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

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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.

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**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 suppurration.\(^7\) Cerebral MAC infection is very uncommon, and MAC-related IRIS of the central nervous system (CNS) is even rarer.\(^1\)\(^1\)\(^2\) 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 intermitter 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 vomiting. HAART was prescribed in April 2008 and continued for 14 months with satisfactory resolution of symptoms. 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.

In the present case, the patient initially presented with DMAC infection with mycobacteremia, pneumonia, empyema, and peritonitis. After commencing HAART and discontinuation 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\(^1\)\(^3\) 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.

**Discussion**

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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 anti-retroviral-naïve. Although MAC could be cultured from affected tissue, French et al16 and Shelburne et al17 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 $7.8 \times 10^6$ copies/mL (range, $1.4 \times 10^4$–$3.9 \times 10^5$ 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 low25 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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/sex</th>
<th>ART</th>
<th>Duration on HAART</th>
<th>Manifestations Brain image</th>
<th>CD4 at diagnosis (cells/mL)</th>
<th>PVL at diagnosis (copies/mL)</th>
<th>Adjunct therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>35/M</td>
<td>2 NRTI + PI</td>
<td>~25 mo</td>
<td>Headache, fever, dizziness, vomiting</td>
<td>210</td>
<td>&lt;400</td>
<td>Excision</td>
<td>Survived</td>
</tr>
<tr>
<td>21</td>
<td>41/M</td>
<td>2 NRTI + PI</td>
<td>2 mo</td>
<td>Headache, fever, dizziness, vomiting</td>
<td>37</td>
<td>382957</td>
<td>Enucleation</td>
<td>Survived</td>
</tr>
<tr>
<td>22</td>
<td>22/M</td>
<td>NRTI, NRTI1, PI</td>
<td>~2 y</td>
<td>Headache, fever, dizziness, vomiting</td>
<td>80</td>
<td>&lt;400</td>
<td>NRTI</td>
<td>Died</td>
</tr>
<tr>
<td>23</td>
<td>36/M</td>
<td>2 NRTI + PI</td>
<td>4 mo</td>
<td>Headache, fever, dizziness, vomiting</td>
<td>170</td>
<td>14210</td>
<td>Steroid</td>
<td>Survived</td>
</tr>
<tr>
<td>24</td>
<td>23/M</td>
<td>2 NRTI + PI</td>
<td>~17 mo</td>
<td>Headache, fever, dizziness, vomiting</td>
<td>20</td>
<td>170000</td>
<td>Steroid</td>
<td>Died</td>
</tr>
<tr>
<td>25</td>
<td>51/M</td>
<td>2 NRTI + PI</td>
<td>2 mo</td>
<td>Headache, fever, dizziness, vomiting</td>
<td>70</td>
<td>77600</td>
<td>Steroid</td>
<td>Survived</td>
</tr>
</tbody>
</table>

CNS = central nervous system; HAART = highly active antiretroviral therapy; IRIS = immune reconstitution inflammatory syndrome; MAC = Mycobacterium avium complex; PR = present

References


