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Cytomegalovirus Central Nervous System Compartmentalization in a Patient Presenting with AIDS

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Cytomegalovirus (CMV) is a ubiquitous virus that infects almost all human being at some time in their lives and anti-CMV antibodies are usually found in the majority of healthy adults (40 to 100%).[1] Even if CMV infection is usually asymptomatic or pauci-symptomatic in immune competent hosts, serious complications have been constantly described in newborns and in patients affected by immune deficiencies.[2] In HIV-positive patients with extremely low CD4+ T lymphocytes serious end-organ CMV infections have been reported (retinitis, colitis and, although debated, pneumonias). Central nervous system (CNS) involvement is rare (less than 1% of CMV infections) but aggressive (with approximately 100% mortality if untreated); neurological presentation can be polymorphic and brain imaging may mimic other CNS opportunistic diseases:[3] timely and appropriate diagnosis may significantly impact patients' outcomes. We here describe a case of CMV encephalitis presenting concomitantly with other CNS opportunistic infections and with a slow response to antiviral treatment.

We report the case of a 42-year old patient of sub-Saharan African origin. After a two-week history of fever and headache he was admitted to the neurology ward and HIV-positivity discovered. HIV RNA (336135 copies/mL) and CD4+ T lymphocytes cell count (22/mm^3, 1%, CD4/CD8 ratio 0.0) were

consistent with very late presentation. Cranial CT scan showed two hypodense lesions (left cerebellar emisphere and left temporal cortex); brain magnetic resonance revealed T2 and FLAIR hyperintensity in left basal ganglia, temporo-occipital areas and left cerebellum as well as multiple diffuse contrast-enhanced cortical and subcortical lesions. Cerebrospinal fluid (CSF) analysis showed 8 cells/mL (lympho-monocytes), reduced glucose (50 mg/dL versus 103 mg/dL, plasma sample) and increased protein concentration (135 mg/dL): both *Toxoplasma gondii* and CMV DNA were positive (CMV-DNA 194380 copies/mL versus 25385 copies/mL, plasma sample) while HIV RNA was 55 copies/ml. Biopsy of purple skin lesions, esophagoduodenogastroscopy and fibrobronchoscopy were consistent with disseminated Kaposi's sarcoma (T1I1S1). Patient complained of headache, confusion and hallucinations; ataxia was revealed at neurological examination. Considering the radiological pattern, patient's immune depression and positive CSF nucleic acids sulfadiazine and pirymetamine were started for treating neurotoxoplasmosis (for two weeks, than changed to atovaquone plus pirymetamine for further two weeks and finally changed to atovaquone plus azitromicin for emerging side-effects). Other CSF investigations (including Ziehl-Nielsen stain, Mycobacterium tuberculosis DNA and colture) were negative: treatment for disseminated CMV infection (intravenous gancyclovir at 5 mg/kg twice daily) was started. After 14 days gancyclovir was reduced to a once-a-day schedule and tenofovir/emtricitabine/efavirenz was started; two weeks later gancyclovir was withdrawn. Ten days later neurological symptoms worsened (including visual and auditory hallucinations) a new brain MRI was performed: minimal changes in the already described lesions (central long TR-hyper-intense cerebellar and temporal lesion with mild contrast enhancement) and the appearance of several small nodules (2 to 7 mm size) in both cerebellar hemispheres and cortex (Figure 1). The new spinal tap showed 40 cells/mL (lymphomonocytes), reduced glucose (33 mg/dL verus 85 mg/dl, plasma sample) and increased proteins (148 mg/dL). CSF and plasma HIV RNA were respectively 55 and 28 copies/mL while CSF CMV-DNA was 31340 copies/mL (and not detectable in the simultaneous

plasma sample); contemporary CD4+ T lymphocytes count was 32/mm^3 (4%, CD4/CD8 ratio 0.1). Twice-daily gancyclovir was re-started and then secondary prophylaxis maintained (valganciclovir 900 mg once-daily) while he continued receiving anti-toxoplasma treatment. Neurological symptoms and brain MRI improved at subsequent controls (at 3 and 6 months) and CMV-DNA remained undetectable both on plasma (3 and 6 months) and on CSF (3 months).

Cytomegalovirus CNS involvement is uncommon and hardly diagnosed; the virus may cause encephalitis, ventriculitis, myelitis, retinitis, radiculoganglionitis and peripheral neuropathies. Even if it has been recognized in 12% of autopsies from AIDS patients[4], CMV CNS involvement may be asymptomatic or mimic several other conditions[5]. Imaging findings in AIDS-associated cytomegalovirus encephalitis that have been described range from ventriculitis (more common) to solitary mass lesions (less frequent).[6,7] There is no consensus on the duration of antiviral therapy but adequate treatment may be longer than what currently suggested for CMV retinitis (14-21 days).[7,8]

The case here reported depicts a patient presenting with several opportunistic diseases: neurotoxoplasmosis, Kaposi's sarcoma and disseminated CMV disease. Brain MRI worsening with the appearance of contrast-enhancing lesions may be associated with immune-reconstitution inflammatory syndrome (IRIS): the excellent one month antiviral response as well as the previous observation of IRIS related to end-organ diseases may support such hypothesis while CD4+ T lymphocites and raltegravir effect on first-phase viral load decay may be against it. CMV CNS involvement was not initially considered given the observed multiple comorbidities: antiviral treatment duration was probably not adequate given the end-organ disease. Furthermore gancyclovir CNS penetration is not completely defined; in non-human primates and in a single case-report CSF gancyclovir was 15.5 to 17% of plasma concentrations.[9,10] Secondary prophylaxis appears however appropriate in such cases: current guidelines recommend discontinuation of secondary prophylaxis in HAART-recipients once a sustained (3 to 6 months) CD4+ T cells above 100 cells/mm^3 is obtained. The discovery of CMV

replication in CSF despite undetectable plasma CMV DNA is rather interesting since it may represent CNS compartmentalization: this feature has been reported in two patients.[11,12]

This case of central nervous system CMV involvement in a HIV-positive patient with multiple opportunistic comorbidities questions the appropriate duration of anti-cytomegalovirus treatment: the possible plasma/CSF CMV dissociation may suggest a delayed CNS clearance or an incident immune-reconstitution syndrome.

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