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CASE REPORT

CD8 T lymphocytes encephalitis mimicking brain tumor in HIV-1 infection

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Introduction

Combined antiretroviral therapy (cART) has led to considerable improvement in the spectrum of disorders affecting the central nervous system (CNS). The majority of focal brain presentations are due to toxoplasmosis, non-Hodgkin's lymphoma, and progressive multifocal leukoencephalopathy. Other causes are much rarer (Moulignier et al. 1994, 1996; Saravanan and Turnbull 2009). A growing number of severe, acute inflammatory leukoencephalopathies, whose causes remain to be identified, have been recently reported (Tavazzi et al. 2010). These include highly destructive forms of HIV-associated leukoencephalopathy (Langford et al. 2002), "burnt out" forms of HIV encephalitis (Scaravilli et al. 2007), immune reconstitution inflammatory syndrome (IRIS) (Venkataramana et al. 2006), brain tumefactive demyelination (Saravanan and Turnbull 2009; Solomon et al. 2013), and discordant HIV diseases (Canestri et al. 2010). A series of cases of diffuse encephalitis with marked perivascular infiltration by CD8 T lymphocytes with corticosteroid-responsive brain inflammation have been described as CD8 encephalitis (Lescure et al. 2013; Gray et al. 2013). Brain MRI shows characteristic perivascular punctuate or linear gadolinium-enhanced lesions, better seen in T1 spin echo with magnetic transfer, that are poorly delineated in T2-weighted images (Lescure et al. 2013). We describe the first biopsy-proven focal CD8 encephalitis (CD8-E) mimicking a brain tumor in a HIV+ patient.

Case report

A 27-year-old HIV-1-infected Guinean woman, with satisfactory HIV-infection control for 2 years (CD4 count 150/μl, plasmatic HIV-viral load (plVL) <20 copies/ml) under cART raltegravir, emtricitabine, and tenofovir, was admitted in September 2011 for a wasting syndrome due to EBV-positive stage IV Hodgkin's lymphoma (HL). CD4 count at HL diagnosis was 5/μl, CD8 count was 58/μl, and plVL was <20 copies/ml. She was treated with 5-monthly cycles of ACVpD (adriamycin, cyclophosphamide, VP-16, and dacarbazine) without bleomycin because of previous pneumonia, leading to complete remission with a normal bone marrow biopsy and a negative total body PET scan after treatment completion. In November 2011, plVL was once detectable at 450 copies/ml. In February 2012, she was admitted for subacute headaches,

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confusion, and seizures. The CD4 count was 103/μl, CD8 count was 782/μl, and plVL was <20 copies/ml. Brain MRI revealed multiple right intra-axial frontal gadolinium-enhanced lesions with important perilesional edema and mass effect (Fig. 1a–d). Systemic investigations were all noncontributory. A brain biopsy (March 2012) was studied after formalin fixation and paraffin embedding. Immunohistochemistry was performed with the ABC peroxidase/DAB method (Ventana automation). Antibodies used were CD20 Dako, clone L26, dilution 1/200; CD3 Novocastra, polyclonal, dilution 1/800; CD4 Novocastra, clone 1F6, pure; CD8 Dako, clone C8/144B, dilution 1/50; CD68 Dako, clone KP1, dilution 1/100; and p24 Dako, clone Kal-1, dilution1/5. Examination demonstrated a dense infiltration by normal CD3+, mostly CD8+ lymphocytes, with rare CD4+ lymphocytes and exceptional CD20 lymphocytes, no HIV-p24-positive macrophages, and important microglial activation with many CD68+ macrophages and microglial cells (Fig. 1e, f) consistent with CD8-E (Miller et al. 2004; Gray et al. 2013). A Klüver–Barrera staining was done; it showed slight demyelinization with rare myelin debris in one or two macrophages without perivascular predominance, not suggestive of ADEM. No Reed–Sternberg cells were identified, and analysis for T cell receptor-γ gene rearrangement was negative. Extensive investigations regarding viral (HIV-1, EBV, HHV-6, HHV-8), bacterial, or fungal infection of the CNS were negative. As recommended (Lescure et al. 2013), intravenous (IV) methylprednisolone 1 g/day for 5 days led to rapid clinical improvement. The patient was discharged with tapering prednisone (1 mg/kg) and the same cART regimen. In July 2012, she was fairly adherent to cART and had stopped prednisone. General and neurological examinations were

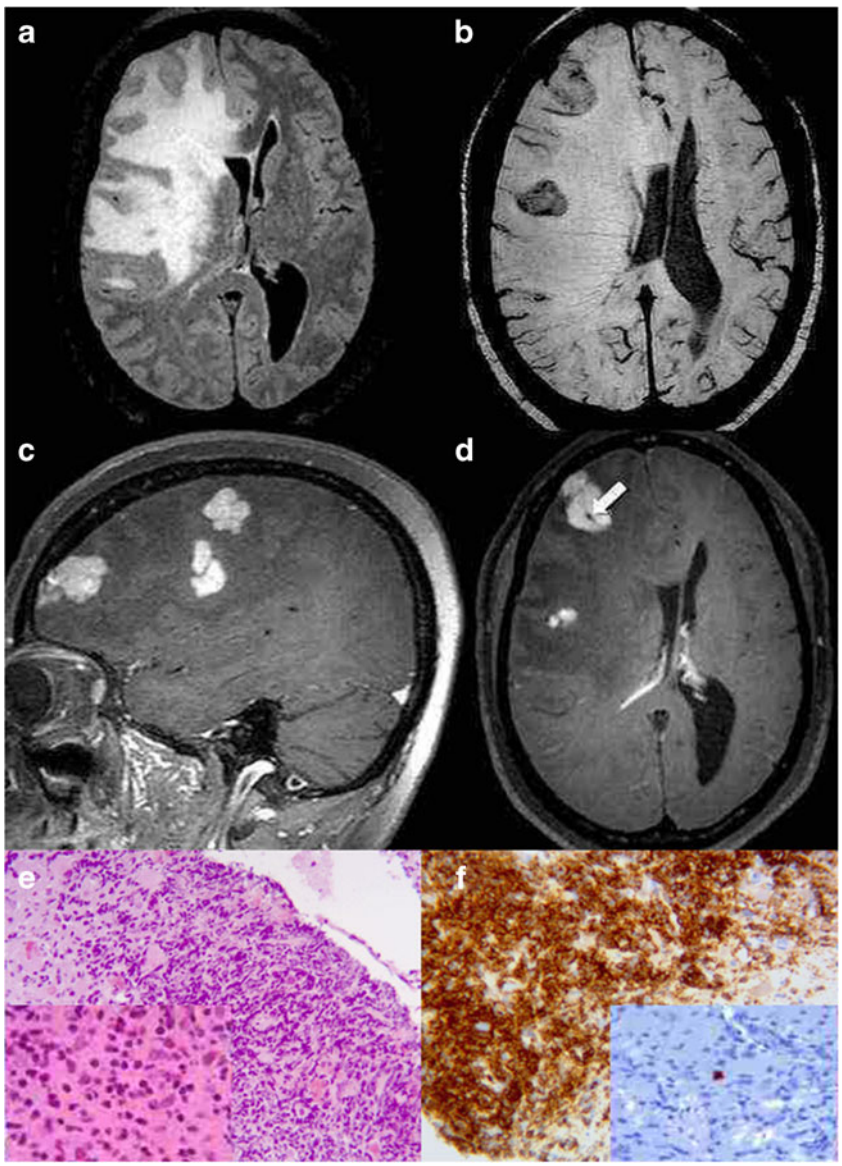

Fig. 1 Brain MRI and stereotactic biopsy. **a** Axial fluid-attenuated inversion-recovery high-signal-intensity lesions, surrounded with important edema and mass effect. **b** T2-weighted and susceptibility-weighted images show low-signal intensity. **c** Sagittal and **d** axial T1-weighted images show homogenous gadolinium enhancement. Biopsy trajectory is identified by an *arrow* on postgadolinium axial T1 images identified. **e** Dense lymphocytic infiltrate of brain parenchyma (hematin–eosin, objective ×16; *insert*, objective ×40). **f** Most lymphocytes are CD3/CD8+ T cells (CD8 immunohistochemistry, objective ×16) associated with only very few B lymphocytes (*insert*: CD20 immunohistochemistry, objective ×16)

normal. CD4 count was 349/μl, CD8 count was 1,488/μl, and plVL was 277 copies/ml. She was admitted in October 2012 for subacute changes in her mental status, headache, and seizures. She had stopped cART a few weeks ago. CD4 count was 175/μl, CD8 count was 1,333/μl, and plVL was 23032 copies/ml. Brain MRI showed the same lesions. PET scan demonstrated multiple supraclavicular and axillary lymphadenopathies. Surgical axillary lymph node biopsy revealed normal polyclonal CD8+ lymphocyte infiltration without HL. As an aspecific inflammatory response on the first brain biopsy was questioned, although MRI proved the right trajectory in the lesion (Fig. 1d), a second biopsy was performed in the anterior lesion that confirmed the same typical CD8-E features (Gray et al. 2013), without any lymphomatous, tumoral, or Reed–Sternberg cells nor infectious agents. The patient rapidly improved with methylprednisolone administered intravenously (1 g/day for 5 days) and discharged on prednisone administered orally (1 mg/kg) and the same cART. She stopped her treatment after several weeks and was found dead in February 2013.

Discussion

CD8-E is a HIV-driven complication occurring in four triggering conditions: minor infection in well-controlled patients, CNS immune reconstitution inflammatory syndrome, virological escape, and cART interruption (Lescure et al. 2013). In our case, two mechanisms could be proposed: the transient viral escape or the rapid immune reconstitution following HL-induced immunosuppression. The moderate adherence to cART could have maintained CD8+ lymphocyte activation.

CD8-E manifests as an acute or subacute decline in brain function with dizziness, headache, memory disorders, and confusion with seizures and sometimes status epilepticus (Lescure et al. 2013). Lumbar puncture (LP) classically disclosed lymphocytic meningitis with a majority of CD8− T cells, at least >65 %. Brain MRI is the cornerstone of the diagnosis, demonstrating poorly delineated T2 hyperintensities localized in both white and gray matter enhanced on postcontrast T1 spin echo with magnetic transfer sequences (Lescure et al. 2013). In such clinical settings without any identified infectious agent, the LP and radiological features suffice to initiate glucocorticoid treatment without further pathological examination.

Brain biopsy is mandatory in case of pseudotumoral presentation. Main differential diagnoses are lymphoma, glial tumors, acute disseminated encephalomyelitis, tumefactive demyelination, all excluded in the absence of monoclonal proliferation or tumoral cells, and aggressive demyelination. In some cases of CD8-E, CD8 lymphocytic infiltration was massive “pseudolymphomatous” (Gray et al. 2013), but not macroscopically organized as a tumor. In our case, the hypothesis of a lymphoma was highly unlikely as we performed two brain biopsies in two different locations and a thorough pathological examination of a lymph node with no evidence of tumoral or Reed–Steinberg cells. Moreover, analysis for T cell receptor-γ gene rearrangement was negative twice.

CD8+ T cells are the primary effector of the immune system, chiefly responsible for killing infected cells. Present only in small numbers within the normal CNS, they play a multifaceted role exerting cytotoxic as well as regulatory functions (Willing and Friese 2012). The presence of viral antigen during periods of HIV-1 replication amplifies the migration of both CD8+ and CD4+ T cells into the CNS/CSF (Spudich and González-Scarano 2012). Essential for viral clearance in virus-induced encephalitis, CD8+ cytotoxic T lymphocytes (CTL) can also cause severe tissue-destructive immunopathology (Willing and Friese 2012). The hallmark of CD8-E is the intense infiltration by CD8+ CTL, perturbing the delicate balance of intraparenchymal CD8+/CD4+ T cells at the origin of the immunopathological reaction, as observed in autoimmune diseases (Gray et al. 2013; Willing and Friese 2012). Favorable outcome was always associated with less severe and more mixed inflammatory reaction including not only abundant CD8+ lymphocytes but also a number of CD4+ lymphocytes (Gray et al. 2013). Like our patient, death was observed in patients who had severe inflammation with CD8+ CTL but weak or absent CD4 response in the brain tissue (Gray et al. 2013). An inflammatory response, once established, may give rise to a self-sustaining state of cellular activation. Unrestrained activation or autoreactivity of CD8+ CTL can lead to CD8-E by promoting a self-amplifying loop of CD8+ T cell-mediated CNS tissue destruction (Gray et al. 2013; Willing and Friese 2012).

In conclusion, CD8+ lymphocyte infiltration in a HIV-infected patient's brain biopsy, without any identified causative agents, should not lead to the diagnosis of unspecific inflammatory response, before having ruled out CD8-E that can be healed with rapid glucocorticoid treatment and optimal control of HIV replication (Lescure et al. 2013; Gray et al. 2013).

Conflict of interest The authors declare that they have no conflict of interest.

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