Clinical Case Report

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Nonopportunistic infection leading to rapidly progressive dementia in a patient with HIV/AIDS

A case report

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Abstract

Rationale: Cognitive dysfunction is a common presenting symptom in patients with HIV/AIDS. It is usually directly associated with HIV infection or due to opportunistic infection. Rapidly progressive dementia, however, is rarely observed in acute HIV infection or during immune reconstitution. Recently, a case of Creutzfeld-Jakob disease (CJD) has been reported in a patient with chronic HIV infection. The incidence of CJD is not known to be increased among immunocompromised patients.

Patient concerns: We here report the case of a 59-year-old male patient with a recent diagnosis of HIV/AIDS and Pneumocystis jiroveci pneumonia presenting with secondary behavioral changes and disorientation. Over the course of several weeks, progressive dementia developed characterized by apraxia, gait ataxia, and mutism.

Diagnoses: After the exclusion of common HIV-associated neurologic conditions, the clinical course as well as findings on electroencephalogram (EEG), magnetic resonance imaging (MRI), and a positive 14-3-3 assay converged into a probable diagnosis of CJD. The diagnosis was later confirmed histopathologically.

Outcomes: Palliative care was provided, and the patient passed away within 2 months of symptom onset.

Lessons: HIV/AIDS is an important stratifying condition during the work-up of many clinical syndromes including encephalopathy but may prematurely exclude important differential diagnoses. Non-opportunistic etiologies have to be considered as part of a secondary workup as this case of concomitant AIDS and CJD demonstrates. Rapidly progressive dementia should be distinguished from delirium as early as possible in order to be able to choose the correct diagnostic pathway. Despite the common occurrence of neurologic syndromes in the setting of immunodeficiency, an analytical diagnostic approach is advisable to minimize diagnostic bias.

Abbreviations: AIDS = acquired immunodeficiency syndrome, ART = antiretroviral therapy, CJD = Creutzfeld–Jakob disease, cMRI = cranial magnetic resonance imaging, CSF = cerebrospinal fluid, EEG = electroencephalogram, HIV = human immunodeficiency virus, PET = positron emission tomography, RPD = rapidly progressive dementia.

Keywords: AIDS, cognitive decline, Creutzfeld–Jakob disease, HIV-1, HIV-associated dementia, prion disease, rapidly progressive dementia

1. Introduction

Cognitive dysfunction is common in patients with AIDS due to HIV-associated encephalopathy, opportunistic infections, and immune reconstitution. Moreover, various degrees of cognitive impairment are also observed over the course of time in well-controlled HIV infection, although rapidly progressive dementia is rare.[1] HIV status is therefore an important decision node in diagnostic algorithms of encephalopathy and encephalitis.[2] Clinical decision making, however, is still influenced by heuristics from the pre-antiretroviral therapy (pre-ART) era when non-opportunistic conditions had little prognostic relevance in the HIV-infected population.[3] We here present a case of a patient with HIV/AIDS and rapid cognitive decline that highlights the importance to approach HIV-positive patients with elusive clinical presentations in an analytical manner.

2. Case report

A 59-year-old HIV-positive Caucasian male was admitted through our clinic with a 2-week history of altered mental status. He had been diagnosed with HIV/AIDS WHO Stage IV ($CD4^+$ cell nadir: 10 cells/μL) and *Pneumocystis jiroveci* pneumonia 3 months before the current admission upon return from a wintertime retreat in Thailand. The past medical history was notable for the use of anabolic steroids but no further known comorbid conditions or major surgeries. The patient reported not to take any regular medication and had not had a drink in more

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The requirement for ethical approval was waived for the present single case report. In accordance with Swedish law, informed consent for the anonymous publication of details from the case was obtained postmortem from the patient's daughter as the surviving next of kin.

The authors report no conflicts of interest.

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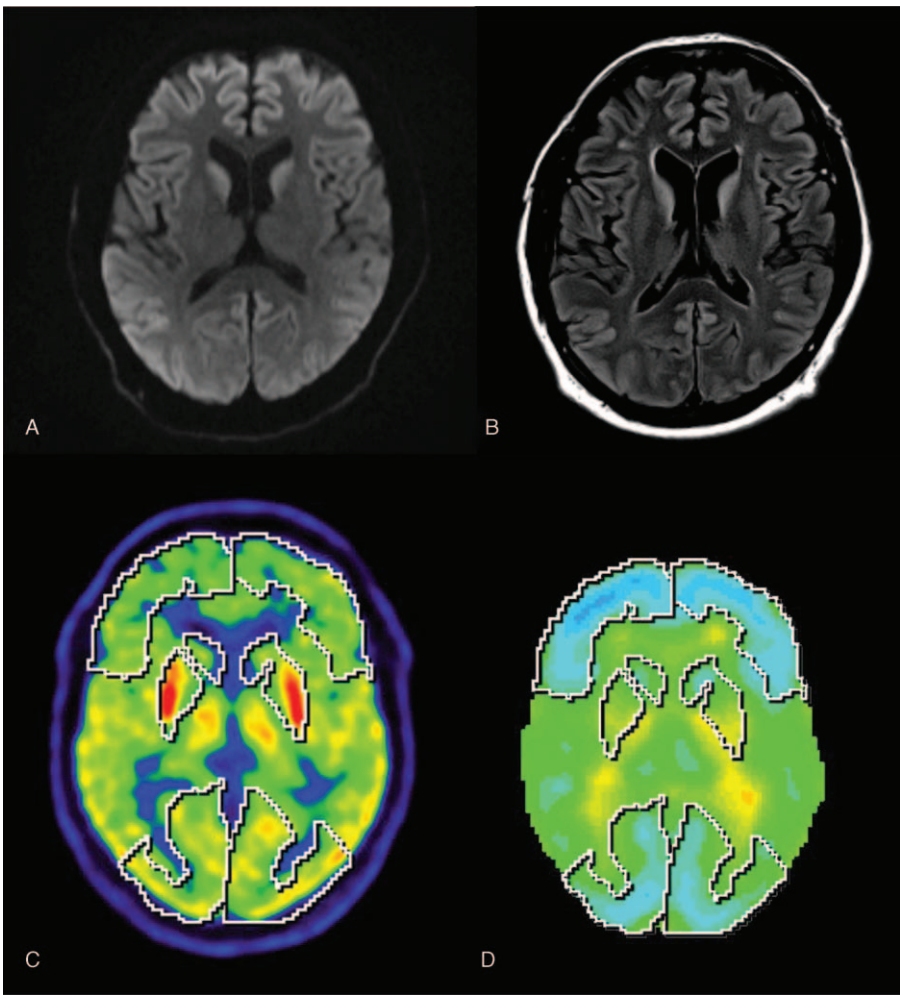

Figure 1. A–D: Brain MRI (A + B): Diffusion-weighted images b1000 (A) and FLAIR (B) at the level of the basal ganglia show mildly restricted diffusion and FLAIR hyperintensity, respectively, bilaterally in the caudate nuclei as well as in the frontal cortex, parietal cortex, and cingulate gyrus. Brain FDG-PET (C + D): A transaxial section at the level of the basal ganglia (C) demonstrates decreased uptake in the frontal and occipital cortex, moderately decreased uptake in caudate nuclei, as well as enhanced uptake bilaterally in the putamen. Significant metabolic changes as compared with the normal references (SD) are shown by semi quantitative VOI-based analysis (D). FDG, fluorodeoxyglucose (18F).

than a decade after a period of alcohol abuse. Family history was negative for neurodegenerative disorders. During his initial admission for HIV/AIDS, treatment with cotrimoxazole and betamethasone was initiated as well as ART with tenofovir, emtricitabine, and dolutegravir. Due to concomitant mild confusion and headaches, a cranial magnetic resonance imaging (cMRI) and cerebrospinal fluid (CSF) analysis were performed and found to be normal. Recovery was uneventful. Cognitive function returned to baseline within a few weeks and was ascribed a nonspecific HIV-associated neurocognitive disorder. The patient was deemed compliant in outpatient care as documented by a favorable decline in HIV viral load. However, after 2 months, friends and relatives started noticing an altered behavior such as getting lost in familiar environments and missing out on scheduled appointments. Upon clinical assessment, the patient denied any subjective complaints. He appeared well and alert, yet mildly disoriented being insecure about the situation and location. The remaining sensory and motor function was normal. Vital signs were normal. Laboratory tests revealed leukocytosis at 8900/μL, while the remaining blood count, electrolytes, creatinine, liver function tests, and thyroid-stimulating hormone were within normal range. HIV-RNA in plasma was detectable at low levels (217 copies/mL) and $CD4^+$ cell counts increasing (100/μL). The initial workup was directed toward common viral, bacterial, fungal, and parasitic opportunistic central nervous system pathogens. Upon lumbar puncture, the blood–brain barrier was intact with no discernible intrathecal inflammation. Opening pressure was normal (<20 cmH_2O). CSF analysis for herpes simplex virus 1 and 2, enterovirus, varicella zoster virus, human herpesvirus 6, JC-virus and toxoplasma (polymerase chain reaction), as well as cryptococcal antigen were negative. HIV-RNA in CSF was undetectable (<20 copies/mL), while Epstein–Barr virus was detected at <500 copies/mL, which was considered to be nonspecific. Serologic tests of endemic tick-borne encephalitis and syphilis were negative. In addition, whole genome sequencing of CSF detected no relevant viral, bacterial, or parasitic nucleic acid. A follow-up cMRI revealed signal abnormalities mainly in the caudate nuclei, frontal cortex, and parietal cortex bilaterally without focal contrast-enhanced lesions (Fig. 1A, B). Taken together, these findings in the absence of intrathecal inflammation argued against specifically HIV-related neurological complications. Initially, the patient's mental

state appeared to be fluctuating and was therefore still classified as a delirium. We subsequently turned to differential diagnoses outside of the HIV-associated spectrum of diseases. The patient's electroencephalogram (EEG) revealed a diffuse slow-wave basic rhythm (1.5–4 Hz) with periodic triphasic spike and wave complexes especially in the frontal region. Although this picture is most commonly associated with metabolic or toxic encephalopathies, there was no indication of recent drug use or intoxication. Serum levels of ammonium and lactic acid were normal. To exclude an idiosyncratic adverse drug reaction, the patient's antiretroviral regimen was changed to abacavir, lamivudine, and darunavir/ritonavir, while pneumocystis prophylaxis was changed to atovaquone. Nevertheless, his condition evolved into marked apraxia with incipient gait ataxia and involuntary myocloni over the course of 3 weeks. Neuronal autoantibodies in serum and CSF were negative. Conversely, neurofilament light protein (6670 ng/L, ref. < 1850 ng/L) and tau-protein (>2000 ng/L, ref. < 400 ng/L) were markedly elevated indicating significant neuronal degeneration. An fluorodeoxyglucose (18F)-positron emission tomography (PET)/computed tomography (CT) of the brain was ordered to more sensitively depict functional abnormalities (Fig. 1) and revealed a marked hypometabolism in the frontoparietal and occipital cortex (Fig. 1C, D). The combined radiographic, electroencephalographic, and clinical picture ultimately raised suspicion of Creutzfeld–Jakob disease (CJD). 14–3–3 protein was detected in CSF suggesting a probable case of CJD according to CDC's criteria.[4] A positive real-time quaking-induced conversion assay (RT-QuiC) further added to in vivo diagnostic accuracy.[5] At this point, the patient had become bedridden, virtually mutistic with a marked myoclonus. He was transferred into hospice care where he passed away 8 weeks after symptom onset. Cerebral autopsy confirmed the presence of prion protein and a spongiform encephalopathy.

3. Discussion

CJD is a rare neurodegenerative disorder caused by the accumulation of an altered prion protein (PrPSc) that induces perpetual misfolding of its own kind in a domino-like fashion. The disease leads to progressive destruction of cortical neurons and is invariably fatal. It is an important cause of rapidly progressive dementia characterized by myoclonus, cerebellar dysfunction, and akinetic mutism.[6] While a majority of cases (90%) are sporadic, iatrogenic cases through surgical transplantation and contamination as well as familiar cases do occur. Confirmation relies on cerebral histopathology, which is usually made postmortem. Recently, a case of CJD has been described in a patient with well-controlled HIV infection.[7] We now report a case of CJD in a patient who had only recently been diagnosed with AIDS. To our knowledge, there is no evidence of a permissive effect of immunosuppression on the incidence of CJD. The biphasic development of cognitive impairment within a few months from being diagnosed with HIV/AIDS posed a significant diagnostic challenge: Intuitively, we assumed an association with HIV infection. However, after initially revolving around an HIV-centered diagnostic plan without success, we decided to rephrase our diagnostic approach in a more syndromic way acknowledging the progressive features of dementia.[8] The striking abnormalities on PET/CT finally corroborated our suspicion of CJD, which, in hindsight, had been suggested by the typical clinical course and EEG findings early on. The major cognitive pitfalls involved in the somewhat delayed recognition of this rare differential diagnosis were a combination of framing and anchoring heuristic [9]: The seemingly apparent etiologic role of HIV infection made anything unrelated appear unlikely and precluded an unbiased analytical approach to rapidly progressive dementia. Furthermore, the distinction between reversible delirium and rapidly progressive dementia is challenging especially outside of critical care settings and diagnostic criteria are poorly defined.[10] Longitudinal testing for mental status changes is key for the identification of progressive cognitive decline in true neurodegenerative dementia.[11] However, non-specialized physicians are prone to underuse this important diagnostic tool due to its time-consuming nature leading to a suboptimal choice of differential diagnoses. As a lesson from the presented case, we would therefore like to encourage fellow clinicians to implement training of broad analytical diagnostic reasoning as opposed to heuristic automatisms into lifelong learning schedules early on. More specifically, we would also like to underline the importance of actively considering rare nonopportunistic diseases as part of secondary diagnostic approaches to elusive clinical syndromes in immunocompromised patients.

Author contributions

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