AIDS-Associated Cytomegalovirus Infection Mimicking Central Nervous System Tumors: A Diagnostic Challenge

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We reviewed cases of cytomegalovirus (CMV) infection of the central nervous system (CNS) that initially masqueraded as tumors in 37 of 543 consecutive patients infected with human immunodeficiency virus (HIV) and CMV who were seen at the Pasteur Institute Hospital and Saint-Louis Hospital (Paris) between 1992 and 1994. We detail the clinical features of three patients who presented with ring-enhanced space-occupying lesions mimicking CNS tumors. They were all profoundly immunodepressed (mean CD4 cell count, 13/mm³). Magnetic resonance imaging (MRI) showed enlargement of the spinal cord in one case, consistent with a space-occupying lesion and showing gadolinium enhancement; in the other two cases, ring-enhanced mass lesions were seen in the cerebral hemispheres. In all three cases marked edema and a mass effect were present. Image-guided stereotactic biopsies confirmed the diagnosis of CMV infection. The three patients’ conditions improved with specific therapy. MRI showed enhanced focal intraparenchymal lesions consistent with marked focal necrosis, probably related to the severity of immunodepression, as HIV infection had been diagnosed several years previously. CMV infection should be considered as a cause of ring-enhanced space-occupying mass lesions in patients with HIV-1 infection. Earlier identification of these unusual tumorlike forms of CMV infection by means of MRI should result in improved outcome.

Cytomegalovirus (CMV) infection is the most common opportunistic viral infection associated with HIV infection: it is recognized before death in up to 40% of patients with end-stage AIDS and in up to 90% at autopsy [1, 2]. CMV causes retinitis and gastrointestinal disease, and both the peripheral nervous system and the CNS are vulnerable to CMV infection. The latter causes neurological manifestations ranging from encephalitis to polyradiculomyelopathy and multifocal neuropathy [1, 3]. Autopsy studies have found CMV encephalitis in up to 30% of HIV-infected patients [1, 2], but polyradiculomyelitis occurred in only 2% of patients with AIDS and neurological disease [4]. Spinal-cord involvement may manifest as necrotizing myelopathy with perifocal demyelination [5] or as myelitis with vascular involvement [5, 6]. Diagnosis of CNS CMV infection is difficult because radiological findings are usually normal and CMV is rarely cultured from CSF [1, 5]. In some cases, diffuse and irregular increased signal intensities through the long segment of the spinal cord and cauda equina on T2-weighted MRI [7] or periventricular enhancement after contrast infusion [8] provides diagnostic clues. CNS mass lesions are not a recognized feature of CMV infection. We report three cases of biopsy-proven active CMV infection of the CNS mimicking tumors with unusual gadolinium ring enhancement on MRI. One involved focal myelitis of the conus medullaris and the other two involved focal encephalitis, features that have been reported previously as noted in only one child [9] and two adults [10, 11]. Prompt recognition of this unusual form of CMV infection is important, as it may be treatable if detected early but may not be in the later stages of the disease.

Patients and Histologic Studies

Patients

From January 1992 to December 1994, 543 patients with HIV-1-associated CMV infections were seen in our institutions (Hôpital de l’Institut Pasteur and Hôpital Saint-Louis, Paris). The diagnosis of AIDS was based on the standard epidemiologic surveillance definition of the Centers for Disease Control and Prevention (CDC). In 37 of these 543 patients, neurological signs or symptoms of CMV infection developed: 19 had CNS involvement (encephalitis, myelitis, or encephalomyelitis), and 18 had peripheral nervous system involvement (polyradiculomyelopathies or multifocal neuropathies). The diagnosis of CMV infection in these markedly immunodepressed patients (CD4+ cell count, ≤100/mm³) was made by exclusion of other causes of neurological involvement and on the basis of charac-
teristic CMV histopathologic features and clinical response to anti-CMV therapy. Of the 19 patients with CNS involvement, three presented with pseudotumoral lesions suggestive of a focal space-occupying lesion, with clinical signs of localization and a mass effect. The patients were referred for stereotactic biopsy after failure of antitoxoplasmic therapy. Clinical and histopathologic findings are described below.

**Case 1.** A 33-year-old homosexual man, known to be HIV-1-seropositive since 1987 (CDC stage, IVC2), was admitted in August 1993 for subacute paraplegia. Two weeks prior to admission he complained of a throbbing, bilateral, plantar burning pain that had gradually increased in severity and climbed the legs to the groin in a matter of days. Examination disclosed dysesthesia of both legs, a few errors in sensing the position of the right toe, and brisk reflexes. Sudden onset of bilateral leg weakness and urinary retention warranted admission.

The patient was afebrile, alert, and oriented. Cranial nerve and upper-extremity examination findings were normal, as was the fundus oculi. He had paraparesis, and the deep-tendon reflexes were absent at the lower extremities. The right plantar response was not elicitable, and the left was extensor. T1-weighted MRI showed enlargement of the conus medullaris, with a central ill-defined low-signal region; the latter was enhanced at the periphery after gadolinium infusion (figure 1). MRI of the brain was normal. CSF analysis showed a WBC count of 120/mm$^3$ (90% unaltered polymorphonuclear leukocytes), a protein level of 560 mg/dl, and a glucose level of 40 mg/dL. Gram stains, cultures, tests for cryptococcal antigen, India ink stains, and a VDRL test were all negative. The CD4$^+$ cell count was 21/mm$^3$ (2% of total lymphocytes), and the CD4/CD8 cell ratio was 0.04.

The following day, despite antitoxoplasmic therapy (with pyrimethamine [50 mg/d] and sulfadiazine [6 g/d]), the patient developed flaccid paraplegia and urinary retention necessitating insertion of a subpubine catheter. Emergency decompressive laminectomy at the L1 and L2 levels was performed on the assumption that the cord swelling was due to a tumor. The conus medullaris showed a marked median bend, and the posterior part contained an apparently thrombotic vessel. Microsurgical performance of a midline myelotomy of the conus medullaris disclosed a firm tumor with no clear cleavage, the center of which was necrotic and brittle. The spinal roots were macroscopically normal. Incomplete excision was done.

A few days after surgery, PCR by means of a technique previously published [12] was positive for CMV in the CSF, whereas PCR for varicella-zoster virus (VZV), herpes simplex virus (HSV) types 1 and 2, Epstein-Barr virus, JC virus, Toxoplasma gondii, and Mycobacterium tuberculosis was negative. The patient underwent induction therapy with foscarnet (100 mg/kg iv every 12 hours), and his condition rapidly improved. The power of his lower limbs improved day by day, and he was able to support his weight and take a few steps within a month. CSF sampled 10 days after administration of foscarnet began was clear, with 5 cells/mm$^3$ and a protein level of 80 mg/dL; PCR for CMV was negative. MRI of the spine showed a reduction in the conus medullaris lesion, which was no longer enhanced by gadolinium.

After 5 weeks the foscarnet dosage was reduced for maintenance therapy (100 mg/[kg·d] iv), and the patient gradually regained his autonomy. Two months later, MRI of the spine did not reveal any abnormalities. Four months after onset, the same neurological manifestations developed and a new MRI of the spinal cord showed the reappearance of the initial lesion.
Foscamet was replaced by ganciclovir (5 mg/kg iv every 12 hours), but the patient died a few days later, before further investigations could be performed; he was in a coma and there were no focal signs. Permission for autopsy was refused.

Case 2. A 39-year-old homosexual man who had been HIV-1-seropositive since 1988 (CDC stage, III) was admitted in October 1993 with febrile cephalalgia. He had been receiving trimethoprim-sulfamethoxazole (160/800 mg/d) for 2 years. No abnormalities were found during examination. The CD4 cell count was 10/mm<sup>3</sup> (1% of total lymphocytes; CD4/CD8 cell ratio, 0.01). He was receiving trimethoprim-sulfamethoxazole (160/800 mg/d) for *Pneumocystis carinii* pneumonia, the diagnosis of which had revealed the HIV infection. Brain MRI showed a left ring-enhanced temporoparietal lesion with edema and a mass effect on the left lateral ventricle (figure 2). Despite antitoxoplastic therapy (with pyrimethamine [50 mg/d] and brain biopsy, and antimycobacterial treatment was added to his regimen without effect.

Left hemiparesis appeared with a frontal lobe syndrome 6 weeks after onset. CT-guided stereotactic brain biopsy was then performed. Testing of a ventricular CSF sample yielded the following values: protein, 90 mg/dL; glucose, 20 mg/dL; and normal polymorphonuclear leukocytes, 20/mm<sup>3</sup>. Cultures of blood and CSF for bacteria (including mycobacteria), fungi, and viruses (including CMV and VZV) were negative. PCR of the CSF for CMV was strongly positive. Foscamet (100 mg/kg iv every 12 hours) was prescribed. Aspiration pneumonia occurred immediately after surgery and was treated with broad-spectrum antibiotics. The right hemiparesis diminished within 10 days, but the patient died of acute respiratory distress 23 days after the brain biopsy (10 weeks after onset). Permission for autopsy was refused for religious reasons.

Case 3. A 34-year-old homosexual man who had been HIV-1-seropositive since 1991 (CDC stage, IVC2) was admitted in October 1993 for cephalalgia, right hemiparesis (sparing the face), and aphasia (without fever). The CD4+ cell count was 9/mm<sup>3</sup> (1% of total lymphocytes; CD4/CD8 cell ratio, 0.01). He was receiving trimethoprim-sulfamethoxazole (160/800 mg/d) for *Pneumocystis carinii* pneumonia, the diagnosis of which had revealed the HIV infection. Brain MRI showed a left ring-enhanced temporoparietal lesion with edema and a mass effect on the left lateral ventricle (figure 3). Despite antitoxoplastic therapy (with pyrimethamine [50 mg/d] and sulfadiazine [6 g/d]) yielded slight abatement of the cephalalgia. The patient became progressively listless, and a second CT scan a month later showed an increase in the volume of the right caudate nucleus lesion, emergence of another lesion in the left frontal lobe, and enhancement of the wall of the lateral ventricle (figure 2). He at first refused a
sulfadiazine [6 g/d]), combined with prednisone (40 mg/d) because of the mass effect, the right hemiparesis worsened to hemiplegia.

A CT scan 21 days later showed an increase in the volume of the left parietal lesion. A stereotactic brain biopsy was performed 32 days after onset. Despite histologic signs of CMV infection and no evidence of other lesions, the clinician treating this patient did not at this point believe infection was due to CMV, and no specific treatment was given. Three weeks after the brain biopsy, CMV retinitis and CMV colitis developed. CMV viremia was detected at this time (testing for it had been negative 1 month previously). Induction therapy with foscarnet (100 mg/kg iv every 12 hours) rapidly led to healing of the retinal lesions and disappearance of the diarrhea, and the neurological status also improved.

One month later, only right-upper-limb paresis persisted, with Broca's aphasia. Maintenance therapy with foscavir (100 mg/[kg·d]) was administered via a Port-a-cath system (Pharmacia, North Ryde, Australia). Only a right pyramidal syndrome and Broca's aphasia were noted 4 months after the biopsy, and a control CT scan of the head confirmed the reduced volume of the left temporoparietal lesion. Intravenous ganciclovir was replaced by intravitreal ganciclovir injections (once a week) because of renal impairment and chronic pancytopenia. Fever and diarrhea recurred 3 weeks later, with no worsening of neurological status. Intravenous administration of ganciclovir was started, but the patient died of neurological causes 6 months after onset. Autopsy was not performed.

Histologic Studies

Methods. In each case, three types of biopsy specimens were available: in Bouin fixative for paraffin embedding, snap-frozen at −80°C, and fixed in glutaraldehyde–osmic acid for Epon embedding. Immunocytochemistry techniques were applied with use of the avidin-biotin-complex method (Vector Laboratories, Burlingame, CA) and peroxidase revelation with diaminobenzidine as chromogen. The following antibodies were used: polyclonal anti-SV40 (1/500; Lee Molecular, San Diego); antiglial fibrillary acid protein (1/1000; Dako, Glostrup, Denmark); anti-Toxoplasma (1/200, Bioquote, lickley, UK); anti-herpesvirus types 1 and 2 (1/100, Dako); monoclonal anti-CMV immediate-early nuclear antigen (kindly given by Dr. Marie-Christine Mazeron, Hôpital Lariboisière); and monoclonal anti-VZV (kindly given by Professor Frederic Morinet, Hôpital Saint-Louis). For PCR techniques, biopsy specimens were thawed and homogenized in sterile distilled water. Tissue homogenates were digested with proteinase K, and DNA was extracted with phenol and chloroform and then precipitated with NaAc-ethanol. One microgram of DNA was submitted to amplification of a 170-bp fragment within the Us region of the CMV genome. PCR products were analyzed by electrophoresis through 1% agarose gel containing ethidium bromide and by dot-blot hybridization with a biotinylated probe. Tissue specimen homogenates were also cultured in flasks (to detect a cytopathic effect) for 6 weeks with two subcultures, according to a technique previously described [13].

Results. The three patients' specimens harbored inflammatory lesions of variable intensity. One specimen (case 1) was particularly necrotic, with altered polymorphonuclear cells, a marked macrophagic reaction, and numerous lipophages. Specimens from the two other cases (cases 2 and 3) were comparable, with less necrosis and more vascular modifications (ectatic capillaries with prominent endothelial cells). Cytomegalic cells were present, some with typical eosinophilic intranuclear CMV inclusions (figure 4). They were located inside the capillary endothelium, around the capillaries, or in the heart of the inflammatory reaction (the latter cells probably being of histiocytic lineage). Immunohistochemistry was positive for CMV in all three cases, showing more virus-bound cells than suspected on hematoxylin-eosin staining in cases 1 and 3 (figure 4). Tests for HSV and VZV were always negative. No other opportunistic agents were identified. PCR for CMV was positive in all three cases, whereas tissue culture was always negative.

Discussion

Patient 1 presented with a subacute conus medullaris syndrome, while the other two patients had intracranial space-occupying lesions. All had active focal CMV infection, demonstrated by PCR of CSF, histologic studies, and improvement with anti-CMV therapy. Antitoxoplastic therapy was prescribed because the most common infectious focal brain and spine lesions com-
Plicating AIDS are due to *T. gondii* [2, 4, 14]. All three patients underwent surgery because of suspected tumors.

The diagnosis of CMV CNS infection is difficult because, even for individuals with major inflammatory CMV lesions of the brain, spinal cord, or nerve roots, radiological findings are usually normal and CMV is rarely isolated from the CSF [5, 13, 15]. Cortical atrophy, with or without ventricular enlargement, is seen in only 25% of patients [5]. This is also reflected by the normal or slightly atrophic appearance of the brain or spinal cord at necropsy [5, 14]. The periventricular enhancement after contrast-product infusion is more characteristic but nonspecific [8].

The management of intracerebral focal mass lesions is now well standardized [9], but, apart from toxoplasmosis, few intra-medullary focal syndromes have been reported to occur in the course of HIV-1 infection (reviewed in [14]); they include Brown-Séquard syndrome, multiple sclerosis, malignant gliomas, spinal cord compression by plasmacytomas or immunoblastic sarcomas, and syphilis [16]. Differential diagnoses of CNS mass lesions enhanced by contrast products include toxoplasmosis [17], primary CNS lymphoma [10, 18], and, more rarely, mycobacterial [18, 19] or fungal [10, 14] abcesses and tumors [20]. HSV encephalitis may mimic—at least initially—a temporal lobe tumor, because of the marked necrosis, perilesional edema, and hemorrhage [21].

More rarely, VZV may cause focal encephalitis [22]. One case of focal CMV encephalitis in an HIV-1-infected homosexual man involved a ring-enhancing cerebellar CT lesion [10], but the lack of immunohistochemical analysis and the improvement evident on subsequent CT scans without specific treatment made it difficult to ascribe this lesion to CMV alone. Only one other biopsy-proven case of focal CMV encephalitis has recently been described (the second case described in this publication was unconfirmed) [11].

A case similar to case 1 has been reported and involved a child [8]. A perinatally HIV-infected 7-year-old girl had focal necrotizing myelitis in the cervical spinal cord. MRI revealed a swollen cervical spine with a cystic formation, which showed ring enhancement after gadolinium infusion; the causal link with CMV was not initially suspected. At necropsy, the cervical spinal cord was swollen, with cystic paracanalicular destruction of segment C7, corresponding to the MRI abnormality. Histologic studies provided evidence of necrotizing myelitis extending to segments C2–C7, with typical CMV lesions and positive immunostaining; no other lesions were detected. The spinal roots did not show any histologic signs of inflammation or disintegration.

CMV can cause multisystem disease in patients with AIDS, and the only other described CMV-induced mass lesions in organs other than the CNS were pseudotumors of the cecum [23], gastrointestinal tract [24], and submandibular gland [25].

CMV encephalomyelitis is characterized by five histopathologic features—nodular encephalitis, isolated inclusion-bearing cells, focal parenchymal necrosis, ventriculoencephalitis, and necrotizing myeloradiculitis—that may occur singly or in combination [26]. Of these, only necrotizing lesions can be detected macroscopically [27, 28]. In a minority of brains infected by CMV, some well-delineated foci of necrosis in the centrum semiovale, cerebellar white matter, and brain stem, although usually microscopic, can be detected macroscopically as zones of softening and of grey discoloration [27, 28]. Clearly delimited zones of necrosis deep in the pia mater, involving the dorsal, lateral, and ventral columns of the spinal cord, have been found at autopsy in patients with clinical features of ascending myelitis [14, 27]. Inflammation and necrosis of the walls of leptomeningeal vessels have been described, but vasculitis within the spinal cord is unusual [28]. In case 3, we cannot exclude the possibility that the lesion could have disseminated from primary ventriculitis.

In our patients, MRI showed focal, enhanced intraparenchymal lesions consistent with marked focal necrosis but nonspecific for infections or tumors. This prominent necrosis may be related to the marked immunodepression of these patients, in whom HIV infection had been diagnosed some years previously. In addition, necrotic forms with a periventricular encephalitic location have never been described as occurring in adults without AIDS and are specific to this disease. The mechanism behind the necrosis is uncertain. Direct CNS invasion by CMV can result in inflammatory necrosis with an astrocytic response to injury, notably after a large viral inoculum [29]. Vasculitis or periventricular inflammation related to CMV [5], in addition to extensive cord infarction due to CMV arteritis [6], has also been described. Another pattern of lesion, characterized by a mass encasing the spinal cord from level T9 and extending distally to involve the thecal sac, was related to CMV vasculitis of the vasa vasorum, resulting in massive root infarction [30]. The vessel endothelium was swollen and cytomegalic cells were located inside the capillary endothelium in the cases we report.

Ganciclovir and foscarnet are used increasingly with the growing incidence of CMV disease and with the improved survival rate among persons with AIDS who receive the drugs for longer periods; ganciclovir- or foscarnet-resistant CMV infection is also increasingly frequent [1]. Patients with AIDS can also be coinfected with multiple strains of CMV that may have varying degrees of susceptibility to antiviral therapy [31]. This, in addition to the extent of the necrotic lesions, could explain the poor response to therapy. Ganciclovir therapy can clinically stabilize CMV retinitis but does not appear to prevent or cure CMV encephalitis [32]. Combined ganciclovir and foscarinet therapy is now being used and is synergistic against CMV in vivo [33], although the optimal doses remain to be defined.

The fact that neuroimaging reveals focal CNS lesions in at least some cases of CMV infection is consistent with both the clinical and pathological features of the disease, but they were...
not previously recognized as a feature of the infection in patients with AIDS. As illustrated by the cases we describe, a slowly progressive CNS mass lesion in an HIV-infected subject that does not rapidly respond to antitoxoplasmic therapy could be a CMV abscess or "cytomegaloviroma." Differentiation from other recognized or unrecognized causes is not currently possible on the basis of clinical or radiologic grounds or CSF analysis, and recent studies suggest that PCR, although sensitive, is more [13] or less [34] specific for CMV CNS infection. We consider it important to perform biopsies in such cases, as earlier recognition and treatment may improve the outcome for these patients.

References