Cerebral *Mycobacterium avium* abscesses: Late immune reconstitution syndrome in an HIV-1-infected patient receiving highly active antiretroviral therapy

Claude Fortin MD FRCP, Danielle Rouleau MD FRCP

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A patient who developed an atypical manifestation of *Mycobacterium avium* complex (MAC) infection almost two years after starting effective highly active antiretroviral therapy is described. The recurrence, manifested as brain abscesses in the central nervous system, was an uncommon form of MAC disease usually reported postmortem. An increased CD4 cell count, localized and suppurative infection, and the absence of systemic evidence of infection were consistent with a late immune reconstitution syndrome. The present case report adds to the understanding of MAC disease in HIV-infected patients.

Key Words: Central nervous system infections; Immune reconstitution syndrome; *Mycobacterium avium* complex

The introduction of highly active antiretroviral therapy (HAART) in 1996 dramatically decreased the incidence of opportunistic infections (OIs) in HIV patients. There has also been a reduction in AIDS-related mortality and hospitalization (1). At the same time, however, clinicians began to describe unusual clinical presentations of previously common OIs, which were identified or worsened during the first few weeks after the initiation 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 the immune reconstitution syndrome (IRS) (2-4). A classic example, the so-called paradoxical reaction, involves the worsening of tuberculosis after patients commence both antimycobacterial therapy and HAART (5-7). Other early descriptions of IRS include localized *Mycobacterium avium* complex (MAC) lymphadenitis (8-11) and cytomegalovirus vitreitis; however, OI-associated IRS has now been described for most opportunistic pathogens (2-4).

The relapse of MAC disease after stopping maintenance therapy usually occurs because of failed or discontinued HAART, and presents as disseminated MAC disease with CD4 counts of less than 50 cells/ μ L (12,13). MAC-IRS most commonly presents as focal lymphadenitis without mycobacteremia, with or without suppuration (8-11). Other localized MAC-IRS have included skin disease (14,15), isolated pulmonary disease (16,17), bowel involvement (18), and osteomyelitis including

Abcès à *Mycobacterium avium* cérébral : syndrome de reconstitution immunitaire tardive chez un patient infecté par le VIH-1 sous HAART

On décrit ici le cas d'un patient qui a développé une manifestation atypique d'infection à CMA (complexe *Mycobacterium avium*) près de deux ans après le début d'une HAART efficace. La récurrence sous forme d'abcès cérébral au niveau du système nerveux central s'est révélé être une présentation rare de maladie à CMA habituellement signalée à l'autopsie. Une augmentation de la génération des CD4, une infection localisée et suppurative et l'absence de signe systémique d'infection concordaient toutes avec un syndrome de reconstitution immunitaire tardive. Ce cas nous permet d'approfondir notre compréhension de la maladie à CMA chez les patients infectés par le VIH.

vertebral involvement (19). We report the case of an HIV-1-infected patient who developed an unusual and potentially devastating localized brain infection due to MAC almost two years after starting effective HAART and 17 months after attaining a sustained elevation of CD4 cell count over 150 cells/ μ L. The patient had been previously treated for disseminated MAC disease, and maintenance therapy had been stopped following a sustained increase in his CD4 cell count.

CASE PRESENTATION

A 36-year-old man was diagnosed with AIDS in May 2000 when he presented with oropharyngeal candidiasis, *Pneumocystis carinii* pneumonia and disseminated MAC disease. The MAC isolate growing in blood cultures was sensitive to clarithromycin in vitro. The patient's initial CD4 count was 10 cells/ μ L and his viral load was 217,163 copies/mL. Candidiasis and *P. carinii* pneumonia were successfully treated with standard regimens. Treatment for MAC was initiated with clarithromycin, ethambutol and rifabutin. After one month, the rifabutin was switched to levofloxacin to minimize interactions with the protease inhibitors to be included in the HAART regimen. Initial HAART included d4T, 3TC, saquinavir and ritonavir.

Clinically, the patient improved during the following months. Due to a suboptimal virological response after six months with a viral load of 14,120 copies/mL, the regimen was changed to didanosine, efavirenz and lopinavir/ritonavir using

Département de Microbiologie médicale et Infectiologie, Centre Hospitalier de l'Université de Montréal, Université de Montréal, Montréal, Québec
Correspondence and reprints: Dr Claude Fortin, Département de Microbiologie médicale et Infectiologie, Centre Hospitalier de l'Université de

Montréal : Hôpital Notre-Dame, 1560, rue Sherbrooke Est, Montreal, Quebec H2L 4M1. Telephone 514-890-8000 ext 24720,

fax 514-412-7545, e-mail claud.fortin.chum@ssss.gouv.qc.ca or claudfortin@hotmail.com

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Figure 1) Computed tomography scan of the brain after contrast administration, demonstrating the two lesions with significant perilesional edema

an HIV-1 virtual phenotypic assay. At this time, the CD4 count was 80 cells/ μ L. Six months following this change in treatment, the patient had a viral load of less than 50 copies/mL and a CD4 cell count of 220 cells/ μ L. Given the clinical stability of the patient after one year of MAC therapy and his significant immunological response to HAART, therapy for MAC was discontinued. The following year was uneventful, except for an episode of self-limited gastroenteritis in July 2002. A complete workup was administered, and blood cultures for mycobacteria and a duodenal biopsy for acid-fast bacilli (AFB) were both found to be negative. The patient's CD4 T-cell count dropped to 80 cells/ μ L during the acute illness, but returned to 150 cells/ μ L one month later.

In October 2002, the patient presented with an acute neurological syndrome consisting of headaches and expressive aphasia. He was afebrile with no other complaints. The physical examination was unremarkable except for aphasia, which spontaneously resolved within a few hours. A computed tomography (CT) scan of the head showed two hypodense lesions with ring enhancement – one in the right temporal lobe measuring 0.9 cm $\times$ 0.7 cm and the other in the left temporoparietal area measuring 1.2 cm $\times$ 1.3 cm (Figure 1). A lumbar puncture revealed no white or red blood cells, a glucose level of 2.5 mmol/L and a protein level of 0.56 g/L. The cerebrospinal fluid cryptococcal antigen test was negative, as were smears and cultures for bacterial, mycobacterial and fungal pathogens. The patient's viral load was less than 50 copies/mL and his CD4 cell count was 170 cells/ μ L.

The initial diagnosis was toxoplasma encephalitis, and a standard antitoxoplasma regimen was started. After 12 days of therapy, the patient presented with generalized tonicoclonic seizures. A second CT scan showed progression of the two lesions with new cerebral edema. Treatment for toxoplasmosis was discontinued and a brain biopsy was performed. Tissue pathology demonstrated reactive gliosis, lymphocyte infiltration, foamy mononuclear cells and the absence of giant cells and granulomas. A Ziehl-Neelsen stain showed numerous

AFB, and all other stains were negative. Cultures grew MAC after five days, and the isolate remained sensitive to clarithromycin *in vitro*. A surgical approach was deemed too complicated because the lesions were bilateral. The patient was started on azithromycin 600 mg daily, ethambutol 1000 mg daily and rifabutin 150 mg every other day (the dose was adjusted for concomitant use of lopinavir/ritonavir). A follow-up CT scan showed complete regression of the two lesions by August 2003. At this time, the patient was asymptomatic; his CD4 cell count and viral load were 300 cells/ μ L and less than 50 copies/mL, respectively. Antimycobacterial therapy was stopped in September 2003, one year after the clinical episode. In October 2003, a follow-up CT scan showed new contrast enhancement in the temporal area while the patient remained asymptomatic; antimycobacterial therapy was then restarted with azithromycin and ethambutol. Since then, the patient has remained well, apart from two episodes of drug-related pancreatitis. The latest follow-up CT scan in July 2004 was normal. The patient remains on the antimycobacterial regimen.

DISCUSSION

The present case of central nervous system (CNS) MAC disease relapsing after sustained adequate immune recovery and virological control under HAART represents a rarely described syndrome, which is consistent with a diagnosis of MAC-IRS. First, the immune reconstitution was documented by a significantly increased CD4 cell count of 170 cells/ μ L at the time of cerebral abscess development, a level at which pre-HAART disseminated MAC disease would not be expected in HIV-infected patients. Second, the localized, suppurative infection without bacteremia was unusual for classic MAC disease in HIV patients. Finally, there was no evidence of a systemic inflammatory response. The present case of MAC-IRS is unique because of its late occurrence after starting HAART, and because of the CNS localization. The usual time of occurrence of IRS is within eight weeks of starting HAART (2). Previously reported cases of MAC-IRS have been localized to non-life-threatening sites, such as the lymph nodes (8-11), soft tissue (14,15) and musculoskeletal involvement (19). Another potentially devastating site of occurrence – spine involvement with possible spinal cord compression – has also been reported (19).

Other possible explanations for the relapse in our patient include noncompliance, a drop in CD4 cells during the patient's gastroenteritis episode, and a period of immune reconstitution that was too short. However, we believe that our patient was compliant with his HAART and anti-MAC medication because he was evaluated at each medical visit and periodically by a clinical pharmacist. As well, the patient's decreased CD4 cell count during the gastroenteritis (80 cells/ μ L) rebounded rapidly, and was too short of a duration to explain the relapse. In addition, specific investigations for MAC disease at that time were negative.

CNS MAC disease is rare, typically diagnosed postmortem and usually presents as meningitis in profoundly immunosuppressed patients (20-21). To our knowledge, there is only one previously reported case (22) of localized cerebral disease after discontinuation of secondary prophylaxis in a patient with immune reconstitution recognized as MAC-IRS. This case, reported by Murray et al (22), was an HIV-infected patient treated for disseminated MAC in 1982 who was maintained on a standard secondary prophylaxis regimen. HAART was started in 1996. By March 1998, the patient's CD4 cell count had

increased from 10 cells/ μ L to 294 cells/ μ L, and his viral load became undetectable. Maintenance therapy for MAC was discontinued, and azithromycin 600 mg twice a week was administered. In November 1998, the patient presented with a symptomatic 3 cm solitary lesion of the left frontal lobe and a CD4 cell count of 210 cells/ μ L. A subsequent excisional biopsy showed AFB in tissue pathology, and cultures grew an isolate resistant to clarithromycin in vitro. Resistance of the relapsing isolate could be explained by exposure of suboptimal cerebrospinal fluid concentrations to the macrolide azithromycin. Data describing the penetration of macrolides into the CNS are lacking (23). Compared with the present case, this previously reported patient had a recurrence despite having been treated for a longer period of time and having stopped secondary prophylaxis at a higher CD4 cell count. This patient also underwent an excision of the lesion, a procedure that could not be done for our patient. The present case appears to be the first case described in which the patient was treated without surgery.

The reported incidence of relapsing MAC disease in AIDS patients after the interruption of maintenance therapy is very

low (approximately 0.9 per 100 person-years) (24). Relapses are usually secondary to failed or discontinued HAART, and not to MAC-IRS. There are acceptable guidelines that outline when to discontinue primary and secondary prophylaxis for OIs in AIDS patients with HAART-related immune reconstitution (25). However, clinicians must always exercise caution when stopping maintenance therapy for MAC disease and remain vigilant for unusual presentations. CNS relapses can lead to considerable morbidity, may necessitate invasive procedures, such as brain biopsy and neurosurgery, and could potentially lead to the use of second-line agents for which less clinical experience exists due to resistant isolates. Given the potentially devastating consequences of such an immune reconstitution, clinicians should be aware of this entity, even if the overall occurrence of MAC remains rare after discontinuing secondary prophylaxis in HAART responders.

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