

# Immune reconstitution inflammatory syndrome involving the central nervous system in a patient with HIV infection: a case report and review of literature

Lorenzo Zaffiri, Rajanshu Verma, Kevin Struzzieri, Joanne Monterroso,  
Donald H. Batts, Mark E. Loehrke

Department of Internal Medicine, Western Michigan University School of Medicine,  
1000 Oakland Drive, Kalamazoo, Michigan 49008

## SUMMARY

IRIS is described as a paradoxical deterioration of clinical status upon initiation of combined anti-retroviral therapy (cART) in patients with HIV infection. Immune reconstitution inflammatory syndrome (CNS-IRIS) involving the central nervous system is rarely reported. We describe the case of 57-year-old man who developed a fatal case of CNS-IRIS. A rapid deterioration of neurological status was associated with progression of patchy T2-weighted hyperintensities involving different vascular territories on brain MRI.

Diagnosis of CNS-IRIS is based of laboratory and radiologic findings, however brain biopsy is supportive. Despite immune restoration being involved in clinical deterioration, discontinuation of cART is not recommended. The use of corticosteroids is highly controversial. Prompt recognition of CNS-IRIS is crucial for preventing neurological complications and ensuing sequelae.

**KEY WORDS:** CNS-IRIS, HIV, cART.

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## INTRODUCTION

Combined active antiretroviral therapy (cART) remains the cornerstone of treatment of HIV infection. However, it has introduced a new spectrum of complications, which may affect the outcomes (Shelburne *et al.*, 2002; Mocroft *et al.*, 2003). Immune reconstitution inflammatory syndrome (IRIS) is a potentially life-threatening condition that occurs in a subset of HIV+ patients following initiation of cART. It is characterized by paradoxical worsening of patient's clinical condition attributable to recovery of the immune system following introduction of cART (Shelburne *et*

*al.*, 2003). Rarely IRIS may affect the central nervous system (CNS), especially in the setting of AIDS-related opportunistic infections like tuberculosis, cryptococcal disease, cytomegalovirus (CMV) retinitis, and progressive multifocal leukoencephalopathy (PML) (Shelburne *et al.*, 2004).

We describe an interesting case of CNS-IRIS in HIV+ patient, who developed rapid decline of mental status following initiation of cART. This case demonstrates the dilemma in establishing a diagnosis and the lack of guidelines for prevention and treatment of CNS-IRIS.

## CASE REPORT

A 57-year-old Caucasian man diagnosed with HIV-1 infection in 2003 presented with a 3-week history of dyspnea, weight loss, right-sided weakness and slurred speech. The patient admitted to

### Corresponding author

Lorenzo Zaffiri M.D., PhD.  
Department of Internal Medicine  
WMU School of Medicine  
1000 Oakland Drive, Kalamazoo, Michigan 49008  
E-mail: lorenzozaffiri@gmail.com

having stopped antiretroviral therapy 3 years ago due to non-compliance. On admission his HIV-RNA viral load (VL) was 270,000 copies/ml and CD4+ T-cells count of 24 cells/mm<sup>3</sup>. Broncho-alveolar lavage grew *Pneumocystis jiroveci*. Brain MRI showed a small acute infarct in the left precentral gyrus (Figure 1a-b). The patient was discharged after a week on darunavir boosted with ritonavir, emtricitabine and tenofovir, trimethoprim-sulfamethoxazole and aspirin as treatment for HIV infection, PJP and stroke.

The patient presented at follow-up visit 3 weeks after initiation of cART in altered mental status and admitted to the hospital. Cerebrospinal fluid (CSF) studies were consistent with a picture of aseptic meningitis: WBC 56 cells/ml (neutrophils 76%, monocytes 28%) glucose 43 mg/dl and protein 64 mg/dl. CSF stain and cultures for mycobacterial, bacterial, and fungal pathogens were negative as well as Lyme, VDRL and cryp-

tococcal antigen detection. An extensive viral panel via polymerase chain reaction including herpes-simplex virus-1 and 2, varicella-zoster virus, JC virus, cytomegalovirus and Epstein-Barr virus was negative.

His CD4+ T cells count had increased to 99 cells/mm<sup>3</sup> and VL decreased to 1300 copies/mL. The patient's clinical condition continued to deteriorate. He developed status epilepticus, requiring treatment with levetiracetam and mechanical ventilation. His cART regimen was continued, assuming a beneficial effect of the selected regimen through CNS penetration. The patient demonstrated a partial improvement of his mental status following initiation of intravenous methylprednisolone to control systemic inflammation. He became alert but remained severely aphasic and with right-sided monoparesis. However, his clinical status deteriorated again when corticosteroids were slowly tapered down.

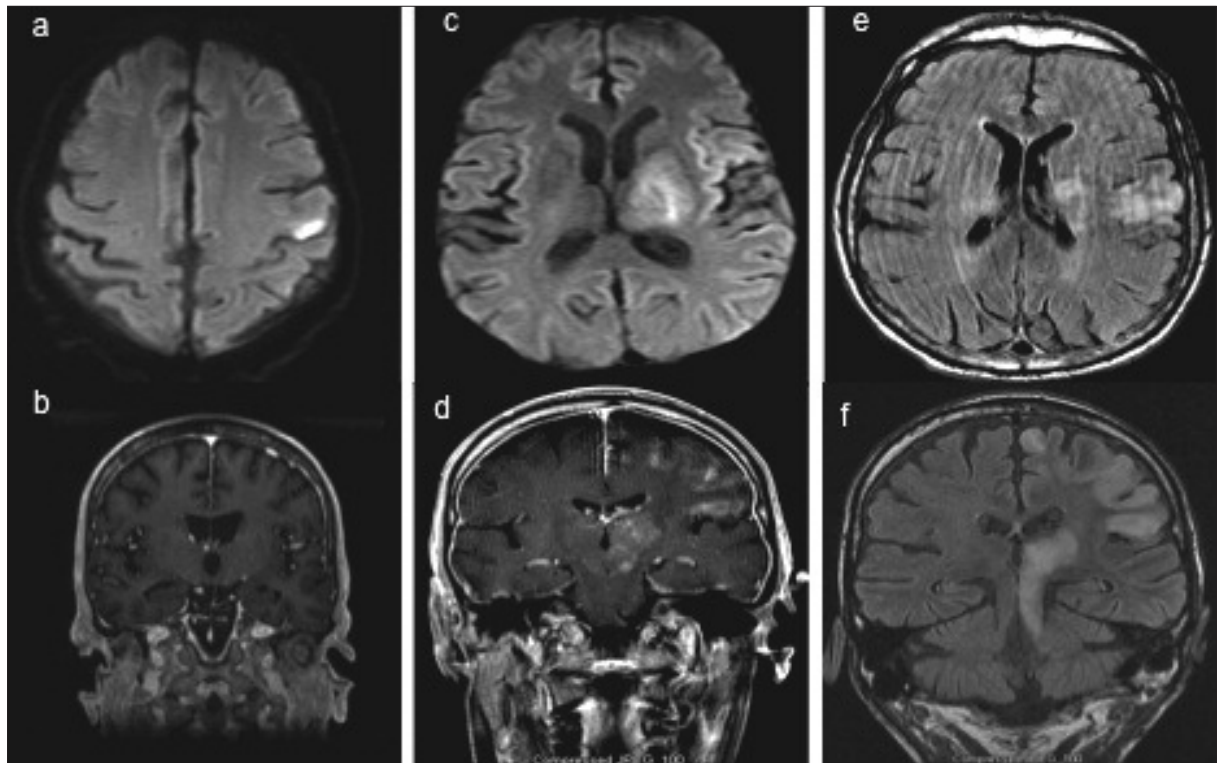


FIGURE 1A-E - Brain MRI images were taken during admission (a-b), 24 days (c-d) and 31 days (e-f) after the initiation of cART. Upper row axial diffusion sequences; lower row FLAIR and T1-weighted brain MRI images with gadolinium. On admission, diffusion images showed a small area of acute infarction involving the left precentral gyrus (a-b). T1-weighted and FLAIR images 24 days (c-d) and 31 days (e-f) following the initiation of cART demonstrated extension of hyperintensity signals involving the left frontal, left corona radiata, thalamus and hypothalamus bilaterally.

He eventually expired following 40 days of hospitalization.

The rapid neurologic decline was associated with a progression of patchy T2-weighted hyperintensities involving different vascular territories such as left frontal parenchyma, left corona radiata, internal capsule, left thalamus, pons, midbrain and cerebellum as shown in a series of brain MRIs (Figure 1 c-f).

## DISCUSSION

Our patient developed a rapid clinical decline associated with a marked and diffuse deterioration of neurological imaging suggestive of CNS-IRIS following initiation of cART. The history and clinical presentation involved a broad differential diagnoses including CNS opportunistic infections, cerebrovascular accident, CNS primary malignancies, autoimmune diseases, as well as drug toxicities. Although a definitive histopathological diagnosis could not be made, our patient met the proposed clinical and radiological criteria used in defining the diagnosis of CNS-IRIS. Moreover, the presence of increased WBC in CSF as well as an extensive negative microbiological work-up supported this diagnosis.

Up to 35% of patients receiving cART will develop IRIS (French, 2007). In a cohort of 461 patients CNS-IRIS occurred in 0.9% of adults after introduction of HAART (Johnson *et al.*, 2010). The majority of cases occur within the first 60 days of initiating cART and the risk of developing IRIS is increased when cART is started in proximity to the diagnosis of opportunistic infections (McCombe *et al.*, 2009). On the basis of immune response towards opportunistic pathogens, it is possible to describe two forms of IRIS. Unmasking-variant IRIS is considered when cART and the consequent immune reconstitution reveals previously subclinical opportunistic infections, while paradoxical-variant IRIS is defined when deterioration of a successfully treated opportunistic infections is observed following introduction of cART (Muller *et al.*, 2010).

The pathophysiology of IRIS remains unclear. However, its occurrence is strongly correlated to the time of initiation of cART and the presence of opportunistic infections. Following introduction of cART, there is a rapid recovery of memory T

cells. These lymphocytes are able to penetrate peripheral non-lymphoid sites, recognize previously encountered antigens and rapidly mount an inflammatory response. Most paradoxical inflammatory responses observed during IRIS are directed against opportunistic pathogens, which are already present at the beginning of cART (Shelburne *et al.*, 2005; Martin-Blondel *et al.*, 2011).

Diagnostic criteria and standard treatment have not yet been defined. CNS-IRIS should be suspected when patient presents with:

- a rapid deterioration of clinical and neurological status following initiation of cART;
- decrease of HIV-RNA VL greater than 1 log;
- clinical, laboratory and radiological signs and symptoms consistent with inflammation;
- lack of correlation between symptoms and a newly acquired infection, a previously present opportunistic infection or drug toxicity (Johnson *et al.*, 2010).

Although cART and the immune reconstitution are considered causes of IRIS, stopping cART is not recommended. The resumption of HIV viral replication will cause disease progression. More debatable is the use of systemic corticosteroids due to lack of clinical trials to establish the risks and benefits of initiating an immune-suppressive therapy in immune-deficient patients. It has been suggested to tailor the dose and duration of systemic corticosteroids accordingly to the clinical presentation (Johnson *et al.*, 2011).

In conclusion, CNS-IRIS is an uncommon and life-threatening disorder induced by initiation of cART and reconstitution of immune functions. It is characterized by a paradoxical deterioration of the clinical and neurological status. Knowledge and prompt recognition of the clinical signs and symptoms is fundamental in the management of this HIV-associated CNS disorder.

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