuroimaging provides the clinician with important tools for characterization of brain disease in life. Thus, careful correlation of magnetic resonance (MR) images with pathologic findings is helpful in understanding the potential usefulness of this imaging procedure. We describe six patients with CMV encephalitis demonstrated at autopsy in whom negative MR images were obtained within 1 month of death. Our experience demonstrates that the manifestations of this encephalitis may be very subtle or undetectable by MR imaging even when the disease is at an advanced stage. Thus, MR imaging is unreliable for detection of CMV encephalitis.

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Methods

Autopsies of HIV patients at Washington School of Medicine were reviewed for the period 4/92 to 4/94. Consent for all autopsies was routinely obtained from the appropriate family members according to hospital policy. Thirteen subjects with CMV encephalitis had clinical evaluations and cerebrospinal fluid (CSF) available for review and analysis. In eight of these cases MR scans were available, six of them within 25 days of death. We review these six cases to correlate pathologic findings with MR imaging at an advanced stage of CMV encephalitis.

Magnetic resonance (MR) images were produced with 1.0 or 1.5-T superconducting magnets (Magnetom: Siemens, Iselin, NJ and Signa; General Electric, Milwaukee, WI) and a standard head coil. Axial T1-weighted (400–600/11–15 [TR/TE]), proton density-weighted (2400–3000/20–30), T2-weighted (2400–3000/90–95), and enhanced T1-weighted (400–800/11–22) spin-echo MR images were performed on all patients. Enhanced images were obtained immediately after IV administration of 0.1 mmol/kg gadopentetate dimeglumine (Berlex, Wayne, NJ). Sagittal and coronal images were evaluated when available. One patient had addi-

tional fast spin echo proton density-weighted (2150/13) and T2-weighted (3000/95) axial images. Other technical parameters included 3 to 6 mm slice thickness, 128–256 × 256 matrix and 20, 22, 23 or 25 cm field of view.

At autopsy the brains were placed in 10% buffered formalin for 2–8 weeks, then paraffin-embedded according to a standard protocol. In each case at least 10 sections (frontal cortex, basal ganglia, hippocampus, thalamus, occipital cortex, midbrain, pons, medulla, cerebellum and spinal cord) were stained with hematoxylin-eosin and examined microscopically.

Cytomegalovirus infection was defined by the identification of typical cytomegalic cells on stained tissue section. The pathology of all cases reported in this manuscript were classified as cases of CMV ventriculoencephalitis. This is a distinctive neuropathologic entity characterized by the presence of cytomegalic cells, microglial nodules, necrosis, macrophage infiltration and astrocytosis in the ventricular/periventricular areas.

The MR images and microscopic images were jointly reviewed by the neurologist, a neuroradiologist and a neuropathologist. The presence and location of MR detected white matter disease, defined as abnormally increased signal intensity on proton density-weighted and T2-weighted images, and the presence, location and intensity of abnormal contrast enhancement on the enhanced T1-weighted images were noted. Lesions detected on imaging were then correlated to the brain specimens collected from the area of interest at autopsy.

Results

The cases presented all developed cytomegalovirus encephalitis. Retrospective analysis of cerebrospinal fluid from these and other autopsy proven cases has been reported elsewhere (Arribas *et al*, 1995). When CSF is sampled during active CMV encephalitis, CMV DNA is routinely detected by polymerase chain reaction (PCR). More detailed histories are provided illustrating the clinical course, imaging and pathologic findings in our cases.

Case 1

This 51 year old man contracted HIV from blood products required for treatment of his factor 9 deficiency syndrome. His mental status rapidly declined shortly after he developed CMV pneumonitis. On his terminal admission serum sodium was 126 mEq/l, CSF had no nucleated cells, protein of 129 mg/dl and glucose of 45 mg/dl. A seizure occurred 3 days after admission. Symptomatic therapy was instituted but the patient died 10 days after admission. An MR scan 14 days prior to death (Figure 1) revealed ventriculomegaly and prominence of the cortical sulci due to brain atrophy. On post mortem (Figure 1) the brain had extensive CMV ventriculoencephalitis. Ventricular and periventricular portions of the cerebral hemisphere and brainstem as well as subpial and parenchymal areas were involved. Extensive microglial nodular encephalitis, some with CMV inclusions could be identified. Further, several hemorrhagic areas in pons, parietal white matter, and cerebellum not appreciated on the MR scan consisted of foci of necrotic neurons and neurophil, endothelial prominence, macrophages, and axonal spheroids. These latter lesions were consistent with a hemorrhagic ischemic process associated with CMV vasculitis.

Case 2

This 41 year old homosexual male was diagnosed with HIV in 1987. In 1991 he was treated for *Mycobacterium avium intracellulare* septicemia. Three months later he developed CMV retinitis and ganciclovir therapy was initiated. Additionally, he developed ataxia, dizziness and nystagmus. CMV was detected in CSF by polymerase chain reaction and CMV therapy was increased to induction doses. He developed facial palsy and deafness. His later course was complicated by DDI-associated pancreatitis, and deep venous thrombosis with pulmonary emboli. He died suddenly during a grand mal seizure. His brain MR scan obtained 6 days before death revealed moderate cerebellar atrophy (Figure 2a). Internal auditory canals and cerebelluar pontine angles were normal. No periventricular disease was noted. At autopsy CMV ventriculoencephalitis was identified (Figure 2b). Pontine and medullary involvement extended some distance from the ependymal surface. Microglial nodules studded the pons, medulla, cerebellum and spinal cord.

Case 3

This 43 year old man had advanced AIDS with very low CD4 count and a history of cryptococcal meningitis and CMV retinitis. He had been successfully treated for the cryptococcal disease and was maintained on itraconazole. He was admitted to the hospital because of rapidly progressive weakness. Hypophonia was noted, and ENT examination revealed bilateral vocal cord paralysis requiring tracheostomy. Bilateral CN VI paresis and right facial paresis were noted on neurologic exam. CSF had >1000 nucleated cells/mm^3 with approximately 80% polymorphonuclear cells. CSF glucose was 30 mg/dl and protein was minimally elevated. CMV DNA was detected in CSF by the polymerase chain reaction. Continued CMV therapy with induction doses of ganciclovir and amphotericin therapy was given, but his condition progressed and he expired. MR scan performed 15 days before expiration revealed no meningeal enhancement and

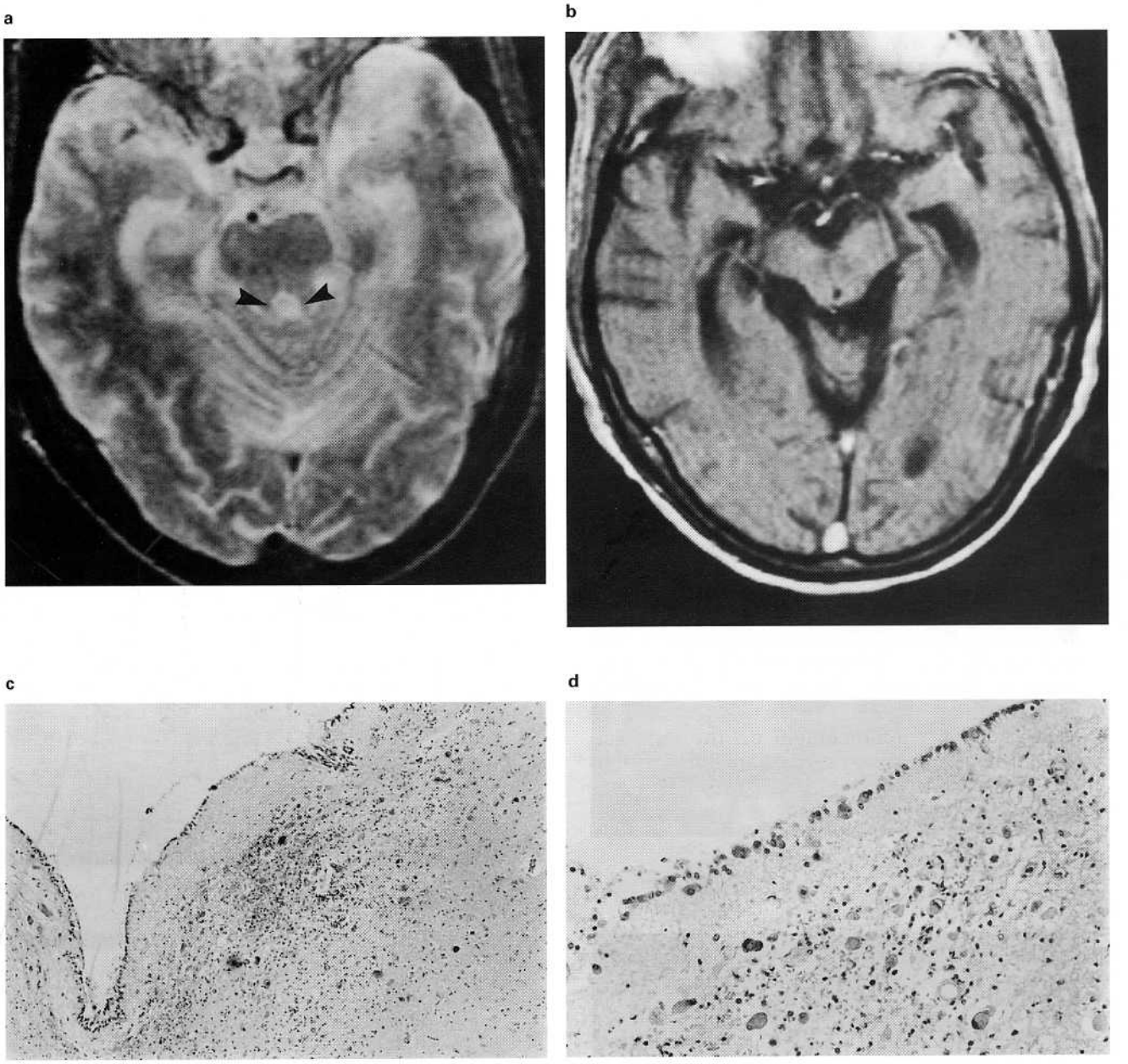


Figure 1 51 year old patient with CMV ventriculitis and encephalitis and pathologically proven severe involvement of hippocampal and aqueduct of Sylvius ependyma. The MR was obtained 14 days prior to death. MR and pathologic illustrations are from corresponding regions of the brain in this case. (a) axial T2-weighted image (2400/90) demonstrate periadequaductal hyperintensity, medial temporal lobe atrophy, and enlargement of the temporal horns. (b) axial enhanced of T1 weighted image (800/22) also shows the atrophy, however fails to demonstrate pathologic enhancement. (c) Pathological involvement of ependyma with sub-ependymal encephalitis at the level of the aqueduct (original magnification $\times 500$). (d) left ventricular ependymitis with cytomegalic inclusions in the ependyma in the subependymal region (original magnification $\times 800$).

no periventricular abnormality (Figure 3a). At autopsy widespread CMV encephalitis (Figure 3b) was detected in sections of cerebral hemispheres, cerebellum, brainstem and spinal cord. Diffuse involvements of the subarachnoid brain parenchyma by CMV infected cells without a significant inflammatory cell response was discovered. CMV related brain destruction was most severe in regions including the pons, medulla and spinal cord where nearly circumferential destruction of brain tissue occurred.

Case 4

This 40 year old man with AIDS and a history of PCP pneumonia, disseminated *Mycobacterium avium*, thrush and anemia, presented with progressive paraplegia. Examination revealed early CMV retinitis and CMV DNA was detected in CSF by

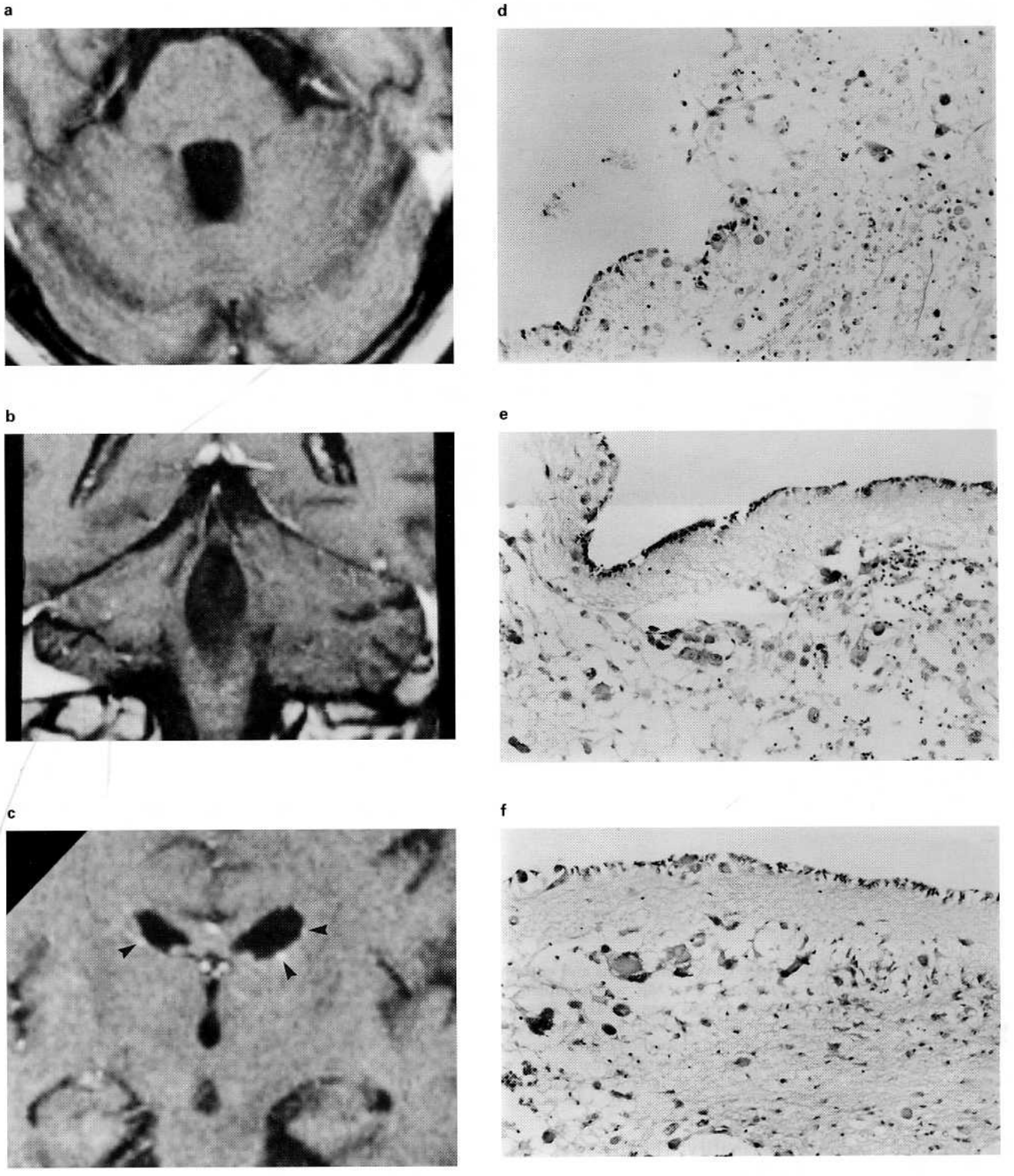
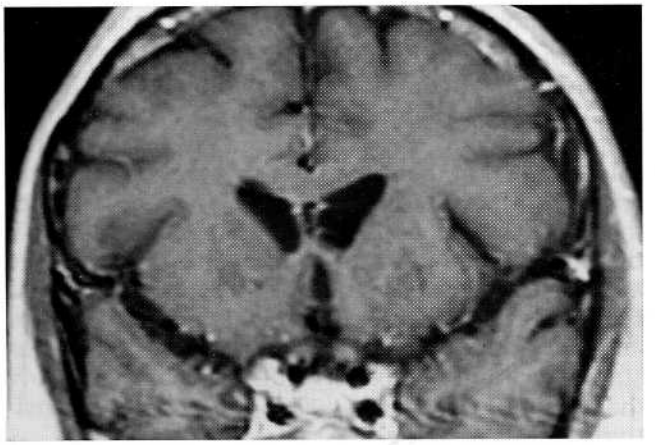


Figure 2 41 year old patient with CMV encephalitis and pathologically proven extensive pontine and medullary involvement and ventriculitis. The MR was obtained 6 days before death. Pathologic illustrations show marked encephalitis in regions of MR scans failing to demonstrate this pathology. (a) axial and (b) coronal enhanced T1-weighted images (600/20) demonstrating cerebellar atrophy without periventricular enhancement. (c) coronal enhanced T1 weighted image (600/20) showing minimal nodular enhancement surrounding the later ventricles. (d) subependymal and ependymal encephalitis at level of fourth ventricle (×800), (e) aqueduct (original magnification ×1000) and (f) left lateral ventricle (×800).

a



b

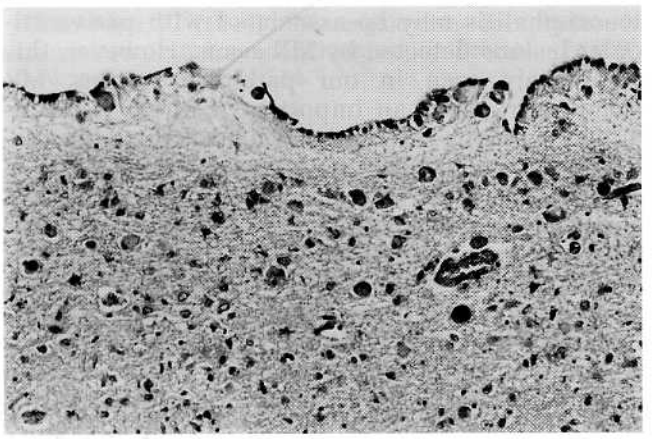


Figure 3 43 year old patient with CMV meningoencephalitis and pathologically proven ependymitis. The MR was obtained 15 days before death. (a) Coronal enhanced T1-weighted image (549/16) fails to reveal periventricular enhancement while (b) marked ependymitis and subependymal CMV encephalitis is demonstrated in the corresponding pathologic sections (original magnification ×800).

PCR. Ganciclovir therapy was started. He demonstrated improved mentation and gait and lived independently for several months, when abrupt deterioration occurred. A repeat scan 25 days prior to his death revealed a new mass lesion in the roof of the right lateral ventricle associated with periventricular enhancement. Noncontrasting nodular and linear ventricle associated with periventricular enhancement. Noncontrasting nodular and linear areas of increased signal were noted within the periventricular white matter and right cerebellum on proton density-weighted and T2-weighted images. The patient and his family elected comfort measures only. At post mortem examination, malignant lymphoma was detected in the basal ganglia, hippocampus and cerebellum. Cytomegalovirus infection involved the same areas and also the thalamus, midbrain, spinal cord and pons.

Case 5

This 43 year old man with advanced HIV developed CMV retinitis and was treated with ganciclovir. Five months later he developed ataxia, nystagmus and progressive dementia. Therapy was changed to foscarnet, but the patient progressed to death. An MR scan performed 24 days before his death, showed progressive atrophy compared with the scan 62 days before death. Minimal white matter pallor was unchanged. No periventricular enhancement was observed. At autopsy the cerebral cortex, cerebellum and brainstem all had periventricular necrosis, astrocytosis, and macrophage infiltrates associated with cytomegalic cells with typical CMV inclusions.

Case 6

This 43 year old man with advanced HIV, CMV retinitis and systemic lymphoma presented with lethargy and changed mental status. An MR scan performed 4 days prior to death revealed cerebral atrophy. Multiple discrete lesions were noted in basal ganglia, caudate nucleus and thalamus bilaterally, as well as pons, cerebellum and gray matter of all lobes of brain. Some showed enhancement. At post mortem these lesions were found to be malignant lymphoma. Some of the lesions had extensive tumor necrosis. The ventricular system and subependymal brain parenchyma were diffusely involved with severe cytomegalovirus encephalitis. The MR scan showed no abnormalities in these areas.

Discussion

CMV encephalitis has been diagnosed primarily at autopsy. This virus is rarely cultured from the spinal fluid, and in the setting of advanced immunodeficiency, other clinical problems tend to obscure the manifestations of CMV. Two effective drugs are currently available for treatment of CMV and therefore early diagnosis is especially important.

Prior reports suggest that computerized tomography (CT) is insensitive for detection of CMV brain disease. Post *et al.* (1986) reported 10 patients with AIDS and pathologically proven CMV brain involvement who had brain CT scans performed. Cortical atrophy and mild hydrocephalus ex vacuo were seen in all patients. These findings are also common in advanced HIV without CMV. In three of the ten cases, periventricular enhancement following double dose of intravenous contrast, widespread white-matter disease, or an enhancing cortical nodule suggested CMV, but in all cases the imaging missed or underestimated the degree of CMV involvement in the brain. Other reports summarized in Kalayjian's review of CMV encephalitis (Kalaygian *et al*, 1993) report 1/4 CTs in his

own series, and 1/12 in the literature demonstrating periventricular enhancement. Ventriculomegaly, though slightly more common, is of little diagnostic value in identifying CMV disease because of its non-specificity.

Because MR brain scanning is more sensitive for several pathologic processes in HIV including progressive multifocal leukoencephalopathy (PML), manifestations of HIV encephalitis and toxoplasma encephalitis, MR has become the preferred imaging modality for AIDS patients presenting with progressive neurologic disease. Some reports suggest that MR is also more sensitive than CT for detection of periventricular abnormalities associated with CMV encephalitis. Radiologic reports demonstrate white matter and periventricular lesions in reported cases of CMV encephalitis (Ramsey and Geremia, 1988; Davenport *et al*, 1992; Tien *et al*, 1993). Kalayjian reported periventricular abnormalities in 4/4 patients in his series (Kalayjian *et al*, 1993). Holland *et al* (1994) noted that 5/6 cases of autopsy proven CMV encephalitis had periventricular hyperintensity while 3/6 showed meningeal enhancement on MR scans. Diffuse white matter hyperintensity was seen in 1/6 and atrophy in 3/6. However, 3/8 patients with HIV encephalitis also showed periventricular hyperintensity, although none had meningeal enhancement and 4/8 had atrophy.

Consequently, the published literature suggests that periventricular hyperintensity on T2-weighted MR images correlates with CMV ventriculoencephalitis. Although this relationship seems plausible considering the degree of subependymal damage that typifies these cases, our experience suggests that MR scanning may not be sensitive for detecting this pathologic process. Scans of our patients uniformly failed to show unequivocal evidence of periventricular disease. These patients had full blown, clinically symptomatic CMV encephalitis at the time of these MR scans. They died with extensive CMV encephalitis within days of the scans. Yet, these MR scans did not reliably reveal the pathologic process. Further, this was true of all autopsy proven cases at our institution in which MR scans were performed shortly before the patient's death. It is unclear why CMV encephalitis produces such minimal change in some MR scans. Perhaps the lack of inflammatory response, and generally mild impairment of blood brain barrier may be an explanation. Review of the pathologic description of all six cases indicates that the inflammatory response was minimal or absent. Alternatively, the role of our therapeutic efforts in these cases might have modified the interaction of host and virus in these cases. All of these patients received CMV therapy at some point prior to death. However, the author has diagnosed other subjects with similar clinical and CSF presentation who had not received any CMV therapy, and in whom the MR image was similarly non-diagnostic. Thus, it seems unlikely that failing CMV therapy accounts for the insensitivity of MR imaging.

Our conclusion is that MR is insensitive for detection of CMV encephalitis. Active ventriculoencephalitis may be associated with periventricular lesions detected by MR scans. However, this was rarely seen in our pathologic series. MR scanning remains an important method in distinguishing among the causes of neurologic deterioration in advanced HIV patients, but it may fail to detect CMV ventriculoencephalitis. The criteria of abnormal enhancement of T1-weighted or periventricular hyperintensity on T2-weighted MR misses many patients with clinically advanced disease. Therefore, to confirm the diagnosis of CMV encephalitis suggested clinically by progressive encephalopathy, brainstem signs, and cranial neuropathy in patients with far advanced HIV infection, one should rely on supporting laboratory values such as the CSF polymerase chain reaction (Arribas *et al*, 1995; Cinque *et al*, 1992, 1995; Wolf and Spector, 1992; McCutchan, 1995) rather than on MR imaging.

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References

Achim CL, Wang R, Miners DK, Wiley CA (1994). Brain viral burden in HIV infection. *J Neuropath & Exper Neurol* **53:** 284–294.

Arribas JR, Clifford DB, Fichtenbaum CJ, Commins DL, Powderly WG, Storch GA (1995). Level of cytomegalovirus (CMV) DNA in cerebrospinal fluid of subjects with AIDS and CMV infection of the central nervous system. *J Infect Dis* **172:** 527–531.

Cinque P, Baldanti F, Vago L, Terreni M, Lillo F, Furione M *et al* (1995). Ganciclovir therapy for cytomegalovirus (CMV) infection of the central nervous system in AIDS patients: monitoring by CMV DNA detection in cerebrospinal fluid. *J Infect Dis* **171:** 1603–1606.

Cinque P, Vago L, Brytting M, Castagna A, Accordini A, Sundqvist V-A, Zanchetta N, Monforte AD, Wahren B, Lazzarin A, Linde A (1992). Cytomegalovirus infection of the central nervous system in patients with AIDS: Diagnosis by DNA amplification from cerebrospinal fluid. *J Infect Dis* **166:** 1408–1411.

Davenport C, Dillon WP, Sze G (1992). Neuroradiology of the immunosuppressed state. *Radiologic Clinics of North America* **3:** 611–637.

Drew W, Mintz L, Miner RC, Sands M, Ketterer B (1981). Prevalence of cytomegalovirus in homosexual men. *J Infect Dis* **143:** 188–192.

Gallant JE, Moore RD, Richman DD, Keruly J, Chaisson RE, the Zidovudine Epidemiology Study Group (1992). Incidence and natural history of cytomegalovirus disease in patients with advanced human immunodeficiency virus disease treated with zidovudine. *J Infect Dis* **166:** 1223–1227.

Ho M (1990). Epidemiology of cytomegalovirus infections. *Rev Infect Dis* **12** (suppl 7): S701–710.

Holland NR, Power C, Mathews VP, Glass JD, Forman M, McArthur JC (1994). Cytomegalovirus encephalitis in acquired immunodeficiency syndrome (AIDS). *Neurology* **44:** 507–514.

Kalayjian RC, Cohen ML, Bonomo RA, Falnigan TP (1993). Cytomegalovirus ventriculoencephalitis in AIDS. A syndrome with distinct clinical and pathologic features. *Medicine* **72:** 67–77.

McCutchan J (1995). Cytomegalovirus infections of the nervous system in patients with AIDS. *Clin Infect Dis* **20:** 747–754.

Post MJD, Hensley GT, Moskowitz LB, Fischl M (1986). Cytomegalic inclusion virus encephalitis in patients with AIDS: CT, clinical and pathologic correlation. *AJN* **7:** 275–280.

Ramsey RG, Geremia GK (1988). CNS complications of AIDS:CT and MR findings. *AJR* **151:** 449–454.

Tien RD, Felsberg GJ, Osumi AK (1993). Herpesvirus infections of the CNS: MR findings. *AJR* **161:** 167–176.

Wiley CA, d Nelson JA (1988). Role of human immunodeficiency virus and cytomegalovirus in AIDS encephalitis. *Am J Path* **133:** 73–81.

Wolf DG, Spector SA (1992). Diagnosis of human cytomegalovirus central nervous system disease in AIDS patients by DNA amplification from cerebrospinal fluid. *J Infect Dis* **166:** 1412–1415.