

Central nervous system immune reconstitution disease presenting with vasculitis-like lesions

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ABSTRACT

The immune reconstitution inflammatory syndrome (IRIS) identifies a spectrum of clinico-pathological entities resulting from either paradoxical worsening or unmasking of previously quiescent disorders following the initiation of combination antiretroviral therapy (cART). The central nervous system (CNS) is a major target tissue for IRIS, and inflammatory forms of cryptococcosis and progressive multifocal leukoencephalopathy (PML) are well known manifestations of CNS-IRIS. We here describe the case of a patient who developed focal neurological disease two months after initiation of cART and one month after successfully treated herpes zoster. Magnetic resonance imaging (MRI) showed vasculitis-like lesions but cerebrospinal fluid analysis failed to reveal the presence of varicella-zoster virus or other opportunistic pathogens. The clinical and radiological picture improved dramatically following treatment with intravenous high dose corticosteroids and remained stable during the subsequent follow-up. CNS-IRIS may present in the form of vasculitis-like inflammatory CNS lesions that respond to anti-inflammatory treatment.

Migrants and Poverty (NIHMP) is the leader of the "Internal Evaluation Package". As a result more than 2,000 young migrants are expected to be reached by HIV/AIDS prevention campaigns planned in order to meet specific needs of different groups of migrants in each one of the seven participating Countries.

Introduction

Central nervous system (CNS) complications are a major threat of advanced HIV-infection. Their incidence and prevalence, however, has significantly decreased following the introduction of combination antiretroviral therapy (cART) [1]. Furthermore, their long-term prognosis has improved, resulting in increased survival times [2]. During the last decade, however, an increasing number of cases have emerged of HIV-induced CNS complications likely associated with cART-induced immune reconstitution.

The immune reconstitution inflammatory syndrome (IRIS) or immune restoration diseases (IRD) comprises a wide spectrum of clinico-pathological entities defined by the presence of HIV infection, ongoing cART, decreased HIV-1 RNA level from BL, symptoms or signs of inflammation, and clinical course not consistent with the expected course of previously diagnosed opportunistic infections (OI), the expected course of newly diagnosed OI or drug toxicity [3,4]. The disease manifestations of IRIS are more frequent in patients with low CD4+ cell counts at the start of cART, and

are attributed to either paradoxical worsening or unmasking of previously quiescent disorders following therapy-induced immune reconstitution. These have been linked to a wide variety of pathogens, the most common being *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, *Cryptococcus neoformans*, *Pneumocystis carinii*, cytomegalovirus (CMV) and varicella-zoster virus (VZV). Clinical manifestations may vary and involve virtually all tissues [3,4].

IRIS manifestations involving the CNS are particularly severe and life-threatening [5,6]. These mostly include new onset or paradoxical worsening of CNS infections, such as progressive multifocal leukoencephalopathy (PML)[7], cryptococcosis [8,9] or HIV encephalitis [10,11], which are characterized by atypical, inflammatory features. There are cases of CNS-IRIS, however, where inflammatory lesions are not obviously accompanied by the presence of specific pathogens [11,12].

We here describe the case of a patient who developed neurological disease associated with vasculitis-like CNS lesions a few weeks after initiating cART.

Case Report

In September 2001, a 39 year-old homosexual man, known to be HIV-1 seropositive since 1984, came to our attention. His CD4+ cell count was 6/ μ l and plasma HIV-1 RNA (VL) 95.000 copies/ml.

The patient had had esophageal candidiasis in 1984, syphilis in 1999 and herpes zoster in 2000. He had taken various combinations of antiretroviral drugs from 1987 to 1999. He also reported a history of seizures since 1994, described as generalized, accompanied by loss of consciousness and preceded by aura. No abnormalities were ever disclosed by several computed tomography scan or magnetic resonance imaging (MRI) brain examinations. At the time of our first observation, the patient was taking diphenylhydantoin, phenobarbital and carbamazepine.

He was given zidovudine (switched to stavudine after a few weeks because of myelotoxicity), lamivudine and lopinavir/r. In October 2008, he had thoracic herpes zoster that was successfully treated with valaciclovir (1 gram three times a day for 10 days). The CD4+ cell count was 15/ μ l and VL 1200 copies/ml. In November 2001 patient presented with hypoesthesia and difficulty coordinating the movements of his left hand. Brain MRI showed a

“vasculitis-like” lesion of the right ascending frontal gyrus, with linear enhancement after gadolinium administration (Figure 1a,b). Electroencephalogram (EEG) and carotid artery ultrasonography were unremarkable. Standard cerebrospinal fluid (CSF) examination showed normal values; no viral genomes, including DNA of herpes simplex viruses type 1 and 2, VZV, CMV, Epstein-Barr virus, human herpesvirus-6, JC virus, and HIV-1 RNA were detected by polymerase chain reaction. CD4+ cell count was 70/ μ l and VL undetectable.

Symptoms worsened progressively during the following weeks with onset of frank paresis of the left arm and dysarthria. In January 2002, brain MRI showed an increased size of the right frontal lesion, which was still enhancing and a new enhancing lesion of the left anterior frontal region (Figure 1c,d). CD4+ cell count was 67/ μ l and VL undetectable (stavudine was self-suspended by the patient and then changed to didanosine). Because of the persistence of neurological symptoms and progression of MRI lesions, the patient was treated with high doses intravenous methylprednisolone, 1 gram a day for five days, which was followed by immediate clinical improvement and reduction of the enhancement of the MRI lesions (Figure 1e,f). Steroid treatment was tapered with oral prednisone, 50 mg for two weeks, then slowly reduced over a

FIGURE 1. Sequential MRI findings at FLuid-Attenuated Inversion Recovery (Flair) axial sequences (a,c,e,g,i) and T1 axial sequences following Gadolinium administration (b,d,f,h,j).

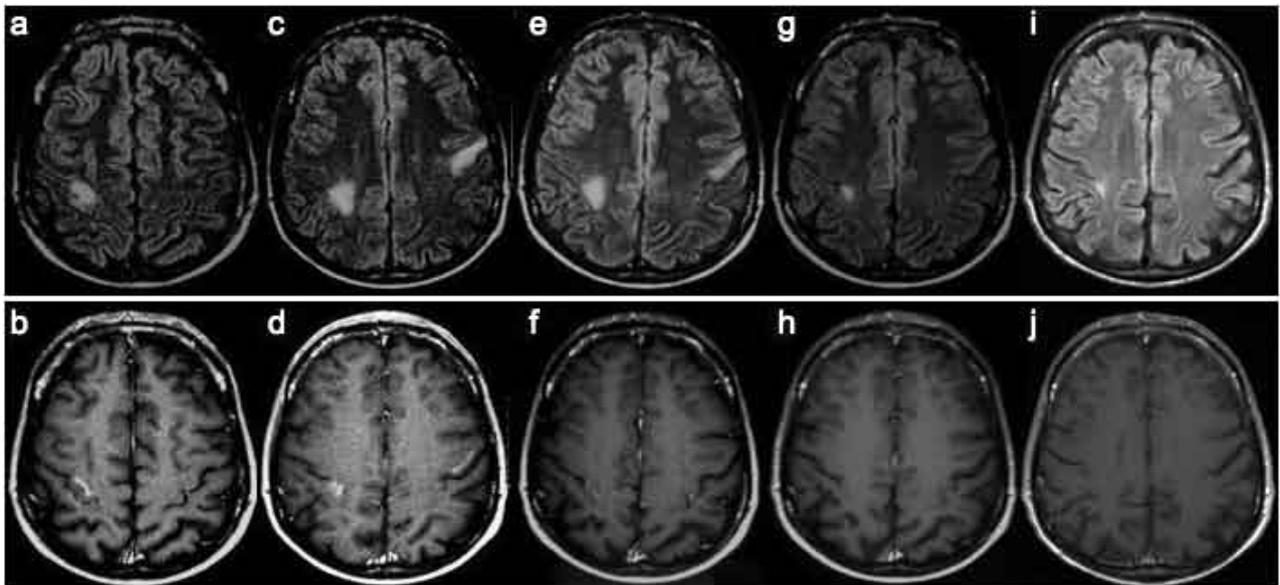
a,b. At onset of symptoms of CNS-IRIS (November 2001). Hyperintense lesion in the subcortical right frontal region (a), which shows linear enhancement after Gd administration (b).

c,d. Two months after onset (January 2002). Further extension of size and signal intensity of the right lesion and new onset of a second small hyperintense lesion in the cortico-subcortical left frontal white matter (c). The right lesion shows a patchy contrast enhancement whereas enhancement appears linear in the left lesion (d).

e,f. Following IV high dose corticosteroids (February 2002). Reduction of both size and signal intensity of both lesions (d) and markedly reduced contrast enhancement, with only mild residual enhancement of the right frontal lesion (j).

g,h. Twenty-two months after onset (July 2003). Further reduction of signal alteration (g) and no longer evidence of contrast enhancement in both lesions (h). There is evidence of focal cortical atrophy in the lesions.

i,j. Eight years after CNS-IRIS (December 2008). Residual small FLAIR hyperintensity corresponding to the right frontal lesion (i), with no contrast enhancement (j). Cortical atrophy is increased.



total of five weeks. The patients neurological conditions remained stable in the subsequent months, with resolution of the dysarthria and persistence of only mild left hand hypostenia. An MRI performed in July 2002 showed a reduced size of both lesions, which were no longer enhancing after gadolinium (Figure 1g,h). At this time CD4+ cell count was 135/ μ l and VL undetectable.

During the subsequent follow-up the patient continued cART with didanosine, lamivudine (later switched to tenofovir and emtricitabine) and lopinavir/r, followed by a continued increase in CD4+ cell counts and persistently undetectable VL. The hand hypostenia remained unchanged and no modifications were shown by brain MRI performed once yearly. However, seizures became more frequent with onset of both generalized and partial episodes. EEG showed a gradual appearance of diffuse slow paroxysmal abnormalities, more evident in the left temporal regions and associated with a mild decrease of the general activity. Antiepileptic therapy was changed several times because of intolerance or inefficacy.

At the last follow-up in December 2008, the patient was still on cART and anti-epileptic therapy. CD4 cell count was 494, and VL undetectable. His neurological conditions are stable with residual motor impairment of the left hand and inactive lesions at MRI (Figure 1i,j).

Discussion

This report describes a patient with vasculitis-like brain lesions occurring in the setting of cART-associated immune reconstitution and fulfilling the criteria for IRIS. Both neurological picture and MRI lesions worsened progressively during the first weeks of cART and disease remission was achieved by administration of high dose intravenous corticosteroids. Consistent with IRIS definition, the clinical picture appeared to be sustained by inflammation: MRI lesions enhanced after gadolinium administration at presentation and during clinical progression, and both clinical and MRI picture improved markedly following anti-inflammatory therapy.

MRI lesions resembled those observed in CNS vasculitis outside the context of HIV infection. Pathologically, CNS vasculitis is defined by the presence of inflammation of blood vessels, including arteries and veins of any caliber [13]. In our patient, the MRI picture of multiple, bilateral FLAIR hyperintense signal alterations involving the deep white matter at the cortical-subcortical junction, and showing a linear enhancement, was consistent with the involvement of small vessels. Small vessel vasculitis is most frequently observed in association with autoimmune connective tissue disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis, Behcet disease) or infections [13]. Infectious causes include VZV infection [14], neurosyphilis and neuroborreliosis, but also less frequent diseases, such as rickettsiosis and fungal infections [13]. Of note, VZV infection is a relatively frequent IRIS-related pathogen. Herpes zoster is

observed at higher than expected frequency after the initiation of cART [15] and VZV encephalitis or myelitis have been reported in the context of cART-related immune reconstitution [16,17].

Our patient had herpes zoster three weeks before onset of neurological symptoms, strongly suggesting that VZV could also be implicated in the CNS-IRIS episode through reactivation and centripetal spread to the CNS. Because of the time elapsing between the successfully treated herpes zoster and the CNS episodes, the absence of active VZV replication in CNS at the time of CNS-IRIS and the response to corticosteroids only, without antiviral therapy, we hypothesize that VZV played a role in this episode of CNS-IRIS through "post-infectious" mechanisms. Such mechanisms would involve inflammation directed against residual virus, or viral antigens or even self-antigens, the latter being disclosed by the infection and the consequent tissue damage, and are indeed suggested for several immunopathological CNS diseases, such as the acute demyelinating encephalomyelitis (ADEM) and multiple sclerosis (MS)[18].

On the other hand, brain biopsy was not performed and thus the possibility that VZV or another microbial agent could have had a more active role in our case cannot be ruled out. Alternatively, it is also possible that, in the first weeks of cART, an initially but abnormally reconstituted immune system paradoxically attacked normal self-antigens, in the absence of any infectious cause. Of note, the history of seizures in our patient suggests pre-existing tissue damage, which might have also concurred to the CNS-IRIS episode.

A number of cases of CNS-IRIS have been reported in the literature, more frequently associated with PML, cryptococcosis, HIV encephalitis, and also VZV infection, and either presenting a few weeks-months after starting cART or showing paradoxical worsening during treatment [7-11, 16, 17]. A case similar to that here described was reported by van der Ven et al. [12], in which brain biopsy showed the presence of vasculitis mainly affecting small vessels. No pathogen DNA or antigen was found after extensive search, except for *Mycobacterium chelonae* DNA, identified by PCR, but the significance of this finding is unclear. The disease remitted with cART interruption, but worsened again when treatment was resumed. As in our case, clinical symptoms responded to high dose intravenous corticosteroids, although recurrence of symptoms was observed at low oral doses.

In general, management of IRIS includes treatment of both the underlying infection, if any, and anti-inflammatory treatment, based on the principle that inflammation is key component of the picture. Indeed, a common pathological feature of CNS-IRIS is the presence of inflammatory tissue infiltrates. In cases associated with viral infections, but also in cases where no infectious is identified, the histopathological examination consistently shows the presence of parenchymal and perivascular lymphocytes, predominantly composed of CD8+

cells, with occasional CD3+ and CD4+ cells and macrophages [10-12].

Although corticosteroids are the mainstay of treatment of CNS-IRIS, experience remains anecdotal, and optimal dosage and duration of administration are not established. Our patient was not given antimicrobial or antiviral treatment at the time of neurological disease, but responded dramatically to high dose intravenous corticosteroids. This approach is frequently used in neurology for the treatment of several conditions, including acute MS attacks and autoimmune vasculitis and is usually associated with brisk improvement of the clinical picture and MRI lesions. Alternative regimens, used in IRIS-PML, have included courses of oral prednisone (1-2 mg/Kg per day) or equivalent doses of oral or intravenous dexamethasone, with

variable success [7]. Corticosteroids are given cautiously in patients with HIV infection, because of potential deleterious effects on the immune system and potential reactivation of infections. In our case, we observed no obvious short or long-term damage that could be associated with the use of steroids.

In conclusion, CNS-IRIS may present with vasculitis-like lesions. "Post-infectious" mechanisms may be implicated in the pathogenesis and there are clues from the literature and from this report that VZV is a major candidate trigger agent. Because inflammation is a key component of the disease, these forms benefit from the use of corticosteroids. However, schedules for administration, effects on immune cell counts and function and side effects, especially in HIV-infected patients with low CD4 cell counts remain to be established.

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