

# Cryptococcal meningitis in an HIV-1-infected person: relapses or IRIS? Case report and review of the literature

G. NUNNARI, M. GUSSIO, M.R. PINZONE, F. MARTELLOTTA<sup>1</sup>,  
S. COSENTINO, B. CACOPARDO, B.M. CELESIA

Department of Clinical and Molecular Biomedicine, Division of Infectious Diseases, University of Catania, Garibaldi Nesima Hospital, Catania, Italy

<sup>1</sup>Department of Medical Oncology, National Cancer Institute-IRCCS, Aviano (PN), Italy

**Abstract.** – After starting highly active antiretroviral therapy (HAART), HIV-infected patients may experience what is termed immune reconstitution inflammatory syndrome (IRIS). IRIS is characterized by a paradoxical inflammatory response to either previously or recently treated infections or unmasked subclinical infections, when the patient regains the ability to mount a suitable immune response against specific antigens or pathogens. Cryptococcal IRIS (C-IRIS) is thought to be mediated by recovery of *Cryptococcus*-specific immune responses, resulting in exaggerated host inflammatory responses. In HIV-positive subjects, two distinct modes of presentation of C-IRIS are recognized, “paradoxical” and “unmasking” C-IRIS. “Paradoxical” C-IRIS presents as worsening or recurrence of treated cryptococcal disease following HAART initiation, despite microbiological treatment success. In the “unmasking” form, patients with no prior diagnosis may develop acute symptoms of cryptococcosis, such as meningitis or necrotizing lymphadenopathy, after starting HAART.

Here, we present the case of an HIV-positive man, who developed cryptococcal meningitis two months after having started HAART and experienced several meningeal relapses and a “paradoxical” C-IRIS during the following year.

**Key Words:**

Antiretroviral therapy, Cryptococcal meningitis, HIV.

## Introduction

Since its introduction, highly active antiretroviral therapy (HAART) has led to reduced mortality and morbidity and immunological reconstitution, with a significant decrease in the appearance of AIDS-related opportunistic illnesses (OIs) and the emergence of non-AIDS related events and malignancies, such as pancreatic, lung, colon and liver cancer<sup>1-14</sup>. Nonetheless, viral persistence in viral reservoirs and residual viremia still represent major obstacles to HIV eradication<sup>15-24</sup>.

HAART-induced immunological recovery may be associated with the reactivation of latent infections, such as those due to *Mycobacterium tuberculosis*, *Mycobacterium avium*, *Cytomegalovirus*, *Pneumocystis jiroveci* and *Cryptococcus neoformans*<sup>23</sup>. Immune reconstitution inflammatory syndrome (IRIS) is characterized by a paradoxical inflammatory response to either previously or recently treated infections or unmasked subclinical infections, when the patient regains the ability to mount a suitable immune response against specific antigens or pathogens<sup>25</sup>. IRIS has been reported to have an overall prevalence at least as high as 10-25%<sup>24</sup>. This syndrome often occurs during the first two weeks of antiretroviral treatment among patients beginning HAART early after an OI, with low baseline CD4 T-cell count (< 100/μl) and an excellent virological response to therapy<sup>27-30</sup>.

Cryptococcal IRIS (C-IRIS) is thought to be mediated by recovery of *Cryptococcus*-specific immune responses, resulting in exaggerated host inflammatory responses. In HIV infection, this reversal is driven by HAART, but C-IRIS has also been described as occurring after solid organ transplantation or during pregnancy<sup>31-33</sup>. In HIV-positive subjects, two distinct modes of presentation of C-IRIS are recognized, “paradoxical” and “unmasking” C-IRIS<sup>34</sup>. “Paradoxical” C-IRIS presents as worsening or recurrence of treated cryptococcal disease following HAART initiation, despite microbiological treatment success. In the “unmasking” form, patients with no prior diagnosis may develop acute symptoms of cryptococcosis, such as meningitis or necrotizing lymphadenopathy, after starting HAART.

Here, we present the case of an HIV-positive man, who developed cryptococcal meningitis two months after having started HAART and ex-

perienced several meningeal relapses and a “paradoxical” C-IRIS during the following year.

### Case Report

In May 2007, M. M., a 42-year-old man having sex with men, was admitted to our Department, due to sharp headache, with neither fever nor neurological signs.

Since January 2007, he had mucocutaneous lesions highly suggestive for Kaposi’s sarcoma in his penis, arms and legs; in March 2007 he was diagnosed with HIV infection in another Outpatient Unit, his CD4 T-cell count was 56 cells/ $\mu$ l and HIV RNA viral load was 52,298 copies/mL. HAART was started with Emtricitabine-Tenofovir-Lopinavir/r (FTC-TDF-LPV/r).

On admission, his CD4 T-cell count was 76 cells/ $\mu$ l and HIV RNA viral load was 650 copies/mL. Cerebral computerized tomography (CT) did not show any pathological alteration. A lumbar puncture (LP) was performed and cerebrospinal fluid (CSF) culture was positive for *C. neoformans*. On the basis of these findings, a 18-day course of intravenous Amphotericin B (AmpB) was started (total dose 900 mg), followed by maintenance therapy with Fluconazole (Flu) (400 mg orally every day), while on HAART.

Although maintenance therapy with Flu was never interrupted, during the following 10 months the patient had some meningeal relapses (Table I). A LP was performed in 4 of these episodes (1, 8, 9 and 10 months after the first one) and each time CSF had the same characteristics: it was clear, with low glucose and high protein levels; cultures always tested positive for *C. neoformans* and negative for common bacteria and *M. tuberculosis*. During each relapse, the patient was treated with AmpB (50 mg/die), followed by maintenance therapy with Flu (400 mg/die). During the last episode, antibiogram showed sensitivity to all the most common antifungal drugs; a cerebral CT scan described the presence of “hypoxia of the right subcortical precentral rostral paramedian parenchyma”, while encephalic magnetic resonance imaging (MRI) showed “areas of aberrant signal in the right caudate nucleus, with strong enhancement after gadolinium infusion, highly suggestive for cryptococcal relapse”.

In July 2008, while still receiving prophylaxis with Flu 400 mg/die, the patient was admitted again to our Department, due to severe headache and vomiting. LP was performed and showed a slightly torbid CSF, with 22 white blood cells/ $\mu$ l,

**Table I.** Viro-immunological, clinical and microbiological aspects of relapsing cryptococcal meningitis, as found in our patient.

Period	May 2007	June 2007	January 2008	February 2008	March 2008	July 2008
CD4 T-cell count (cells/ $\mu$ l)	76	99	211	104	105	362
Viral load (copies/mL)	650	< 50	< 50	< 50	< 50	< 20
HAART	FTV-TDF-LPV/r	FTV-TDF-LPV/r	FTV-TDF-LPV/r	FTV-TDF-LPV/r	FTV-TDF-LPV/r	FTV-TDF-LPV/r
Symptoms	Headache	Headache	Headache	Headache	Headache	Headache
CSF parameters: aspect	Clear	Clear	–	Clear	Clear	Slightly torbid
pH	9	8	–	8	9	8.5
Glucose (mg/dL)	37	39	–	32	30	39
Proteins (mg/dL)	79	61	–	87	80	133
LDH (mg/dL)	44	20	–	24	22	18
Cells/ $\mu$ l	–	4	–	80	1	22
Cultures	Positive for <i>C. neoformans</i>	Positive for <i>C. neoformans</i>	–	Positive for <i>C. neoformans</i>	Positive for <i>C. neoformans</i>	Negative for common bacteria and fungi
Other data	–	–	–	–	–	India Ink stain for Cryptococcus negative; cryptococcal antigen positive (not quantified)

CSF: Cerebrospinal fluid; FTC-TDF-LPV/r: Emtricitabine-Tenofovir-Lopinavir/Ritonavir; HAART: Highly active antiretroviral therapy.

low glucose and high protein levels. India Ink stain was negative, whereas CSF cryptococcal antigen detection was positive. In addition to old lesions, encephalic MRI described new signs of leptomeningeal and cortical inflammation and a right midbrain active inflammatory lesion. While waiting for culture results, empiric antibiotic and antiviral therapy was started with high-dose Cefotaxime sodium and Acyclovir plus Dexamethasone for two weeks, followed by liposomal AmpB 250 mg/die for two weeks and Dexamethasone for a week, without achieving complete clinical resolution. The patient continued to receive HAART, his CD4 T-cell count was 362 cells/ $\mu$ l and HIV RNA was  $< 20$  copies/ml. When finally fungal cultures were reported as negative, symptoms were assumed to be caused by C-IRIS. The patient was treated with Dexamethasone 3 mg/die for 3 months, obtaining a fast and complete resolution of headache. After this period, he began anti-inflammatory therapy with Indomethacin 50 mg/die and then Diclofenac 100 mg/die, for total 6 months.

The patient is currently on HAART and he is in good conditions, just complaining of sporadic episodes of short-term headache.

## Discussion

Even though CNS disease (i.e., meningitis, meningoencephalitis, space occupying brain lesions) represents the most common presentation for C-IRIS, accounting for around 70% of cases, the clinical spectrum of disease also includes necrotic lymphadenopathy, suppurating skin or soft tissue disease and lung disease<sup>34</sup>.

The reported time of onset of paradoxical C-IRIS after the initiation of HAART varied from 1 to 10 months in cohort studies; on the other hand, the median time on HAART was 4 weeks in HAART-associated cryptococcosis<sup>34</sup>. In our case report, the first episode of meningitis occurred two months after starting HAART with FTC-TDF-LPV/r; several relapses occurred during the following 10 months.

Several retrospective studies indicated higher pre-HAART HIV viral load, earlier initiation of antiretroviral therapy and greater CD4 T-cell increase in the first 6 months of HAART as risk factors for paradoxical C-IRIS<sup>29,35,36</sup>. However, in prospective studies HIV viral load, time to start HAART and baseline CD4 T-cell count were not risk factors for C-IRIS<sup>36-38</sup>. Analogously, it is not

clear if markers of fungal burden, i.e. higher serum cryptococcal antigen (CrAg) titer, may predict the risk for C-IRIS<sup>36-38</sup>. In a prospective cohort, the paucity of CSF inflammation (CSF protein  $< 50$  mg/dL and WBC  $< 25$  cells/ $\mu$ l) prior to HAART was associated with a seven-fold increase in IRIS risk<sup>37</sup>. As for HAART-associated cryptococcosis, the incidence may be as high as 33% in individuals with subclinical cryptococcal antigenemia, without fluconazole preemptive therapy<sup>39,40</sup>. Although HAART-associated cryptococcosis has been described even among subjects who were serum CrAg negative before HAART initiation, pre-HAART screening for cryptococcal antigenemia may be a useful strategy for identifying and treating subclinical infection and reducing the incidence of HAART-associated cryptococcosis, especially in high prevalence regions<sup>34</sup>.

Clinical presentation of meningeal C-IRIS is indistinguishable from relapses, so culture results may help discriminating between them<sup>34</sup>. In our case, CSF cultures were always positive for *C. neoformans*, with the exception of the last episode, when only CSF cryptococcal antigen tested positive. Therefore, it may be hypothesized that the last episode was due to C-IRIS, whereas the previous clinical events were due to relapsing cryptococcal meningitis. However, it should be taken into account that a negative cryptococcal culture is not an absolute requirement for the diagnosis of IRIS, given the variable timing of CSF culture sterility in patients treated with AmphB or high-dose fluconazole. In fact, if patients commence HAART shortly after antifungal therapy, they may still have positive CSF culture when they present with paradoxical C-IRIS. Nevertheless, a positive fungal culture after 3 months of antifungal therapy is considered as therapeutic failure, excluding the diagnosis of C-IRIS<sup>32</sup>.

Without secondary prophylaxis or effective immune reconstitution, HIV-positive patients with cryptococcal infection are at high risk for relapses. Until recently, life-long maintenance therapy to prevent disease relapse was recommended for all patients with HIV after successful completion of primary induction therapy for cryptococcal meningoencephalitis. However, on the basis of recent evidences, the Infectious Diseases Society of America (IDSA) guidelines suggest considering discontinuation of suppressive therapy during HAART in patients having received at least 12 months of antifungal therapy, with a CD4 T-cell count  $> 100$  cells/ $\mu$ l and an undetectable or very low HIV RNA level sustained for  $> 3$  months<sup>41</sup>.

## Conclusions

C-IRIS therapeutic management may require the use of anti-inflammatory drugs, in addition to HAART and antifungal therapy<sup>41</sup>. In case of severe CNS complications, i.e. elevated intracranial pressure, oral prednisolone (0.5-1 mg/kg/die) and possibly dexamethasone at higher doses may be used. In our case report, the patient experienced a rapid response to corticosteroids. Time of response to anti-inflammatory therapy is not predictable and a strict follow-up is required. Considering that prolonged steroid therapy is not free of side effects, Nonsteroidal Anti-Inflammatory drugs (NSAIDs) may be effective substitutes. In our case, steroid therapy was discontinued, because of the appearance of peripheral edema, moon facies and exacerbation of Kaposi's skin lesions. Switch to NSAIDs, which were administered for further seven months, was associated with a complete and prolonged remission of symptoms.

## Conflict of Interest

None to declare.

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