Cerebral microsporidiosis manifesting as progressive multifocal leukoencephalopathy in an HIV-infected individual - a case report

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Abstract
Microsporidia have become increasingly recognized as opportunistic pathogens since the genesis of the AIDS epidemic. The incidence of microsporidiosis has decreased with the advent of combination antiretroviral therapy but it is frequently reported in non-HIV immunosuppressed patients and as a latent infection in immunocompetent individuals. Herein, we describe an HIV-infected male (46 years) with suspected progressive multifocal leukoencephalopathy that has not responded to optimal antiretroviral therapy, steroids, or cidofovir. Post-mortem examination revealed cerebral microsporidiosis. No diagnostic clue however, was found when the patient was alive. This report underscores the need for physicians to consider microsporidiosis (potentially affecting the brain) when no other etiology is established both in HIV, non-HIV immunosuppressed patients and in immunocompetent individuals.

Keywords: Microsporidiosis, Cerebral lesions, HIV, Progressive multifocal leukoencephalopathy

Case report
A 46-year-old homosexual male presented at the emergency room on February 22, 2002 for a 5-month progressive visual impairment, headache and occurrence of right hemiparesis in the last week.

He was diagnosed with HIV infection in December 1987. His past history was not significant except for varicella in July 1996. At this previous time, his CD4⁺ count was 650 cells/μL (24%) with a CD4⁺/CD8⁺ ratio of 0.37. In July 2000 and November 2001, the CD4⁺ cell counts were 420 and 330 cells/μL, respectively. No HIV-1 viral load measurements were available for these dates. Until he was admitted to our hospital, the patient had declined any antiretroviral therapy.

At admission, he was afebrile and his physical examination was unremarkable except for right hemiparesis and left homonymous hemianopsia. His complete blood count (CBC), liver function tests and routine biochemistry were within normal limits. The CD4⁺ count was 340 cells/μL (16%) with a CD4⁺/CD8⁺ ratio of 0.20. A brain CT-Scan and a magnetic resonance imaging (MRI) revealed multifocal coalescent lesions with no mass effect and very little or no enhancement in the white matter of upper left parietal and left occipital, right temporal and frontal lobes with cerebral atrophy, suggestive of progressive multifocal leukoencephalopathy (PML) (Figure 1, panels a and b).

Serologic tests for syphilis (RPR and Treponema/TP-PA), EBV-VCA IgM, toxoplasmosis (IgG and IgM) and search for cryptococcal antigen were negative. The patient had positive results for EBV-EBNA-1 IgG, CMV IgG, hepatitis C (anti HCV), hepatitis A, anti HBs, anti HBc. The HBs Ag was negative. He was started on AZT 300/3TC 150 mg (Combivir®) BID and lopinavir 200/ritonavir 50 mg (Kaletra®) 2 tablets BID. The HIV viral load was not performed (for technical reasons) before initiating antiretroviral therapy, but after two weeks it was 2 279 (3.36 log₁₀) HIV-1 RNA copies/ml. Because of clinical deterioration, dexamethasone was initiated on March 15, 2002, and continued until April 8, 2002. Since no clinical improvement was apparent, i.v. cidofovir (5 mg/kg) and probenecid twice at one week intervals, then every 2 weeks were started on April 11, 2002 and continued until February 3, 2003. His immune status
improved, and on June 10, 2002, the CD4+ count showed 440 (26%) with a CD4+/CD8+ ratio of 0.38, whereas the viral load decreased to 91 HIV-1 RNA copies/mL. Moreover, the patient reported a subjective improvement of his right hemiparesis. On June 26, 2002, AZT was replaced by D4T to avoid anemia due to AZT and probenecid interaction.

The patient was again hospitalized on August 22, 2002 for fever (39°C), seizures and status epilepticus, necessitating admission to the Intensive Care Unit (ICU), for intubation and mechanical ventilation. Anti-convulsive therapy with phenytoin and lamotrigine was then initiated.

Laboratory analysis revealed this time a CD4+ count of 380 (21%) with a CD4+/CD8+ ratio of 0.38 and a HIV viral load below the limit of detection (<50 HIV-1 RNA copies/mL). The brain lesions had not changed since the previous brain MRI. A lumbar puncture was performed on August 23, 2002. The cerebrospinal fluid (CSF) examination revealed proteins 0.53 g/L (normal 0.1-0.5), and glucose 4.3 mmol/L (normal 2.2-3.9). Tests for viral DNA of Poliovirus JC, BK virus, CMV, PCR for herpes group viruses (HSV-1, HSV-2, VZV, CMV, EBV, and HHV-6/7-8), Mycobacterium tuberculosis, and search for cryptococcal antigen and VDRL all remained negative in CSF. Plasma CMV DNA, urine cultures, blood cultures for bacteria, Mycobacteria and fungi were negative.

An ophthalmologic examination confirmed bilateral blindness of the central origin, but showed no retinitis, keratoconjunctivitis or deep corneal stromal infection. He was discharged on September 19, 2002, and was seen every two weeks at the Ambulatory Unit. On September 23, 2002 his HIV viral load was again below the limit of detection; CD4+ count was 350 cells/μL (22%) and CD4+/CD8+ ratio was 0.36.

Despite an optimal control of HIV infection and continuous combination antiretroviral therapy (cART), the patient's status did not improve and he was re-admitted to the ICU for status epilepticus on April 28, 2003, intubated and mechanically ventilated. A subsequent brain MRI showed no change as compared with the previous examinations, but was still suggestive of PML. At admission, lactic acid and CK levels, as well as platelet count, remained within normal limits. AST and ALT were slightly elevated: 65 and 67 U/L respectively. While in the ICU, the patient developed multiorgan failure with rhabdomyolysis (CK 47,500), elevated liver enzymes (AST 2 557 U/L), elevated LDH (4 070 U/L) and disseminated intravascular coagulation: thrombocytopenia (12 × 10⁹/L), diminished fibrinogen levels, increased prothrombin time (INR). Lactic acid levels rapidly increased to 17.11 mmol/L on April 29, 2003 before he expired. Rhabdomyolysis and lactic acidosis were probably the consequences of repeated muscular convulsions. Blood
and Nosema
gen. are:
1200 species [1,2]. The most common human path-
etics, peritonitis, cardiac, sinusal, urinary, pulmonary, renal or
tal involve have been reported [3].
been detected in clinical samples from intestines,
small arteries, biliary tracts, urine, sinuses, and brain [4,5].
Whereas the incidence of microsporidiosis has decreased
people since the availability of cART, this infection has been increasingly reported in non-HIV-
individuals, such as solid organ and bone marrow
transplant recipients, as well as in cancer, diabetic and eld-
erly patients [6].
been reported in immunocompetent persons [6,7] and in
solid organ transplant recipients of latently infected donors
[8]. We decided to report this case 12 years later because
of this new emerging evidence and increased interest.
Moreover, we now seek to alert physicians to potentially
include microsporidiosis in the differential diagnosis not
in HIV-infected patients.
Cerebral microsporidiosis was first reported in 1959
[cited by reference 5] and 12 cases due to E. cuniculi, all
in HIV-infected persons, can be found in the medical liter-
from 1991 to 1998 [9]. Several other cases were
described in immunosuppressed, transplant recipients
and HIV-infected individuals [6,10]. In addition, one
case was reported in an immunocompetent patient, dis-
playing hemiparesis and epilepsy [7]. Some diagnosed
patients benefited from treatment with albendazole, which
is active against E. cuniculi [11].
In this case report, cerebral microsporidiosis was doc-
umented post mortem by morphologic examination of
brain samples. Interestingly, this diagnosis was not ini-
tially considered when the patient was living. The patient
presented with no other clinical manifestations such as
diarrhea, keratoconjunctivitis, sinusitis, cholangitis, hep-
itis, renal injury, which may have suggested a microspori-
dial infection. In addition, his CD4+ count at admission
and 2 months prior was greater than 330 cells/μL in the
absence of antiretroviral therapy. Moreover, the brain CT-
Scan and MRI findings were suggestive of PML [12].
Unfortunately, no tests for microsporidia were per-
formed and no treatment was initiated while the patient
was living, thus, there was no logical reason to suspect
microsporidiosis. At necropsy, no other techniques, such as
tissue culture, monoclonal antibodies staining, PCR
amplification of ribosomal RNA or DNA were performed
to identify and characterize the implicated microsporidian
species.
It is unclear as to how and when the patient acquired
this infection. Microsporidiosis can be transmitted by a
respiratory route, contaminated water or food, contact

Discussion
Microsporidia are widely recognised pathogens in both
invertebrates and vertebrates [1].
Microsporidia belong
to the phylum Microsporidia, with more than 144 genera
and 1200 species [1,2]. The most common human path-
gen. are: Encephalitozoon, Enterocytozoon, Pleistophora
and Nosema.
Microsporidia are small (1.5-2.5 μm × 2.5-4 μm), oval
shaped, obligate intracellular microorganisms found in
epithelial and endothelial cells, fibroblasts, macrophages,
astrocytes [1,2]. Although their human pathogenic po-
tential has been reported, they have become increasingly
recognized as opportunistic pathogens with the advent
of the AIDS epidemic [2].
Initially, Enterocytozoon bieneusi
was identified as a cause of diarrhoea and Encephalitozoon
(E.) intestinalis (formerly Septata intestinalis), and E. cuni-
culi for diarrhoeal or disseminated illnesses [2,3].
Microsporidial hepatitis, sclerosing cholangitis, perit-
onitis, cardiac, sinusal, urinary, pulmonary, renal or
ocular involve have been reported [3]. Microsporidia
have been detected in clinical samples from intestines,
livers, muscles, corneas, kidneys, adrenals, gonads, ganglia,
small arteries, biliary tracts, urine, sinuses, and brain [4,5].
At necropsy, no other techniques, such as
tissue culture, monoclonal antibodies staining, PCR
amplification of ribosomal RNA or DNA were performed
to identify and characterize the implicated microsporidian
species.
It is unclear as to how and when the patient acquired
this infection. Microsporidiosis can be transmitted by a
respiratory route, contaminated water or food, contact
with animals (such as dogs and rabbits), birds, invertebrates or by contact with an infected person [2]. In spite of well-preserved CD4+ counts and CD4+/CD8+ ratios, this patient presented with diminished CD16+56+ cell counts (10–60 cells/μL; normal 130–700) - the main subpopulation of natural killer (NK) cells. This reduced cell count may have, in part, contributed to his illness. Unfortunately, this finding was not considered during his hospitalisations. Although the T-cell mediated responses are the main protective mechanisms against microsporidiosis, the NK cells may contribute to the immune response and control of this infection [13].

There is growing evidence that latent microsporidiosis is common in immunocompetent individuals and could, therefore, be reactivated during immunosuppression, such as in HIV-infected and immunosuppressed persons, the elderly, transplant recipients, as well as in patients with malignancies or diabetes [6,14]. It is, therefore, possible that our patient experienced a reactivation of latent microsporidiosis that he had acquired before becoming HIV-infected. The diminished CD16+56+ cell counts may likely be responsible, at least in part, for the reactivation.

We would suggest that cerebral microsporidiosis should be considered in the differential diagnosis of brain lesions in HIV-infected as well as in other immunossuppressed patients or transplant recipients, particularly when the etiology is unknown. We would suggest that urinary and CSF specimens should be submitted for detection of Microsporidia. A pre-emptive treatment with albendazole may be considered when the brain lesions do not improve despite optimal HIV control, improved immunity and treatment for other suspected brain lesions.

Collectively, given the ubiquitous nature of microsporidia; their multiple routes of transmission; the potential that a latent infection may be reactivated or transmitted through donated organs; and the multitude of clinical manifestations, this infection should be considered in the differential diagnosis, when no definite etiology is established.

Consent
Written informed consent for autopsy was obtained from his mandatory and friend, the only next of kin to the patient. A copy of the written consent is available for review by the Editor-in-Chief of this journal. At the time of manuscript writing (11 years after patient’s death) we were unable to identify an individual from whom to seek consent for publication. We informed the Ethical Research Committee and a waiver was granted for consent to publish this case report.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
MA drafted the manuscript and revised all versions. L-GL contributed to the care of the patient and revised all versions of the manuscript. CB contributed to neuroradiologic examinations, provided MRI images and interpretation and revised the manuscript for publication. YR performed the neuropathological examination, documented the cerebral microsporidiosis, provided the brain section images and interpretation, and revised the manuscript. ET was responsible for the primary care of the patient, revised the draft, prepared the figure for publication and was responsible for the final manuscript. All authors have read and approved the final manuscript.

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