Clinical Reasoning: Rapidly progressive dementia in a patient with HIV after an exotic journey

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Section 1

A 62-year-old man presented to the Emergency Department of Sant'Orsola-Malpighi University Hospital in Bologna, Italy, because of a rapidly progressive cognitive decline. He had recently come back to Italy after a 3-month journey in Brazil because relatives found him confused while speaking over the phone. Because of global slowing, disorientation, and confabulation, which developed over the previous 2 months, he underwent a brain MRI in Brazil, which showed cortical atrophy and multiple white matter lesions with no contrast enhancement. No further clinical information about the medical assessment in Brazil was available.

Since age 34 years, the patient was on highly active antiretroviral therapy (ART) (abacavir 600 mg/d, lamivudine 300 mg/d, darunavir 800 mg/d, and ritonavir 100 mg/d) for HIV infection with good adherence. His medical history was also relevant for hypertension, diabetes, squamous cell carcinoma of the anus, psoriatic arthritis, including skin psoriasis, dactylitis, nail dystrophy, a negative rheumatoid factor, and diffuse proliferative lupus-like glomerulonephritis.

At the first medical evaluation, the patient was drowsy, spatially and temporally disoriented, with reduced verbal fluency, miotic reagent pupils, and a mask face. He also had axial and limb plastic hypertonia and dystonia of both hands. Arterial pressure was 130/80 mm Hg, heart rate was 90/min, and arterial blood gas test was within the normal range. A cerebral CT scan was also unremarkable. Blood examinations, including a toxicology screen, were normal, except for mean corpuscular volume 105 fL, mean corpuscular hemoglobin 38 pg, aspartate aminotransferase 80 U/L, lactate dehydrogenase 331 U/L, and C-reactive protein 1.65 mg/dL. The patient underwent a lumbar puncture to rule out infectious diseases.

CSF analyses revealed proteins 93 mg/dL, glucose 70 mg/dL, leukocytes 1/mmc, immunoglobulin G 11.8 mg/dL, albumin 69.1 mg/dL; the albumin CSF/serum ratio was 20.8, indicative for abnormal permeability of the blood–CSF barrier. Blood testing for autoimmune diseases was negative except for antinuclear antibody 1:80. Plasma CD4 count was 275/mmc (25%). EEG examination documented asymmetric and pseudo-periodic slow spike discharges with maximum amplitude in the right temporal region (figure 1A).

A thorough anamnesis with the relatives revealed a recent relapse of psoriatic arthritis, treated with methylprednisolone, hydroxychloroquine, and methotrexate.

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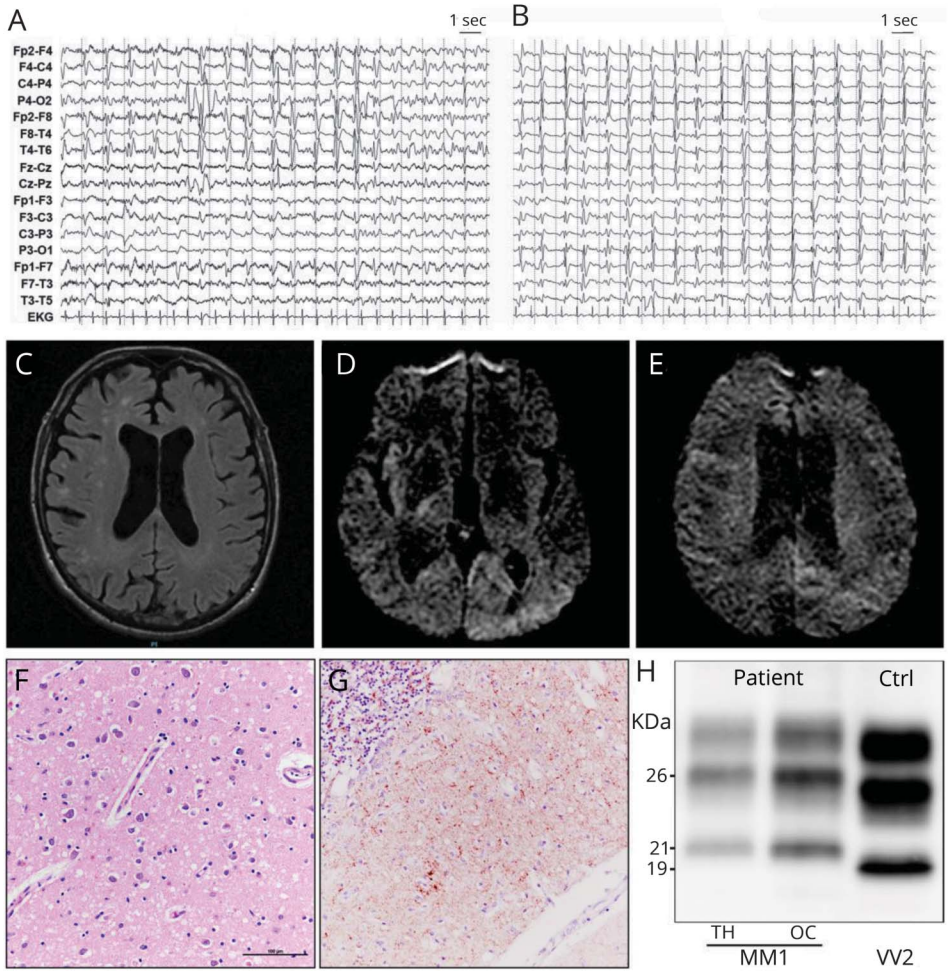
Consequently, CD4 recovery was tested suboptimal in the last months (<400 copies/mmc).

Based on clinical history, laboratory analysis, and EEG results, the primary suspected diagnosis was an infectious disease.

Questions for consideration:

1. Which neuroinfections would you consider in the differential diagnosis?
2. Which initial empiric antimicrobial therapy would you prescribe?

Figure Results of EEG, brain MRI, and pathologic investigations



Serial EEG recordings show pseudo-periodic discharges of slow spikes with asymmetric distribution (maximum amplitude on right temporal region) at hospital admission (A) and generalized triphasic sharp-wave complexes in late stage (B). Brain MRI shows multiple frontoparietal white matter hyperintensities on fluid-attenuated inversion recovery (C), while diffusion tensor imaging sequences are negative (D, E). Moderate spongiform change in the temporal cortex can be seen (F, hematoxylin & eosin stain, ×200). PrP^{Sc} staining with primary antibody 3F4 reveals focal synaptic immunoreactivity in the molecular layer of cerebellum (G, ×200). After proteinase K digestion, Western blot analysis shows PrP^{sc} type 1 (21 KDa; TH = thalamus; OC = occipital cortex) in our patient and PrP^{sc} type 2 (19 KDa) in a control participant with sporadic Creutzfeldt-Jakob disease VV2 (H).

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Section 2

In addition to the most common agents associated with meningoencephalitis in Italy (e.g., herpes simplex virus [HSV] 1–2, pneumococcus), we investigated bacteria (*Treponema pallidum*, *Mycobacterium tuberculosis*), neurotropic viruses (West Nile, Zika, Chikungunya, and Dengue), and *Cryptococcus neoformans/gattii*, which account for the majority of cases of acute or chronic meningoencephalitis in Brazil.[1–3] Moreover, we looked for opportunistic neuroinfections such as other herpesviruses, JC virus, *Toxoplasma*, and fungi, which may affect HIV-infected patients without optimal CD4 recovery.[4]

Given the broad spectrum of possible infectious etiologies, we started an empiric therapy based on ceftriaxone (2 g bid), fluconazole (100 mg/d), and acyclovir (750 mg tid). We also added methylprednisolone (40 mg/d) for suspected HSV encephalitis and phenytoin by taking into account the clinical status of the patient and the result of the EEG. However, all serum or CSF microbiological investigations as well as CSF oligoclonal bands were negative. Given the absence of clinical improvement and the inconclusive microbiological tests, the antimicrobial therapy was stopped and corticosteroids tapered.

Other HIV-associated neurocognitive disorders to be considered include the following:

(i) HIV-associated dementia (HAD), characterized by subacute subcortical dysfunction, such as mental slowing, memory and executive function impairment, apathy, and depression. This form typically occurs in advanced and untreated HIV infection with CD4 cell counts <200 cells/mmc. In contrast, patients on ART may only occasionally develop mild cognitive impairment.[4,5]

(ii) HIV-associated malignancies (e.g., primary CNS lymphoma), which typically present with focal neurologic signs or cognitive or behavioral changes, depending on the location of the mass. These are commonly associated with CD4 cell counts <200 cells/mmc.[4]

(iii) CSF viral escape syndrome, which is a rare condition presenting with severe neurologic deficits in ART-treated patients, related to HIV replication in the CSF despite low or absent viral levels in the blood. In most cases, CSF viral drug resistance is documented, suggesting a compartmentalization of the resistant virus within the CSF.[5]

(iv) CD8+ encephalitis, a treatable acute encephalopathy characterized by diffuse perivascular and intraparenchymal CD8 infiltration, typically occurring in patients with apparently stable ART.[6]

Question for consideration:

1. Which tests would you order to support this diagnostic orientation and identify these diseases?

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Section 3

Blood viral load (HIV RNA) was low (1,271 copies/mL); otherwise, the virus was absent in the CSF. Therefore, we excluded HAD, CSF escape syndrome, and CD8 encephalitis, as they are typically associated with detectable HIV load in the CSF. We searched for neoplastic and leukemic cells in CSF, which were absent.

In the following few days, the clinical picture deteriorated further. On neurologic examination, verbal stimuli were not effective, noxious stimuli induced a withdrawal response, while stimulus-evoked myoclonus in the 4 limbs, startle response, and primitive reflexes appeared. At this time, the EEG showed diffuse periodic sharp-wave complexes (figure 1B), a distinctive pattern observed in Creutzfeldt-Jakob disease (CJD), metabolic encephalopathies, and a minor proportion of other rapidly progressive dementias.[7]

In the meantime, the patient's clinical status worsened to akinetic mutism associated with flaccid tetraparesis. Because CJD became the primary suspected diagnosis, we decided to repeat the brain MRI and perform CSF 14-3-3 and total tau (t-tau) analyses. Specifically, we searched for fluid-attenuated inversion recovery (FLAIR) or diffusion-weighted imaging (DWI) hyperintensities in the striatum or at least 2 cerebral cortical regions, or a positive protein 14-3-3 assay or increased t-tau levels above 1,250 pg/mL, all supporting the clinical diagnosis of probable CJD with good sensitivity and specificity.[8,9]

Brain MRI showed only marked and diffuse cortical atrophy; FLAIR sequences disclosed multiple frontoparietal white matter hyperintensities and diffusion tensor imaging sequences were negative (figure 1, C–E). However, the 14-3-3 protein was positive and t-tau levels were markedly increased (19,200 pg/mL) in the CSF.

Question for consideration:

1. Given the inconclusive EEG, MRI, and surrogate CSF biomarker results, which test can support the diagnosis of CJD in vivo with the highest accuracy?

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Section 4

Prion detection in CSF by real-time quaking-induced conversion (RT-QuIC) assay was positive.[8]

The patient died 4 months after symptom onset. Neuropathologic and molecular analysis confirmed the diagnosis of definite sporadic CJD (sCJD) MM1 subtype according to the Parchi et al. classification (figure 1, F–H).[7]

Discussion

sCJD belongs to the human transmissible spongiform encephalopathies or prion diseases, a group of neurodegenerative disorders characterized by brain deposition of a misfolded form of the cellular prion protein (PrP^{Sc}). Although sCJD typically manifests as a rapidly progressive cognitive decline associated with multifocal signs (i.e., cortical, subcortical, and cerebellar), the disease demonstrates a broad phenotypic heterogeneity. The 6 clinicopathologic subtypes of sCJD identified to date largely correlate at the molecular level with the genotype at the polymorphic codon 129 (methionine [M] or valine [V]) in *PRNP* and the type (1 or 2) of PrP^{Sc} accumulating in the brain (e.g. MM1, MM2, MV2, and VV2).[7]

Among the diagnostic investigations supporting the clinical diagnosis of CJD, brain MRI with DWI sequences and the CSF surrogate protein markers 14-3-3 and t-tau have an overall better diagnostic accuracy than the EEG.[9] Nevertheless, about ~10% of patients with CJD, as in the present case, do not show the typical hyperintensities on DWI sequences.[9] Similarly, the calculated sensitivity of CSF 14-3-3 and t-tau protein assays in a recently published large cohort of definite sCJD was 83.3% and 88.2%, respectively, with a significant variability depending on the disease subtype.[8] Furthermore, it is well-established that both surrogate CSF biomarker assays and brain MRI may generate false-positive results, especially in cases of encephalitis, acute brain injuries, and other rapidly progressive dementias.[8]

The recent development of prion RT-QuIC, a novel assay for the ultrasensitive detection of abnormal prion protein in CSF with increasing sensitivity (~96%) and specificity (100%), has significantly improved the overall diagnostic accuracy in vivo,[10] making it the most powerful currently available tool for the clinical diagnosis of CJD. Notably, at variance with surrogate CSF protein markers such 14-3-3 and t-tau, recommended in case of a high or moderate pretest probability of sCJD, RT-QuIC can be used as a screening test in cases of progressive neurologic syndromes because of its high specificity. The present report nicely demonstrates the potential usefulness of a wider application of RT-QuIC in the diagnostic workup of rapidly progressive dementias to include cases with a relatively low pretest probability of CJD. Indeed, in our patient, both the recent exotic journey and the history of HIV infection with suboptimal control by ART significantly influenced the diagnostic workup, and concurred together with the inconclusive result of some early investigations to cause a significant diagnostic delay.

Author contributions

Samir Abu-Rumeileh, Simone Baiardi, Piero Parchi: study concept and design, writing of the manuscript. Samir Abu-Rumeileh, Simone Baiardi, Roberto D'Angelo, Nicola Dentale, Giovanni Fasulo, Maria Guarino, Piero Parchi: acquisition and interpretation of data. All authors critically reviewed and approved the manuscript.

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