Two Cases of Long Lasting Bacteremia Due to Mycobacterium avium Complex Despite New Macrolides-containing Regimens in Patients with Acquired Immunodeficiency Syndrome


Abstract

The prognosis of Mycobacterium avium complex (MAC) infection has been improved by new macrolides-containing regimens and the use of highly active antiretroviral therapy (HAART) in the treatment of acquired immunodeficiency syndrome (AIDS). We report on two AIDS cases with long lasting bacteremia due to MAC under this regimen. Both patients experienced problems due to side effects from the anti-MAC regimen and from an immune-reconstitution syndrome related to HAART. MAC infection persisted despite treatment, however, no anti-MAC drug-resistant isolates emerged throughout the clinical course in either case. These cases demonstrate that therapy for disseminated MAC infection is sometimes difficult even with HAART and macrolides-containing regimens. (Internal Medicine 40: 454-458, 2001)

Key words: highly active antiretroviral therapy, immune reconstitution syndrome, clarithromycin, anti-Mycobacterium avium complex drug resistance

Introduction

Disseminated Mycobacterium avium complex (MAC) infection is one of the most frequent complications in patients with advanced stages of human immunodeficiency virus type 1 (HIV-1) infection. In the early 90s, patients with MAC infection were treated with some anti-tuberculosis drugs, although MAC was resistant to these drugs. Eradication of MAC was very difficult and the prognosis was quite poor (1-3). However recently, anti-MAC therapy with a multi-drug combination including clarithromycin improves survival with a median period to bacterial clearance expected to be 4 weeks (4, 5). Furthermore, early commencement with highly active antiretroviral therapy (HAART) has dramatically improved morbidity and mortality from opportunistic infections associated with HIV-1 infection including MAC infection (6, 7). Therefore, HAART is an essential strategy for patients with acquired immunodeficiency syndrome (AIDS). However, if a patient has MAC infection and receives HAART, the patient can suffer from immune-reconstitution inflammation including severe lymphadenitis with pain and fever due to HAART (8, 9).

We describe two cases of disseminated MAC infection in AIDS patients who required several months of treatment before clearance of MAC bacteremia was achieved. Furthermore, we examined the drug resistance of sequential MAC isolates during each clinical course.

Case Report

Case 1

A 22-year-old male hemophiliac with HIV infection had Pneumocystis carinii pneumonia (PCP) and had been treated with sulfamethoxazol/trimetoprim for 4 weeks in March 1998. HAART with stavudine (d4T) 60 mg/day, lamivudine (3TC) 300 mg/day and saquinavir (SQV) 1,800 mg/day was started in April. Soon after, he suffered from fever higher than 39°C and was referred to our hospital on May 2, 1998. According to his previous history, CD4+ T lymphocyte count (CD4 count) was 22 cells/μl prior to commencing HAART. At the time of admission to our hospital, generalized pigmentation was found on his skin and dark spots on his tongue. Findings of laboratory data on admission were as follows: WBC 11,000 cells/μl (normal 3,500–9,000 cells/μl), RBC 2.61×10⁶ cells/μl (normal 3.7–5.6×10⁶ cells/μl), ALT 10 IU/l (normal 0–30 IU/l),

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ALP 567 IU/l (normal 85–340 IU/l), CRP 6.43 mg/dl (normal <0.3 mg/dl), and ACTH 104.3 pg/ml (normal 9.0–52.0 pg/ml). CD4 count of 162 cells/μl indicated a good and quick response to the HAART. HIV-1 viral load in plasma (VL) was 1.1×10^5 copies/ml at that time. He complained of tenderness in the middle of his abdomen. Lymphadenopathy in mesenterium was found by abdominal CT scan and Ga-scintigraphy revealed intensive uptake in the same position. MAC was isolated from the blood and also detected in stool smear. HAART was discontinued and anti-MAC therapy was initiated with clarithromycin 1,200 mg/day, ethambutol 750 mg/day, ciprofloxacin 600 mg/day and amikacin 400 mg/day on May 8 (Fig. 1). As MAC was repeatedly isolated from blood and detected in the stool microscopically, rifabutin 300 mg/day was added to the regimen 7 weeks later. Three months later, anti-MAC therapy had to be stopped because fever continued and it was suspected to be drug induced. Since causal drugs were not determined, all anti-MAC drugs were terminated. And then fever improved within five days after the termination. Subsequently, HAART with d4T 60 mg/day, 3TC 300 mg/day, and indinavir 2,400 mg/day was initiated on September 11 (4.5 months after admission). During his clinical course, rifabutin, clarithromycin and ciprofloxacin were reintroduced but were discontinued because of drug-induced fever. Finally, in November 1998, with a combination of azithromycin 600 mg/day and ethambutol 750 mg/day the MAC bacteremia was cleared. However, MAC culture in the stool remained positive for ten months and finally was reported as negative at the end of February 1999.

Corticosteroids had been administered on May 18, 1998 for adrenal insufficiency (ACTH 104.3 pg/ml), which is a very common complication in disseminated MAC infection. Twenty mg/day of hydrocortisone was also initiated but his fever did not improve. Then steroid was switched to 20 mg/day of prednisolone and tapered. Although HIV-RNA was suppressed below the detectable level (less than 400 copies/ml), CD4 count remained less than 50 cell/μl.

Case 2

A 32-year-old female was admitted to our hospital on August 18, 1998 because of cough and fever higher than 38°C. She had a history of PCP one month earlier. No abnormal physical findings were found except for anemic change in palpebral conjunctiva. Laboratory data on admission were as follows; WBC 11,810 cells/μl, RBC 3.24×10^6 cells/μl, ALT 33 IU/l, ALP 859 IU/l, CRP 5.64 mg/dl, CD4 counts 9.7 cells/μl, and VL 5.4×10^4 copies/ml. HAART was initiated on August 31, 1998 with d4T 60 mg/day, 3TC 300 mg/day, and nelfinavir (NFV) 2,500 mg/day (Fig. 2). MAC was isolated from blood 23 days after initiation of HAART. Anti-MAC therapy was initiated with azithromycin 600 mg/day (soon after, it was changed to clarithromycin 600 mg/day), rifabutin 300 mg/day and amikacin 400 mg/day on September 23, 1998. The anti-MAC therapy was interrupted and altered to azithromycin, amikacin, ethambutol 600 mg/day and spalofloxacin 200 mg/day due to fever, leukocytopenia, and severe nausea on December 15, 1998. Before treatment, MAC was isolated from blood, stool, and...

<table>
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Figure 1. The clinical course of case 1. ▼ indicates the isolates which were examined for drug susceptibility. d4T: stavudine, 3TC: lamivudine, IDV: indinavir, CAM: clarithromycin, EB: ethambutol, CIP: ciprofloxacin, AMK: amikacin.
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1998

Aug 18 Aug 31 Sep 23 Nov 18 Dec 4 Dec 14 1999

(ZDV) d4T 60 mg + 3TC 300 mg + NFV 2,500 mg/day
d4T/3TC/NFV

Rifabutin 300 mg/day
Azithromycin 600 mg/day
Ethambutol 500 mg/day
Amikacin 250 mg/day
Ciprofloxacin 600 mg/day

20 mg/day 12.5 mg/day 10 mg/day 13 mg/day 11 mg/day

Prednisolone

Temperature

40.0
39.0
38.0
37.0
36.0

MAC culture

Blood + + + + - - + + - - - - - - - -
Stool + - - - - - - - - - - - - - - - -
Sputum + -

CD4 (cells/μl) 9.7 54 21 12 14 5 4
V.L. (copies/ml) 5.4×10^4 U.D. 1.1×10^3 1.8×10^3 2.2×10^3 1.2×10^3 U.D.

Figure 2. The clinical course of case 2. ▼ indicates the isolates which were examined for drug susceptibility. ZDV: zidovudine, NFV: nelfinavir.

Sputum. Lymph node swelling was observed in the para-aortic arch on chest X-ray and CT, and in the para-aortic region on abdominal CT. MAC cultures became negative in all specimens after three months of anti-MAC therapy. However, fever was observed due to the fluctuation of adrenal insufficiency. Despite HAART being suspended from November 18, 1998 to February 22, 1999 because of fever, VL was quickly suppressed to an undetectable level (less than 400 copies/ml) in March 1999, following the recommencement of d4T 60 mg/day, 3TC 300 mg/day, and NFV 2,500 mg/day. As the basal plasma ACTH value was 80.7 pg/ml (normal 9.0–52.0 pg/ml), corticosteroids were replaced for the adrenal insufficiency. No bacteria other than MAC was detected in the repeated blood cultures during the clinical course.

**Susceptibility to anti-MAC drugs**

We examined the susceptibility of sequential MAC isolates obtained from blood culture during each clinical course to anti-MAC drugs. Briefly, the isolates were adjusted to McFarland 0.5 after incubation with the Middlebrook 7H9 medium at 35°C in 5% CO2 for 7 days. Three milliliters of culture suspension was diluted with 20 ml of sterilized physiological saline and cultured with various anti-mycobacterial drugs in a 96-well microplate at 35°C in 5% CO2 for 4 days. The standard MAC strain whose MIC values to these drugs were already known was applied as a control. As shown in Table 1, all isolates were susceptible to respective drugs. These results demonstrated that resistant strains to anti-MAC drugs did not emerge throughout their clinical courses.

**Discussion**

Disseminated MAC infection is one of the most common causes of fever of unknown origin (FUO) in patients with AIDS. FUO, diarrhea, and wasting are sometimes the only signs or complications of disseminated MAC infection in AIDS patients. "Immune reconstitution syndrome", has been reported to occur within several weeks following the initiation of HAART (8–11). It is characterized by excessive inflammation, or transient deterioration of clinical symptoms of some opportunistic infections such as disseminated MAC infection, cytomegalovirus infection, lung tuberculosis, and Pneumocystis carinii pneumonia. At this time, HAART or anti-opportunistic infection therapy can be difficult to continue because of fever and/or painful lymphadenitis. In order to control fever caused by the inflammation, corticosteroids may have to be used for long periods, resulting not only in the suppression of CD4 count but also in the persistence of MAC bacteremia. This fact indicated that we should precede anti-MAC therapy to HAART, although eradication of disseminated MAC infection is only achieved after long-term therapy. Consequently, HAART is to be started before clearance of the infection. Once the "The immune re-
constituent syndrome” appears with the simultaneous treatment for MAC infection and HAART, it is necessary to carefully determine the administration of corticosteroids on demand or termination of anti-MAC therapy and/or HAART. Principally, to avoid immune-reconstitution syndrome, opportunistic infections are to be cleared before initiation of HAART. However, how long anti-MAC therapy should precede initiation of HAART remains to be determined.

Anti-MAC therapy with multiple drug combination including clarithromycin has dramatically improved mortality of the infection and shortened the length of time taken to achieve bacterial clearance from blood (4). However, in our cases, MAC bacteremia lasted for several months despite the use of combination therapy. In one case, MAC was still detectable after six months of therapy. A possible explanation for the long lasting bacteremia is that a large amount of MAC can be present in the blood and solid organs, such as lymph nodes of AIDS patients. MAC culture was positive in both blood and stool in this report, this means that MAC infections were disseminated in their organs. Because anti-MAC drugs do not reach a high enough concentration in the lymph nodes these lymph nodes can act as reservoirs for the bacteria. Despite the persistence of disseminated MAC infection, no isolates developed resistance to any of the anti-MAC drugs used in either of the two cases.

Recommended combinations reported for anti-MAC therapy state that three or four drugs should be selected from clarithromycin, azithromycin, rifabutin, ethambutol, ciprofloxacin, sparfloxacin and amikacin (4, 5). However, each drug can induce several side effects even if used as a single antibiotic. In one case, it took more than three months to establish the suitable anti-MAC combination therapy because of side effects. Furthermore, if HAART is co-administered, the possible problems include drug-drug interaction and poor adherence due to the large number of pills required for both therapies. Others have recommended (12) that neither HAART nor anti-MAC therapy should be stopped against this persistent disease. However, as our two cases illustrate the management of disseminated MAC infection in AIDS patients can be troublesome and difficult, and does in fact require the stopping and or changing of both anti-MAC therapy and HAART.

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739, 1997.


