Cytomegalovirus polyradiculomyelopathy in AIDS: a case report and review of the literature

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Cytomegalovirus (CMV) neurologic disease is a serious complication of the acquired immunodeficiency virus (AIDS). We report the case of a 40 year-old woman with AIDS who presented paralysis of lower extremities, areflexia, sensory loss, and urinary retention. CMV polymerase chain reaction (PCR) of cerebrospinal fluid (CSF) allowed confirmation of CMV polyradiculomyelopathy (PRAM).

Key words: Cytomegalovirus, CMV, AIDS, Myelitis, Polyradiculomyelitis, Polyradiculomyelopathy, PRAM, CMV PCR, Ganciclovir, Foscarnet

Cytomegalovirus (CMV) is a common systemic opportunistic pathogen among patients with severe immnosuppression due to bone marrow or solid organ transplants or to the acquired immunodeficiency syndrome (AIDS), causing colitis, retinitis, gastrointestinal infection, pneumonitis, adenopathy, and nervous system involvement (1-4). McCutchan and colleagues recognize at least five distinct neurological syndromes caused by CMV in patients with AIDS, including myelitis/polyradiculopathy, encephalitis, and ventriculonecephalitis in the central nervous system, mononeuritis multiplex in the peripheral nerves, and retinitis (5).

A distinct syndrome of subacute ascending lower extremity weakness with paresthesias and radicular pain, hyporeflexia or areflexia, and urinary retention has been reported and has been termed polyradiculomyelitis (4,6,7), polyradiculopathy (1,3) or polyradiculomyelopathy (PRAM) (8,9).

We describe the case of a woman with AIDS presenting areflexic paralysis of lower extremities, sensory loss, and urinary retention. The presumptive diagnosis of CMV PRAM was confirmed by positive CMV polymerase chain reaction (PCR) in cerebrospinal fluid (CSF). Despite institution of antiviral therapy with ganciclovir, the patient did not present neurological improvement. A review of the literature is done concerning diagnosis and treatment of this condition, which entails an overall poor prognosis.

Case report

A 40 year-old woman with arterial hypertension and a 20 year-history of Human Immodficiency Virus (HIV) was receiving highly active antiretroviral therapy (HAART) with enfuvirtide, tenofovir, and lamivudine (most recent CD4 T-cell count of 0/mm³; HIV viral load of more than 100,000 copies/mL). She complained of headache, mostly in right parietal area, associated with nausea, vomits, and photophobia for a month prior to admission. Approximately three weeks before admission, she developed weakness in the right side of her face. Shortly afterwards, a Foley catheter was placed by a Urology specialist at outpatient basis because she was found with urinary retention. Days before admission, she noticed some weakness in lower extremities, which later progressed to an inability to walk.

Upon evaluation for admission, she was found fully alert and oriented, although she presented with slowed speech. On physical exam, there was decreased sensation in areas corresponding to innervation by right fifth cranial nerve, right nasolabial flattening, and inability to fully close right eye. Examination for sensation demonstrated a sensory level at thoracic level 4 (T4). There was also flaccid tone in lower extremities with 0/5 strength, areflexia in legs, and neutral plantar response to Babinski. Complete blood count (CBC) revealed leukopenia (white blood cell count of 3.3 x 10⁹/L) and normochromic, normocytic anemia (hemoglobin of 9.3 g/dL, hematocrit of 27.3%). No pertinent
findings were found on Computed Tomography (CT) and Magnetic Resonance Imagine (MRI) with contrast enhancement of both brain and spine.

CSF analysis revealed white blood cell count of 118 x 10^6/L (83% polymorphonuclear cells), red blood cell count of 3496 x 10^6/L, glucose of 23 mg/dL, and protein of >500 mg/dL. CSF India ink, gram stain, KOH, acid fast, culture, cryptococcal antigen, toxoplasma IgG, rubella IgG, Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) IgM and IgG were all negative.

In view of Bell’s palsy, meningeal symptoms, thoracic sensory level, areflexic flaccid paralysis, pleocytosis with neutrophilic predominance, hypoglycemia, and elevated protein in CSF, CMV infection in nervous system (specifically PRAM) was considered and intravenous ganciclovir was started.

CMV IgG in CSF was later found to be positive in this patient. PCR for CMV in CSF was also positive, while PCR for HSV-1 and HSV-2 was negative. This is highly specific for CMV neurologic disease, which was already suggested by clinical presentation and findings.

The patient's condition deteriorated during the following 10 days, for which she required ventilatory support. Chest X-rays showed elevation of left hemidiaphragm suggestive of paralysis. Course of hospitalization was complicated by Gram-negative bacteremia and ventilator-associated pneumonia, which resulted in cardiorespiratory arrest and death.

Discussion

CMV neurologic disease is a serious complication of AIDS. It is more common in patients with CD4 T-cell count below 50/mm^3 (10), and is commonly associated to a prior or concurrent CMV disease elsewhere (8).

Kim and colleagues have described the characteristic findings of CMV PRAM according to cases reported in the literature. Symptoms include diffuse leg pain and sacral paresthesias progressing to weakness and flaccid, areflexic paraparesis, as well as urinary retention in more than two-thirds of patients (3). Onset is typically subacute, with a mean duration of symptoms of 2.1 weeks (range of 0.3-6 weeks) (5). Sensory findings include tactile, vibratory, and kinesthetic impairments, and sensory level have been described in some patients (8). Late in the disease, upper extremity weakness may occur (3). Our patient presented characteristic areflexic flaccid paralysis and urinary retention during admission. T4 sensory level was evidenced during initial examination, while upper extremity weakness occurred later on her course of illness.

CSF typically shows marked pleocytosis, consisting of hundreds to thousands of predominantly polymorphonuclear leukocytes (5). In a literature review by Cohen and co-investigators, polymorphonuclear-predominant or mixed pleocytosis was reported in the majority of cases (8) and it was the case in our patient (83% polymorphonuclear cells in her CSF analysis).

Polymorphonuclear pleocytosis has also been described by several other authors (1-4). Glucose levels in CSF may be normal, but marked hypoglycemia can occur, while protein levels are usually moderately elevated (>500 mg/dL), but protein levels were all elevated (>500 mg/dL). In terms of imaging studies, an MRI may show thickened cauda equina in non-contrast images and enhancement of the cauda equina and conus medullaris on postcontrast images (4,6).

Diagnosis of CMV PRAM is based on clinical and CSF findings and on detection of CMV in CSF by culture or PCR (5). Other investigators support the role of characteristic cytomegalic cells with intranuclear inclusions on cytologic examinations of CSF specimens (2,7). At least in the peripheral nerves, CMV induce direct cellular damage and necrosis, probably involving Schwann cells, macrophages, fibroblasts, and endothelium (11). However, despite direct damage, CMV viral culture is often insensitive (4,6,12). Only about one-half of patients with typical clinical and CSF findings have positive cultures (5). Flood et al have analyzed the utility of branched chain DNA assay (bDNA) and CMV antigen assay in the diagnosis of CMV PRAM. When the reference standard of clinical diagnosis of PRAM is used, sensitivity is 94% for both bDNA and CMV antigen, while specificity is 95.24% for bDNA and 85.7% for CMV antigen (12).

Since the advent of the PCR technique, the detection of CMV DNA by amplification has shown great utility in confirming the diagnosis (6), presenting more sensitivity than cultures (1). In a study by Arribas and colleagues, PCR showed high sensitivity and specificity, and appeared to be more useful than clinical neuroradiologic findings for documenting CMV neurologic infection in patients with AIDS (10). They also found that a high level of CMV DNA in CSF was associated with a more severe disease (10). In our patient, CMV PCR allowed to confirm a diagnosis that was suspected clinically, but therapy could not rely on arrival of PCR results and was started empirically based on a presumptive clinical diagnosis.

Rapid institution of treatment might be essential to attain improvement in some patients. Authorities recommend the institution of adequate antiretroviral therapy in patients with HIV to improve prognosis (4). In additional to that, specific antiviral agents against CMV could be advantageous. Ganciclovir, an acyclic nucleoside...
analogue of acyclovir, is a virostatic agent that inhibits viral DNA synthesis (4) and has been used for treatment of CMV disease. However, response to ganciclovir therapy in CMV PRAM might be poor. In a series of patients from de Gans and colleagues, most patients with CMV PRAM did not improve during ganciclovir therapy (7). Similar results have been obtained in a review by Cohen et al: improvement occurred only in six of the 16 patients treated with ganciclovir (8). Response to treatment has been achieved when therapy with ganciclovir was instituted early, suggesting that early intervention might be beneficial (7). Recovery of some neurological function has also been reported after prolonged therapy with ganciclovir, which indicates that indefinite therapy or prolonged maintenance therapy could be required in patients with CMV PRAM (3). Reasons for overall poor response to ganciclovir could be due to virostatic (instead of viroidal) capacity of ganciclovir, severe direct nerve damage by CMV, or development of resistance to ganciclovir. Resistance could be an important consideration in patients with prior ganciclovir treatment.

In our patient, the absence of neurologic improvement and clinical deterioration despite initiation of antiviral therapy with ganciclovir shortly after admission could be attributed to the extend of neurologic disease upon diagnosis. During the first examination, the patient already presented areflexic paraparesis, T4 sensory level, and cranial nerve involvement (Bell’s palsy), which suggest late stage of CMV neurologic disease.

Since many patients fail to respond to ganciclovir, therapy with other antiviral agents or even combination therapy with several agents has been postulated and described in a few cases. Forcarnet, a pyrophosphate analogue, is a virostatic agent that reversibly inhibits the viral DNA synthesis (4). It has been used intravenously, by itself or in combination with ganciclovir, for the treatment of CMV neurologic disease. Prolonged combination therapy with ganciclovir and forcarnet has been effective in some cases of CMV PRAM (13). For patients who have failed or are intolerant to standard therapy, cidofovir may be an effective alternative as it has been used with success in CMV retinitis (14). However, it can cause nephrotoxicity and neutropenia (4) and its application in the setting of CMV PRAM has not been widely reported (1). Based on these findings, these probabilities were considered in our patient, but she died before any of them could be instituted.

Resumen

Citomegalovirus (CMV) puede causar complicaciones neurológicas severas en pacientes con el síndrome de inmunodeficiencia adquirida (SIDA). En este artículo, reportamos el caso de una paciente de SIDA de 40 años de edad que presentó parálisis de las extremidades inferiores con ausencia de reflejos, pérdida de sensación y retención urinaria. La técnica de reacción en cadena de la polimerasa (PCR por sus siglas en inglés) específica para CMV permitió confirmar el diagnóstico de poliradiculomielopatía secundaria a CMV. A pesar de instituir tratamiento con ganciclovir, la paciente no presentó mejoría clínica y eventualmente falleció. Se ofrece una descripción del caso y una revisión de la literatura sobre esta condición.

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References

