Un caso di deterioramento cognitivo associato ad escape virale in un paziente con infezione da HIV.

Symptomatic neurocognitive impairment associated to CNS viral escape in an HIV-1 infected patient: a case report.

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Riassunto

Nonostante la significativa riduzione della mortalità globale tra le persone con HIV nell'era della terapia antiretrovirale combinata (cART), l'infezione cronica da HIV rimane associata a un'ampia gamma di disturbi neurocognitivi. Tale correlazione è attribuibile al marcato neurotropismo del virus, il quale infetta il sistema nervoso centrale (SNC) sin dalle prime fasi dell'infezione primaria. Tuttavia, altri fattori contribuenti includono comorbidità, invecchiamento precoce, vari tipi di demenza, disturbi psichiatrici ed il viral escape a livello del SNC. Quest'ultimo, caratterizzato da livelli rilevabili di HIV-RNA nel liquido cerebrospinale nonostante livelli non rilevabili o più bassi nel plasma, costituisce una sfida significativa nella gestione dell'HIV.

Nel presente caso clinico, descriviamo il quadro di un uomo con infezione da HIV la cui aderenza alla terapia era subottimale. Il paziente è giunto all'attenzione medica manifestando compromissione cognitiva, riconducibile infine a un caso di viral escape. La gestione si è rilevata particolarmente difficile a causa della necessità di selezionare un regime cART con maggiore penetrazione nel liquido cerebrospinale, considerando la sua storia di molteplici fallimenti virologici, mutazioni associate alla resistenza precedentemente rilevate e scarsa aderenza al trattamento.

Abstract

Despite the significant reduction in overall mortality among individuals with HIV in the era of combination antiretroviral therapy (cART), chronic HIV infection remains associated with a broad spectrum of neurocognitive disorders.

This correlation is attributed to the pronounced neurotropism of the virus, which infects the central nervous system (CNS) from the early stages of primary infection. However, other contributing factors include comorbidities, accelerated ageing, various forms of dementia, psychiatric disorders, and CNS viral escape.

The latter, characterized by detectable levels of HIV-RNA in cerebrospinal fluid despite undetectable or lower levels in plasma, poses a significant challenge in HIV management. We herein describe the case of a man with HIV infection whose adherence to therapy was suboptimal.

The patient presented to medical attention with cognitive impairment, ultimately attributed to a case of viral escape. Management was particularly challenging due to the necessity of selecting a cART regimen with enhanced CSF penetration, given his history of multiple virologic failures, previously detected resistance-associated mutations, and poor treatment compliance.

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Background

Over the last three decades, following the introduction of combination antiretroviral therapy (cART), people with HIV (PWH) have experienced less opportunistic infections with an increased overall survival. However, some comorbidities such as HIV-associated neurocognitive impairment have not disappeared and, although uncommon, may strongly impact the quality of life. Abnormalities in memory, concentration, attention, and motor skills are often observed in this population. Previously designated as AIDS-dementia complex, these manifestations are now categorized as HIV-associated neurological disorders (HAND), representing a spectrum of neurocognitive disorders.

This spectrum includes asymptomatic neurocogni-

tive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). cART has significantly diminished the incidence of severe neurocognitive deficits, particularly HAD. Nevertheless, a persistently high prevalence of HAND is observed among PWH, primarily characterized by milder forms such as ANI and MND, collectively accounting for 88% of all HAND cases (1). These disorders may be influenced by several factors such as premature ageing, ART-associated neurotoxicity, psychiatric diseases, polypharmacy, chronic inflammation and central nervous system (CNS) viral escape. The latter is an infrequent event in the setting of neurocognitive impairment and is defined as an increased cerebrospinal fluid (CSF) HIV RNA to levels higher than those detected in paired-plasma samples, it may be symptomatic or not and it represents an important challenge in terms of treatment management (2).

Here we report a case of symptomatic CNS viral escape in an HIV-1 infected patient with previous virological failures whose cART optimization was challenging.

Case report

A 54-year-old male, diagnosed with HIV in 1997 with a nadir CD4+ cells count below 200 cells/ml, was started on dual therapy with AZT and ddC in May 1997 and switched to a 3-drug regimen with AZT/ddC/IDV after 6 months. He had a history of esophageal candidiasis in 2003. Over the subsequent years, multiple antiretroviral regimens (including 3TC, d4T, ddI, ABC, EFV, NVP, ETV, SQV, APV/r, LPV/r, TPV/r, DRV/r) were modified due to virological failures with emergent resistance to NRTI, NNRTI and PI, in the context of erratic adherence. In 2017 he was successfully switched to maraviroc (300 mg od) plus darunavir/ritonavir (800/100mg od) up to September 2020 when the patient discontinued coming to visit. In December 2023, he presented to our outpatient clinic with progressive cognitive impairment and memory gaps. His CD4 count was 575 cells/ml, and plasma HIV RNA was 1350 copies/ml, consistent with suboptimal adherence.

His previous cumulative genotypes (the last one performed five years before) had shown primary resistance mutations as follows: 103N, 108I, 115F, 151M, 184V, 215Y on reverse transcriptase (RT), while 10F, 46I, 54V, 82A/T on protease.

A brain MRI revealed bilateral subcortical T2-hyperintensities in the temporal, frontal, and insular regions, described as demyelinating lesions, consistent with HIV-related encephalopathy. The patient was afebrile, alert, and apathic, but still oriented to time, space, and self. However, there were notable memory gaps, particularly in short-term memory. A diagnostic lumbar puncture was performed, revealing hyperprotidorrachia (128 mg/dl) and 32 cells/microL (93.5% lymphocytes). CSF tested negative for HSV1-2, CMV, EBV, JCV, VZV and Cryptococcal infection, while HIV RNA was 21400 copies/ml, confirming the viral escape. Neurocognitive tests confirmed a moderate impairment. Waiting for the GRT testing on both CSF and plasma HIV RNA, and in the uncertainty of potential additional resistance mutations, the patient was started on a new regimen with DTG (50mg od), DRV/c (800/100mg od) and fostemsavir (700mg od). Due to the lack of data on CSF fostemsavir penetration, doravirine (DOR) as a fourth drug was also added to the regimen. The patient was discharged home and seen again 6 weeks later at the outpatient clinic, where he showed a remarkable clinical improvement, with a re-achieved independence in his daily activities. His plasma HIV RNA was 23 copies/ml and CD4 count was 582 c/ml. The results of previous GRTs, performed both on plasma and CSF, revealed a wild-type virus and CCR5 tropism.

In light of the recent GRTs, fostemsavir was discontinued, and the patient was kept on DOR 100mg + DRV-c 800/100mg + DTG 50mg, all once daily.

The lumbar puncture, which could confirm the regained CSF virological control, was postponed due to the patient's reluctance as he had had 10-day headache after the first procedure.

Given the current clinical benefit, the brain MRI was planned 2 months later.

Discussion

We here present the case of a 54-year-old male living with HIV who experienced a symptomatic CNS viral escape which required optimization of his cART regimen. In treatment-naïve subjects, HIV RNA levels in the CNS are usually one-tenth of those detectable in paired plasma samples and normally below detectable levels when effective cART is administered. CNS HIV viral escape can be defined as either having detectable HIV-RNA levels in the CSF while having undetectable levels in the plasma or having detectable HIV-RNA levels in both CSF and plasma, with higher levels in CSF (3).

This phenomenon is caused by the strong neurotropism of HIV since the beginning of PHI (Primary HIV infection). During this phase, infected T-cells cross the blood-brain barrier (BBB), enabling the virus to infect microglial cells, in which HIV establishes a latent

reservoir and triggers chronic inflammation.
This may lead to a progressive neurocognitive impairment over time and to CNS compartmentalization within the first years after HIV acquisition, which may induce CNS viral escape. Factors associated with higher risk of viral escape are prolonged duration of HIV infection, lower CD4+ T-cell nadir (<200 cells/µL), persistent low-level plasma viremia, poor ART adherence, pre-existing ART resistance and previous regimens including drugs with low CSF penetration. (4)
The neurocognitive impairment in PWH may be multifactorial in nature, including premature ageing, ART-associated neurotoxic effects along with psychiatric comorbidities and polypharmacy. In case of symptomatic viral escape, the choice of the most appropriate regimen should be based on multiple considerations, including individual cART history, cumulative drug resistance mutations (DRMs) and antiretroviral CSF penetration. There are no established guidelines for managing CNS escape and HAND pharmacologically, but clinicians may be assisted by the CNS penetration effectiveness (CPE) score in selecting agents (5).
However, while higher CPE scores have been associated with better virologic outcomes and mild cognitive improvement, they are not as strongly correlated with neurocognitive outcomes (6). This suggests that other factors such as comorbidities and premature aging in PWH may play a role in neurocognitive disorders.
In 2017, our patient was started on DRV/r 800/100mg plus MRV 300mg due to the extensive resistance mutations on reverse transcriptase, and his plasma HIV RNA remained < 50 copies/ml for several months, before being lost to follow-up.
This dual regimen is no longer recommended because of the lower efficacy compared to a standard triple regimen. In our case, in the absence of recent GRTs, an initial four-drug regimen was selected to maximize CNS penetration and optimize the genetic barrier. The selection of agents was guided by different considerations. For DTG the patient was naive to INSTI, DOR may retain activity when viruses are resistant to old NNRTIs, and has a good CNS penetration, while DRV was kept because the boosted PI is unlikely to develop mutations at failure and has a good CPE score. Higher doses of DTG and DRV/c were deemed unnecessary given the resistance pattern. Fostemsavir, whose CNS penetration is still undefined, was temporarily added to the regimen waiting for GRT results and then discontinued. So, six weeks later, following clinical improvement and undetectable plasma HIV RNA, treatment was simplified to a 3-drug regimen (3 fully active drugs).
Two additional considerations deserve attention. First, performing GRTs on both CSF and plasma when the patient is off treatment may fail to detect the real presence of DRMs, due to the absence of selective drug pressure. From this perspective, resistance testing on HIV DNA could help identify archived mutations, although its clinical interpretation remains uncertain so far (7). In such cases, historical genotypes and a detailed drug history are crucial.
Second, the lumbar puncture is an invasive and not well-tolerated procedure. Although it is the best tool to assess the control of viral escape, the patient's reluctance is frequent once he/she is clinically improved, and guidelines are not all consistent on this issue. However, when CSF HIV-RNA cannot be tested, clinicians should always be aware of the potential viral escape and plan an appropriate follow-up. ■

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