Worsening confusion in a patient with HIV and a normal CD4 count.

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Abstract

Rapidly progressive encephalopathy in the HIV-positive patient can present a major diagnostic and management challenge. We report a case of CD8+ encephalitis, a severe but treatable form of HIV-related acute encephalopathy, in a patient with normal CD4 count and undetectable serum viral load. CD8+ encephalitis is characterised by diffuse perivascular and intraparenchymal CD8+ lymphocytic infiltration and can occur in patients apparently stable on antiretroviral treatment, likely due to viral escape into the CNS. Even following severe encephalopathy with a very poor initial neurological status, treatment including high-dose corticosteroids can lead to a favourable prognosis and an excellent neurological outcome, as in our patient.

Case history

A 52 year old black African woman with known HIV infection presented to her local hospital with a 3-week progressive history of confusion, drowsiness, poor balance and mild headache. Three weeks prior to the onset of symptoms, she had returned from a four week holiday in Sub-Saharan Africa. During her holiday she was neurologically well but received antibiotics for a transient cellulitis, having cut her shin while climbing out of a bus. Soon after her return she became confused and disorientated, wandering at night and confabulating. There were no fevers, seizures, weakness or sensory loss.

She was found to be HIV positive 8 years previously but did not present for treatment until 18 months prior to this illness, when combined antiretroviral therapy (cART) was started. On initiation, CD4 count was 550 cells/µL (normal: 500-1500) and plasma HIV viral load was 850000 copies/mL. Her cART on admission included tenofovir, emricitabine, ritonavir and atazanavir and had not been altered for the past year. She had been fully compliant with her medication and had missed no doses during her holiday. Two months prior to her admission, HIV was undetectable in plasma with a CD4 count of 870 cells/µL. There was no previous history of significant HIV-related complications. She had a past history of treated syphilis many years ago but no other significant illness. She was born in Sub-Saharan Africa but lived in the UK for 15 years and was fully independent prior to her illness, in full

time employment. She was a non-smoker with moderate alcohol intake. There was no relevant family history.

On initial examination she was afebrile and normotensive, able to obey commands but disorientated to time and place. She was noted to have a left pronator drift and bilateral extensor plantars. Tone, power, reflexes and sensory examination were otherwise normal. General systems examination was also normal. A CT brain scan showed generalised sulcal effacement indicative of brain swelling and confluent white matter hypoattenuation. Blood tests showed CRP 6 mg/l, normal WBC (8.4 x10^9/L) and unremarkable liver and renal function. She deteriorated quickly following her admission, becoming drowsy and unable to follow commands. Three days after her initial presentation, she was incontinent of urine, was noted to have right arm weakness and her Glasgow Coma Score (GCS) dropped to 10/15. Repeat CT imaging showed worsening cerebral oedema and she was started on Dexamethasone 4mg QDS, IV acyclovir and ceftriaxone. She was urgently transferred to our tertiary neurological centre for further management. She was intubated at the time of transfer and was admitted directly to our Intensive Care Unit.

An MRI head was performed, which demonstrated diffuse and symmetrical T2 hyperintense signal abnormality throughout the cerebral white matter, with some additional involvement of deep grey structures and infratentorial white matter. Striking diffusion restriction was observed, predominantly along the periphery of the confluent white matter changes (Figure 1). Her CD4 count was 220 cells/µL (lowest documented during her admission), CD8 count was 360 cells/µL (normal 150 – 1000) and HIV RNA was undetectable in plasma. Investigations for possible infective causes were all negative. Lumbar puncture was contraindicated due to raised intracranial pressure at that point.

Intermittent lower limb jerking was noted during her admission and an EEG showed generalised slowing consistent with widespread cortical dysfunction, right posterior background suppression, and right frontal sharp waves suggestive of focal cortical irritability: she was started on phenytoin for presumed seizures. However, despite treatment she continued to deteriorate and her GCS dropped to 4. In view of ongoing deterioration in the absence of a confirmed diagnosis, we proceeded to a biopsy of the non-dominant frontal lobe in accordance with the MRI findings, with collection of cerebrospinal fluid (CSF) through the burr hole at the end of the procedure. Histopathology showed a widespread lymphocytic meningoencephalitis characterised by diffuse CD8+ T-lymphocyte infiltrate predominantly in the white matter but also in the grey matter and meninges (Figure 2). There was no evidence of progressive multifocal leukoencephalopathy (PML), demyelinating disorder, vasculitis or granulomatous inflammation on histology. Immunohistochemistry for virus (JC, HSV1/2, HIV) and for toxoplasma was negative. No micro-organisms were detected on special stains to suggest any infection. In addition, CSF collected during the biopsy demonstrated 1100 HIV copies/mL. Parenchymal leakage of HIV into CSF cannot be ruled out but was felt unlikely in the absence of detectable virus within the brain.

Her cART regimen was modified to include raltegravir to achieve better CNS penetration and dexamethasone was increased to 8mg TDS. However, she remained comatose, with no evidence of improvement four weeks after admission; at this point a poor prognosis was anticipated, thus following family discussions a decision was made to withdraw treatment. However, she failed to tolerate extubation and then showed evidence of neurological improvement, with spontaneous eye opening and tracking; treatment with antiretrovirals and steroids was reinstated.

She continued to improve and 6 weeks after her admission she was successfully extubated. One week later she was discharged from ITU to a neurological ward where she continued to improve in alertness and cognition. Lumbar puncture was considered safe at this point, and CSF contained 5 lymphocytes /mm^3, protein 0.44 g/L, glucose 5.1 mmol/L (serum 6.5), while HIV RNA was undetectable. Oligoclonal bands were present in both CSF and serum, a non-specific finding consistent with HIV positive status[1]. A repeat MRI showed improvement of the diffuse widespread signal abnormality involving the cerebral subcortical and deep white matter, with almost complete

resolution of the diffusion restriction and no evidence of cerebral oedema. At 8 weeks from her initial presentation, she was orientated in time and place and responding to questions appropriately. Asymmetrical limb weakness and hyporeflexia was noted at this point, and neurophysiology was suggestive of a critical illness neuromyopathy (low amplitude CMAPs with prolonged duration, myopathic EMG changes). A CD8-related vasculitis was considered unlikely as a cause for the neuropathy, as it was symmetrical, length-dependent and painless: since this was clinically self-limiting a nerve biopsy was not undertaken. She was transferred to our Neurorehabilitation Unit and continued to improve functionally with multidisciplinary rehabilitation: at 18 weeks she was able to transfer unaided and walk with 2 sticks. Cognition also improved, with an increase in her Montreal Cognitive Assessment score from 16/30 (corrected for time in education) to 25/30 over the course of her admission. She was discharged to her own home, and when reviewed 4 months later, her motor system was intact, she was entirely independent and considering a return to work.

Discussion

Differential diagnosis

Our patient had a diagnosis of CD8+ encephalitis, a severe but treatable form of HIV-related acute encephalopathy. On initial presentation the history of subacute confusion in the context of known HIV infection raised a number of potential differential diagnoses, mainly opportunistic infections and neoplasms secondary to immunodeficiency. However our patient's CD4 count in combination with the MRI appearances effectively discounted many of the 'usual suspects', including lymphoma, cryptococcosis, toxoploasmosis, tuberculosis, cytomegalovirus encephalitis and progressive multifocal leukoencephalopathy (PML). Primary CNS vasculitis[2] can be associated with HIV, sometimes in the context of opportunistic infection and can present with encephalopathy, but neuroimaging and histopathology were not in keeping with this in our patient with no evidence of vessel narrowing or irregularity. Likewise an immune reconstitution inflammatory syndrome (IRIS) was considered but was felt to be unlikely in the absence of contrast enhancement[3]. HIV can itself present with an encephalitis, usually acutely in patients with poorly controlled infection and a high peripheral viral load; our patient's infection was well controlled, and the presence of a detectable HIV viral load in the CSF but not in plasma or brain parenchyma would also be more consistent with CD8+ encephalitis than with primary HIV encephalitis. An encephalitis may be seen in the context of HIV compartmentalisation, whereby cell type-specific differences in viral replication and variations in anti-retroviral drug concentrations lead to differential selection pressures and the evolution of a distinct HIV sub-population within the CNS[4] This is usually associated with significantly higher CSF viral loads and a cellular CSF however and was not felt to be likely in this case.

We also considered causes of encephalopathy unrelated to HIV; the peripheral restriction of diffusion on MRI was potentially suggestive of toxic demyelination[5,6]. However, there was no history of recreational drug abuse, exposure to toxins, radiotherapy, or immunosuppressant medication that can cause this picture[5,6]. Common metabolic causes of acute confusion including systemic infections were quickly excluded. Common CNS infections seen outside the context of HIV were also considered and the patient was treated empirically for HSV encephalitis and bacterial meningitis. The recent travel history raised the possibility of malaria or viral haemorrhagic fevers, and these were tested for and excluded.

CD8 encephalitis

The typical clinical presentation of CD8+ encephalitis is that of progressive cognitive impairment, headache and seizures[7]. CSF typically reveals CD8 lymphocytosis and high HIV viral load[7]. MRI shows characteristic changes: diffuse T2 hyperintensities predominantly in the white, but also in the gray matter, and multiple gadolinium-enhancing perivascular lesions which show restriction on

diffusion-weighted imaging[7]. The histopathological hallmark is diffuse perivascular and intraparenchymal CD8+ lymphocytic infiltration and reactive astrocytosis, with inconsistent and weak expression of HIV protein p24 and absence of multinucleated giant cells and CD4+ cells[7,8]. This perivascular infiltration may be detected on post-contrast T1 spin echo MRI imaging, and it is important that this sequence is included in HIV-positive patients with encephalopathy. While in a minority of cases CD8+ encephalitis may develop soon after first initiation of cART, with histological features of an Immune Reconstitution Inflammatory Syndrome (IRIS), CD8+ encephalitis is mostly seen as an unexpected occurrence in patients who are stable on treatment. In these cases there is usually a history of brief treatment interruption or minor intercurrent infection. The common feature between causal groups may be the novel introduction of the HIV virus into the CNS, and one might suggest that intercurrent infection in a stable patient may provide the immune 'distraction' that allows such viral escape to occur. Our patient had a normal CD4 count with fully suppressed HIV two months prior to presentation, and it seems likely that the episode of cellulitis during her trip to Africa may have been important. Why transient CNS viral escape should provoke such a severe inflammatory response in some patients and not others is an interesting question, and is likely to be explained at least in part by genetic factors. HIV compartmentalisation may itself be considered a chronic form of viral escape, usually responsive to changing anti-retroviral drug to achieve greater CNS penetrance, but would not be associated with a prominent CD8+ infiltrate. Brain biopsy in IRIS typically also shows CD68+ macrophage and CD8+ T-cell infiltrates as well as necrotic changes[9], a similar picture to that of CD8+ encephalitis, and there is clinical and histopathological overlap between the two entities.

In a case series by Lescure et al, 14 patients with CD8+ encephalitis received treatment with high-dose corticosteroids, yet outcome was variable: 5 made a complete recovery, 4 survived with significant residual cognitive impairment, and 5 died[7]. Of the 5 patients within that series who required ITU care during their illness, 3 died and 2 had residual cognitive impairment. Our patient is remarkable in that despite diffuse marked cerebral oedema, profound coma and what was felt to be a poor prognosis, she went on to make an almost full recovery following a period of neurorehabilitation.

The differential diagnosis of acute encephalopathy in the HIV-positive patient is wide and can be challenging. CD8+ encephalitis is a treatable CNS complication of HIV: if this is suspected then with early diagnosis (by brain biopsy if necessary) and steroid treatment its prognosis can be favourable even in the face of severe and apparently persistent encephalopathy, as in our patient.

Key Points

- CD8+ encephalitis should be considered in the differential diagnosis of acute confusion in the HIV-positive patient, particularly if CD4 count is normal
- Consider early biopsy in HIV-positive patients with encephalopathy of uncertain cause
- MRI may show diffuse T2 hyperintensities and multiple gadolinium-enhancing perivascular lesions with restriction on diffusion-weighted imaging Including a post-contrast T1 spin echo sequence in MRI scanning may aid diagnosis
- Early treatment with high-dose steroids when this diagnosis is suspected is essential for a favourable outcome
- Prognosis is variable but can be favourable even following severe encephalopathy

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Figure 1.

(A) MRI (axial T2 weighted images) demonstrating confluent white matter hyperintensity with extension into the thalami and basal ganglia.
(B) MRI (diffusion weighted imaging)
B1000 images and ADC maps demonstrating restricted diffusion (corresponding dark ADC signal) peripherally with free diffusion (increased ADC signal) towards the centre of the confluent T2 hyperintense areas

Figure 2.

CD8+ lymphocytic meningoencephalitis. Brain biopsy of the non-dominant frontal lobe revealed (A) Perivascular cuff of lymphocytes with diffusely scattered single lymphocytes in the parenchyma (with high power view in the inset), (B) The lymphocytes were predominantly CD4+ T-lymphocytes among which the vast majority of them expressed CD8 (with high power view in the inset). There was associated macrophage infiltrate (C) and reactive gliosis (D) as seen on CD68 and GFAP respectively. There was no demyelination, infection, granulomatous inflammation or vasculitis. The features supported CD8 encephalitis in view of the clinical history.