Journal of Microbiology, Immunology and Infection (2013) 46, 68–72

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.e-jmii.com

CASE REPORT

Mycobacterium avium complex infection-related immune reconstitution inflammatory syndrome of the central nervous system in an HIV-infected patient: Case report and review

Yi-Chien Lee [a], Ching-Lan Lu [b], Chung-Chih Lai [c], Yu-Tzu Tseng [d], Hsin-Yun Sun [e], Chien-Ching Hung [e,*]

[a] *Department of Internal Medicine, Chia-Yi Christian Hospital, Chia-Yi City, Taiwan*
[b] *Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan*
[c] *Department of Internal Medicine, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung Taiwan*
[d] *Department of Traumatology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*
[e] *Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*

Received 29 July 2011; received in revised form 30 November 2011; accepted 12 December 2011

KEYWORDS
HIV;
Immune reconstitution inflammatory syndrome;
Meningoencephalitis myelitis;
Mycobacterium avium complex

Disseminated *Mycobacterium avium* complex (MAC) infection involves the central nervous system (CNS) less frequently than tuberculosis, and MAC-related immune reconstitution inflammatory syndrome (IRIS) of the CNS in AIDS patients is even more rarely described. We report a case of MAC-related IRIS of the CNS in an HIV-infected patient who presented with meningoencephalitis and myelitis 2 months after discontinuation of antiMAC therapy, when he had achieved prolonged suppression of HIV replication and restoration of CD4 counts to >100 cells/μL for 1 year. Cases of MAC-related IRIS of the CNS reported in the literature are reviewed.

* Corresponding author. Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan.
E-mail address: hcc0401@ntu.edu.tw (C.-C. Hung).

1684-1182/$36
doi:10.1016/j.jmii.2011.12.033

Introduction

Disseminated *Mycobacterium avium* complex (MAC) infection, an important AIDS-defining opportunistic infection commonly occurring in patients with CD4 lymphocyte counts <50 cells/μL, is associated with significant morbidity and mortality, and with shortened survival.[1,2] With the introduction of highly active antiretroviral therapy (HAART) in 1996, the incidences of opportunistic infections, including disseminated MAC (DMAC) infection, and AIDS-related mortality and hospitalization dramatically declined in HIV-infected patients.[3] The beneficial effects of HAART result from gradual restoration of pathogen-specific immune responses, mediated by suppression of HIV-1 replication and increases of CD4 counts.[4,5] However, adverse clinical phenomena, including paradoxical worsening of treated opportunistic infections or unmasking of previously subclinical untreated infections, may develop during the initial months, or even years[6] of HAART. These atypical presentations have since been recognized as inflammatory reactions directed at quiescent opportunistic pathogens following CD4 increases with HAART, otherwise known as immune reconstitution inflammatory syndrome (IRIS). MAC-related IRIS most commonly presents as focal lymphadenitis without mycobacteremia, with or without suppuration.[7–10] Cerebral MAC infection is very uncommon, and MAC-related IRIS of the central nervous system (CNS) is even rarer.[11,12] Herein, we present a case of an HIV-1 infected patient who developed an unusual and potentially devastating meningoencephalitis and myelitis due to MAC infection almost 17 months after commencing effective HAART and one year after attaining a sustained rise of CD4 cell count >100 cells/μL. Reported cases of MAC-related IRIS of the CNS in the literature are reviewed with the aim of better understanding of the rare form of IRIS associated with DMAC infection.

Case report

The 23-year-old homosexual man with HIV infection who was diagnosed in 2006 presented with intermittent fevers and oral candidiasis. HAART was prescribed in April 2008 but he did not continue this treatment due to severe nausea and vomiting. He began to have abdominal fullness, weight loss and intermittent fevers since August 2008 and computed tomography of the abdomen disclosed prominent ascites, marked splenomegaly and multiple confluent enlarged lymphadenopathies in the retroperitoneum and para-aortic regions in October 2008. Excisional biopsy of the inguinal lymph node only revealed histiocytosis. Progressive abdominal distension and dyspnea developed later and chest radiography showed massive left pleural effusion. The CD4 count was 2 cells/μL, and the plasma HIV RNA load (PVL) 77600 copies/mL in November 2008. After admission, HAART with abacavir/lamivudine and lopinavir/ritonavir was initiated and antiMAC therapy was begun with moxifloxacin, amikacin, clarithromycin and ethambutol when MAC was isolated from cultures of pleural effusion, lung biopsy, blood, ascites, bone marrow, and stool specimens. In the following months, the patient had been well and PVL was <50 copies/mL and a CD4 count >100 cells/μL on several occasions for more than one year. Given the clinical stability of the patient after about 14 months of antiMAC therapy and his significant immunological response to HAART, antiMAC therapy was discontinued in February 2010.

In April 2010, the patient presented with a one-week history of low back pain, easily stumbling, and progressive paraplegia. The physical examination revealed an ill-looking man who was afebrile, drowsy, and had neck stiffness and a decrease in muscle power of the bilateral lower extremities. Laboratory investigations showed a CD4 count of 70 cells/μL, PVL<50 copies/mL and a serum cryptococcal antigen titer of <1:2; the remainders were otherwise normal. A magnetic resonance imaging disclosed numerous tiny enhancing nodules diffusely scattered in the bilateral cerebral and cerebellar hemispheres, deep gray matter, brain stem and whole spinal cord (Fig. 1). A lumbar puncture revealed opening pressure, 230 mmH_2O; white cells, 6/μL (L/N, 6/0); protein, 141 mg/dL; and glucose, 32 mg/dL. Under the tentative diagnosis of MAC meningoencephalitis and myelitis, levofloxacin, clarithromycin, ethambutol and rifabutin were resumed. Adjunctive dexamethasone was added at a dose of 4 mg before antiMAC therapy was given with subsequent daily dose of 16 mg. After 5 days of therapy, the patient's consciousness totally recovered and muscle power significantly improved. A second lumbar puncture showed opening pressure, 52 mmH_2O; white cell, 0; protein, 48 mg/dL; and glucose, 58 mg/dL. MAC was subsequently cultured from both blood and cerebrospinal fluid specimens and he was discharged well on the 29th hospital day. The patient remained stable on the antiMAC therapy after discharge.

Discussion

In the present case, the patient initially presented with DMAC infection with mycobacteremia, pneumonia, empyema, and peritonitis. After commencing HAART and continuation of antimycobacterial regimen, good virological response and gradual restoration of immune function were observed. According to the guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents[13] antiMAC therapy that had been given for 14 months with satisfactory resolution of symptoms in our case was ceased after the patient fulfilled the criteria for discontinuing secondary prophylaxis of DMAC infection. However, new onset of neurological symptoms and signs occurred 2 months after ceasing antiMAC therapy despite adequate immunity, which is consistent with a diagnosis of MAC-related CNS-IRIS.

Diagnosis of IRIS of the CNS is difficult because IRIS remains a clinical syndrome with variable presentations and severities, and pathologic and microbiologic investigations of the CNS involvement are limited by potential morbidity related to the diagnostic procedures. According to clinical features defined by Riedel and colleagues[14] our patient fulfills his working definition, except without confirmation by histopathology that may demonstrate T-cell infiltration. Our arguments for MAC-related CNS-IRIS in this case are as follows. First, the immune reconstitution was documented by a sustained increase in CD4 count >100 cells/μL for one

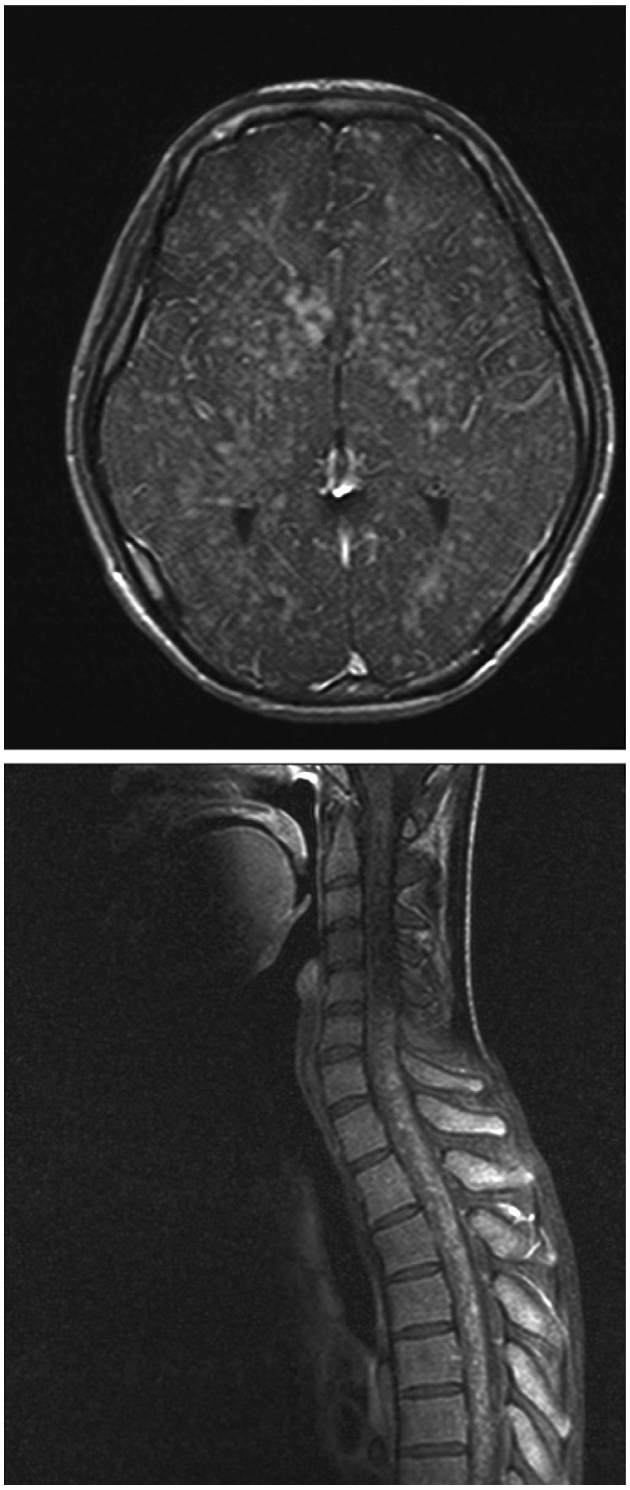

Figure 1. Magnetic resonance scan of the brain and spinal cord demonstrating numerous tiny enhanced nodules scattered diffusely.

year, a level at which DMAC disease would be less likely to occur in HIV-infected patients. Second, our patient had risk factors for the development of IRIS, which include a high baseline PVL and a lower baseline CD4 count before initiation of HAART, rapid decline in PVL after HAART, a high antigenic burden and disseminated infection, initiation of HAART concurrently with or soon after initiation of antimicrobial therapy of an acute infection, and being antiretroviral-naïve.[15] Although MAC could be cultured from affected tissue, French et al[16] and Shelburne et al[17] do not consider mycobacteremia as criteria of exclusion for MAC-related IRIS.

Typically most cases of mycobacteria-associated CNS-IRIS occur within 5 to 10 months after HAART is commenced.[18–20] The present case of MAC-related CNS-IRIS is unique because of its late development after HAART, and because of the CNS localization. MAC-associated CNS-IRIS in HIV-infected patients is rare and a search of the PubMed database (English language publications) identified four reported cases of CNS infection related to IRIS due to MAC infection in patients with AIDS.[12,21–23] The clinical presentations and relationship to timing of HAART of the five cases (including the present case) are shown in Table 1.[12,21–23] All reported cases were male and the median age of the patients was 36 years (range, 24–51 years). The presenting neurological symptoms included headache (2 patients), visual disturbance (1), aphasia (1), disorientation (1), drowsy consciousness (2), and paraplegia (1). The image study of the brain demonstrated hypodensities or ring-enhancing lesions of varying size. Manifestations of IRIS developed after a median of 17 months of HAART (range, 2–25 months). Patients had a median CD4 count of 20 cells/μL (range, 2–80 cells/μL) at baseline and a median plasma HIV viral load of 7.8×10^4 copies/mL (range, 1.4×10^4–3.9×10^5 copies/mL) before beginning HAART. At the time IRIS was diagnosed, the CD4 count had increased to a median of 70 cells/μL (range, 10–210 cells/μL) and the PVL had decreased to below the lower limit of detection in all of the patients. MAC was isolated from affected tissue in four of the five patients and only our patient had documented mycobacteremia. Corticosteroids were prescribed in addition to antimycobacterial drugs in two patients and all-cause mortality rate was 40% (2/5).

MAC-related IRIS may be clinically indistinguishable from active infection, and is mostly benign and self-limiting; however, severe cases and death have been described.[23] Optimal management of the various presentations of MAC-related IRIS of the CNS remains poorly defined because there are no well-conducted randomized treatment trials for these complications related to HAART. Generally, continuation of HAART is recommended and most deteriorating conditions will improve gradually. Use of corticosteroids does not yet document a mortality benefit but is indicated for catastrophic CNS-IRIS in patients who have massive inflammation, resulting in impending brain herniation.[24] In our patient, rapid improvement of neurological symptoms after addition of steroids was observed (about 5 days), which suggests the disease entity as fulminant inflammation involving the CNS, instead of relapsing infection.

The reported incidence of relapsing MAC disease in HIV-infected patients receiving HAART after the interruption of maintenance therapy is very low[25]and relapses are often observed in patients who fail to respond to, or stop, HAART other than to MAC-IRIS. There are well-known guidelines that recommend when to discontinue primary and secondary prophylaxis for several opportunistic infections

Table 1 Demographic, clinical and radiological findings, CD4 and PVL at baseline and diagnosis of IRIS, adjunctive therapy, and outcome for HIV-infected patients with MAC-related CNS-IRIS

Reference	Age/ sex	Manifestations	Brain image	ART	Duration on HAART	Baseline CD4 (cells/μL)	CD4 when IRIS developed (cells/μL)	Baseline PVL (copies/mL)	IRIS PVL (copies/mL)	Adjunct	Outcome
[12]	35/M	Headache, fever, dizziness, vomiting	A 3-cm lesion with perifocal edema	2 NRTI + PI	~25 mo	<10	210	382987	<400	excision	survived
[21]	41/M	Deterioration of visual acuity	Not done	2 NRTI + PI	2 mo	20	37	385000	undetect	enucleation	survived
[22]	36/M	Headache, expressive aphasia,	2 hypodense ring-enhanced lesions	NRTI, NNRTI, PI	~2 y	80	170	14210	<50	nil	died
[23]	51/M	Disorientation, lethargy	A ring-enhanced lesion with mass effect	2 NRTI + PI	4 mo	20	10	170000	<50	steroid	died
[PR]	24/M	Easy falling, drowsy, paraplegia	Numerous enhanced nodules in the cerebrum, cerebellum and spinal cord	2 NRTI + PI	~17 mo	2	70	77600	<50	steroid	survived

CNS = central nervous system; HAART = highly active antiretroviral therapy; IRIS = immune reconstitution inflammatory syndrome; MAC = *Mycobacterium avium* complex; PR = present report; PVL = plasma HIV RNA load.

in AIDS patients with HAART-related immune reconstitution.[13] In the present case, antimycobacterial regimens were discontinued when CD4 count had increased to the recommended cut-off value for discontinuation of prophylaxis for MAC infection, although MAC-associated IRIS of the CNS developed. Therefore, clinicians must always be more cautious when stopping maintenance therapy for MAC disease and remain alert for atypical presentations. Given the potentially devastating consequences of such an immune reconstitution, we should understand this disease entity more, even if the overall occurrence of MAC disease is still rare after ceasing secondary prophylaxis in HIV-infected patients with good response to HAART.

References

1. Hsieh SM, Hung CC, Chen MY, Hsueh PR, Chang SC, Luh KT. Clinical features and outcome in disseminated mycobacterial disease in AIDS patients in Taiwan. *AIDS* 1998;**12**:1301–7.
2. Chaisson RE, Gallant JE, Keruly JC, Moore RD. Impact of opportunistic disease on survival in patients with HIV infection. *AIDS* 1998;**12**:29–33.
3. Palella Jr FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998;**338**:853–60. HIV Outpatient Study Investigators.
4. Autran B, Carcelain G, Li TS, Blanc C, Mathez D, Tubiana R, et al. Positive effects of combined antiretroviral therapy on CD4 + T cell homeostasis and function in advanced HIV disease. *Science* 1997;**277**:112–6.
5. Battegay M, Nuesch R, Hirschel B, Kaufmann GR. Immunological recovery and antiretroviral therapy in HIV-1 infection. *Lancet Infect Dis* 2006;**6**:280–7.
6. Riddell J, Kaul DR, Karakousis PC, Gallant JE, Mitty J, Kazanjian PH. *Mycobacterium avium* complex immune reconstitution inflammatory syndrome: long term outcomes. *J Translation Med* 2007;**5**:50.
7. Phillips P, Kwiatkowski MB, Copland M, Craib K, Montaner J. *Mycobacterial lymphadenitis* associated with the initiation of combination antiretroviral therapy. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999;**20**:122–8.
8. Cabie A, Abel S, Brebion A, Desbois N, Sobesky G. Mycobacterial lymphadenitis after initiation of highly active antiretroviral therapy. *Eur J Clin Microbiol Infect Dis* 1998; **17**:812–3.
9. Dworkin MS, Fratkin MD. *Mycobacterium avium* complex lymph node abscess after use of highly active antiretroviral therapy in a patient with AIDS. *Arch Intern Med* 1998;**158**: 1828.
10. Race EM, Adelson-Mitty J, Kriegel GR, Barlam TF, Reimann KA, Letvin NL, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. *Lancet* 1998;**351**:252–5.
11. Gyure KA, Prayson RA, Estes ML, Hall GS. Symptomatic *Mycobacterium avium* complex infection of the central nervous system. A case report and review of the literature. *Arch Pathol Lab Med* 1995;**119**:836–9.
12. Murray R, Mallal S, Heath C, French M. Cerebral *Mycobacterium avium* infection in an HIV-infected patient following immune reconstitution and cessation of therapy for disseminated *Mycobacterium avium* complex infection. *Eur J Clin Microbiol Infect Dis* 2001;**20**:199–201.
13. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic

infections in HIV-infected adults and adolescents. *MMWR Recomm Rep* 2009 Sep 4;**58**(RR-11):1—166.
14. Riedel DJ, Pardo CA, McArthur J, Nath A. Therapy insight: CNS manifestations of HIV-associated immune reconstitution inflammatory syndrome. *Nat Clin Pract Neurol* 2006;(2): 557—65.
15. Beatty GW. Immune reconstitution inflammatory syndrome. *Emerg Med Clin North Am* 2010;**28**:393—407.
16. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS* 2004;**18**:1615—27.
17. Shelburne SA, Montes M, Hamill RJ. Immune reconstitution inflammatory syndrome: more answers, more questions. *J Antimicrob Chemother* 2006;**57**:167—70.
18. Murdoch DM, Venter WD, Feldman C, Van Rie A. Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study. *AIDS* 2008;**22**:601—10.
19. Crump JA, Tyrer MJ, Lloyd-Owen SJ, Han LY, Lipman MC, Johnson MA. Miliary tuberculosis with paradoxical expansion of intracranial tuberculomas complicating human immunodeficiency virus infection in a patient receiving highly active antiretroviral therapy. *Clin Infect Dis* 1998;**26**: 1008—9.
20. Ramdas K, Minamoto GY. Paradoxical presentation of intracranial tuberculomas after chemotherapy in a patient with AIDS. *Clin Infect Dis* 1994;**19**:793—4.
21. Zamir E, Hudson H, Ober RR, Kumar SK, Wang RC, Read RW, et al. Massive mycobacterial choroiditis during highly active antiretroviral therapy another immune-recovery uveitis? *Ophthalmology* 2002;**109**:2144—8.
22. Fortin C, Rouleau D. Cerebral *Mycobacterium avium* abscesses: late immune reconstitution syndrome in an HIV-1-infected patient receiving highly active antiretroviral therapy. *Can J Infect Dis Med Microbiol* 2005;**16**:187—9.
23. Kishida S, Ajisawa A. Probable cerebral *Mycobacterium avium* complex-related immune reconstitution inflammatory syndrome in an HIV-infected patient. *Intern Med* 2008;**47**:1349—54.
24. Johnson T, Nath A. Neurological complications of immune reconstitution in HIV-infected populations. *Ann N Y Acad Sci* 2010;**1184**:106—20.
25. Currier JS, Williams PL, Koletar SL, Cohn SE, Murphy RL, Heald AE, et al. Discontinuation of *Mycobacterium avium* complex prophylaxis in patients with antiretroviral therapy-induced increases in CD4+ cell count. A randomized, double-blind, placebo-controlled trial. AIDS Clinical Trials Group 362 Study Team. *Ann Intern Med* 2000;**133**:493—503.