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Title: Successful treatment of an AIDS patient with prolonged Mycobacterium avium bacteremia, high HIV RNA, HBV infection, Kaposi's sarcoma and cytomegalovirus retinitis.

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Abstract: We report an AIDS patient with a high HIV RNA copy number in the plasma who was successfully treated for prolonged Mycobacterium avium bacteremia and other complications.
An HIV-infected patient with high fever, anemia, high alkaline phosphatase, cystic lung lesions, hepatitis B virus infection and Kaposi's sarcoma was referred to our hospital. PCR of the blood revealed Mycobacterium avium bacteremia and the time to blood culture positivity was 8 days. The HIV-1 RNA copy number in the plasma was more than ten million copies/ml and the CD4-positive T cell count was 21 cells/μL. Although the high fever resolved five days after therapy for Mycobacterium avium was started, the fever recurred just before starting anti-retroviral therapy (ART) including dolutegravir. The patient experienced repeated but self-limiting bouts of severe inflammation. Mycobacteremia was intermittently detected up to 79 days, suggesting that the recurrent episodes of inflammation were due to the intermittent dissemination of mycobacteria, and that persistent treatment is needed. Five months after the beginning of ART, the HIV-1 RNA copy number in the plasma was still 28000 copies/ml. An HIV drug-resistance test revealed sensitivity to all anti-retroviral drugs. Eleven months after the initiation of ART, the HIV RNA copy number in the plasma decreased to 45 copies/mL and the CD4-positive T cell count recovered to 205 cells/μL. Our case also suggests that dolutegravir can be effective in cases with prolonged high levels of HIV RNA.
Our findings emphasize that prompt diagnosis and persistent therapy for mycobacterial infection are important for successful treatment.

To Reviewer #1

1. Regarding the patient's adherence to treatment, my clinical impression is that there was complete adherence and that it does not affect the substance or the conclusions of this case report. Regarding the possible relationship between adherence and the high plasma viral load, I have commented in the Discussion section as follows:

Regarding the etiology of persistent high HIV RNA in the plasma after initiating ART, possible causes include MAC-induced inflammation, a very large HIV reservoir, poor adherence to ART, and pharmacokinetic-pharmacodynamic factors. The adherence to ART was confirmed to be 100% during his hospitalization. After his discharge, the adherence to ART was evaluated by self-report; however, the patient's report of remaining medication at the time of outpatient consultation was completely correct, and the trough value of DTG concentration, which was relatively low but was still in effective concentration, convinced us of his complete adherence to treatment. Because the high HIV RNA plasma concentration persisted until the inflammation due to dNTM abated, it is reasonable to think that the very large HIV reservoir size and MAC-induced inflammation were the main reasons for the persistent viremia.

2. The Reviewer 1 pointed that description of "Mycobacterium avium-intracellulare complex (MAC) is the most common mycobacterial organism identified" induces misunderstanding.

I meant that *Mycobacterium avium-intracellulare* complex (MAC) was most commonly identified in disseminated NTM infections, as is reported in Reference [2].

To avoid misunderstanding and to minimize the word counts, I deleted the description.

To Reviewer #2

I identify the HIV subtype as subtype B in the CASE REPORT section, as follows:

The HIV genotype of the patient was reported to be subtype B by phylogenetic analysis of the *env* gene.

Successful treatment of an AIDS patient with prolonged *Mycobacterium avium* bacteremia, high HIV RNA, HBV infection, Kaposi's sarcoma and cytomegalovirus retinitis.

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Abstract

We report an AIDS patient with a high HIV RNA copy number in the plasma who was successfully treated for prolonged *Mycobacterium avium* bacteremia and other complications.

An HIV-infected patient with high fever, anemia, high alkaline phosphatase, cystic lung lesions, hepatitis B virus infection and Kaposi's sarcoma was referred to our hospital. PCR of the blood revealed *Mycobacterium avium* bacteremia and the time to blood culture positivity was 8 days. The HIV-1 RNA copy number in the plasma was more than ten million copies/ml and the CD4-positive T cell count was 21 cells/μL.

Although the high fever resolved five days after therapy for *Mycobacterium avium* was started, the fever recurred just before starting anti-retroviral therapy (ART) including dolutegravir. The patient experienced repeated but self-limiting bouts of severe inflammation. Mycobacteremia was intermittently detected up to 79 days, suggesting that the recurrent episodes of inflammation were due to the intermittent dissemination of mycobacteria, and that persistent treatment is needed.

Five months after the beginning of ART, the HIV-1 RNA copy number in the plasma was still 28000 copies/ml. An HIV drug-resistance test revealed sensitivity to all anti-retroviral drugs. Eleven months after the initiation of ART, the HIV RNA copy number in the plasma decreased to 45 copies/mL and the CD4-positive T cell count recovered to 205 cells/μL. Our case also suggests that dolutegravir can be effective in cases with prolonged high levels of HIV RNA.

Our findings emphasize that prompt diagnosis and persistent therapy for mycobacterial infection are important for successful treatment.

Key words; disseminated non-tuberculosis mycobacterium, *Mycobacterium avium*, recurrent inflammation, dolutegravir

Introduction

Non-tuberculous mycobacteria (NTM) can cause opportunistic infections in HIV-infected people, especially in patients with a CD4-positive T cell count of less than 50 cells/μL [1]. Despite the introduction of both anti-retroviral therapy (ART) and primary prophylaxis, high mortality is still reported in HIV-infected patients with disseminated NTM (dNTM) infection [2].

We report here the successful treatment of an AIDS patient with prolonged *Mycobacterium avium* bacteremia, high HIV RNA load, HBV infection, and Kaposi's sarcoma, followed by cytomegalovirus retinitis.

Case report (Fig1)

The HIV infected patient, in his early forties, was referred to our hospital because of continuous high fever, anemia, raised ALP, cystic lung lesions and epigastric pain. On the first medical examination, PCR of the blood revealed *Mycobacterium avium* bacteremia and the time to blood-culture positivity was 8 days. On the fourth day, he was admitted to our hospital. Bronchoscopy was carried out on the next day, and culture of the broncho-alveolar lavage fluid showed *Mycobacterium avium* positivity after 5 days.

The HIV-1 RNA copy number in the plasma was more than ten million copies/mL and the CD4-positive T cell count was 21 cells/μL. HBsAg was detected in the serum, and the Hepatitis B virus (HBV) DNA in the serum was 3300 IU/mL. Biopsy of the stomach tumor performed by the referring medical institution showed proliferation of spindle cells with slit-like vasculature and erythrocyte exudation, and immunohistochemical analysis showed staining of CD31, CD34, D2-40, and HHV8, suggesting the presence of Kaposi's sarcoma.

Therapy for *Mycobacterium avium* was started on the fourth day after bronchoscopic examination, with daily Clarithromycin (CAM) 800 mg, Ethambutol (EB) 750 mg, Rifabutin (RFB) 150 mg.

After five days, the high fever resolved, but 3 weeks later, one day before starting ART with Dolutegravir (DTG), Tenofovir (TDF) and Emtricitabine (FTC), a high fever recurred. In view of the side effects of sulfamethoxazole-trimethoprim used for the prophylaxis of pneumocystis pneumonia, atovaquone was administered instead; however, the high fever did not resolve. Because of the high ALP (2658 U/L), we suspected cholangitis: sulbactam/cefoperazone was administered for 5 days, but was not effective, and the dose of RFB was increased to 300 mg/day on the 34th day. *Mycobacterium avium* bacteremia was detected up to 79 days.

The patient experienced recurrent inflammatory episodes with a high ALP, severe anemia and high CRP for six months after the initiation of anti-mycobacterium therapy, but the episodes spontaneously resolved each time without any change in medication except for red blood cell transfusion. Two months after the initiation of ART, the HIV-1 RNA copy number in the plasma was still 280,000 copies/mL. Three months after the initiation of ART, the HIV-1 RNA copy number in the plasma rose to 440,000 copies/mL. At this point, the urine beta-2 microglobulin concentration was 28032 μg/L and the serum creatinine level increased to 1.56 mg/dl. In view of the nephrotoxicity of TDF, TDF/FTC was changed to Abacavir (ABC) and Lamivudine (3TC); Entecavir (ETV) was added because of HBV infection. Five months after the beginning of ART, the HIV-1 RNA copy number in the plasma was still 28,000 copies/ml.

Because the viral decline after the beginning of ART was extremely slow, genotypic and phenotypic assays for drug resistance were carried out, and the DTG concentration in the plasma was measured 24 hours after oral administration of DTG. On the day that samples for resistance testing and DTG concentration was submitted, cytomegalovirus retinitis supervened. Oral administration of valganciclovir (1800 mg/day) was effective, but after 16 days the WBC decreased to 410 cells/μL and serum creatinine level increased from 0.99 mg/dL to 1.29 mg/dL; valganciclovir was stopped and G-CSF 75 μg was administered intracutaneously. In place of oral valganciclovir, intravitreal ganciclovir 1 mg/0.025 mL was administered once weekly or once every two weeks. After the WBC had recovered, oral valganciclovir (450 mg/day) was administered again. Intravitreal ganciclovir or oral valganciclovir (450 mg/day) did not suppress the WBC. Eleven days after we submitted the sample, results of the genotypic drug-resistance assays were received, reporting no resistance mutation in the reverse transcriptase (RT) or integrase (IN) regions. The HIV genotype of the patient was reported to be subtype B by phylogenetic analysis of the *env* gene. Fifty-eight days after we submitted the sample, the DTG concentration in the plasma was reported to be 0.4 μg/mL, and the DTG dose was changed from 50 mg/day to 100 mg/day (50 mg twice a day). Four months after we submitted the sample, the results were received of the phenotypic drug-resistance assays demonstrating susceptibility (0.5 to 0.6-fold) to all clinically available integrase strand transfer inhibitors (INSTI) (both genotypic and phenotypic resistance assays were carried out in Nagoya Medical Center). Finally, 11 months after the initiation of ART, the HIV-1 RNA copy number in the plasma decreased to 45 copies/mL and the CD4 positive T cell count recovered to 205 cells/μL.

Discussion

Even in the era of ART, high mortality is reported in HIV-infected patients with disseminated NTM (dNTM) infection, especially in cases with a high bacterial load [2]. In our case, *Mycobacterium avium* was directly detected in the blood on the first medical examination by PCR, and culture of the blood showed positive growth in 8 days, suggesting a very high mycobacterial load. Therapy for dNTM was soon started, and the high fever resolved after five days, but 3 weeks later, one day before starting ART, a high fever recurred. Initially we considered several possibilities, including insufficient treatment for dNTM, other infections, and side-effects of drugs used for the treatment of dNTM. Because of the patient's low body weight (47.2 kg), we selected initial dose of 150 mg RFB, in view of the increased risk of uveitis with concurrent use of clarithromycin. We suspected insufficient treatment for dNTM and the dose of RFB was increased to 300 mg/day. Even after that, the patient experienced recurrent inflammatory episodes with a high ALP, severe anemia and high CRP, but the episodes spontaneously resolved each time. The pathological mechanism of these recurrent bouts of self-limiting severe inflammation was not clear. However, since *Mycobacterium avium* bacteremia was intermittently detected from blood up to 79 days, intermittent dissemination of bacteria from intestine to the circulation [3] may have occurred.

Cytomegalovirus retinitis began five months following ART. At this time, cytomegalovirus antigenemia was negative, and the CD4-positive T cell count was 78 cells/μL. It is possible that this cytomegalovirus retinitis was a manifestation of immune reconstitution syndrome.

Regarding the ART, we initially selected DTG, FTC/TDF due to HBV co-infection (but not with TAF because of the known interaction of TAF with RFB). However, due to the high levels of urine beta-2 microglobulin (28000 μg/L) and serum creatinine (1.56 mg/dL), we had to change FTC/TDF to 3TC plus ABC, which finally normalized the urine beta-2 microglobulin.

The continued high plasma HIV RNA copy number (280,000 copies/mL after two months, 440,000 copies/mL after three months, and 28,000 copies/mL after five months of ART) led us to examine the drug resistance of HIV and the DTG concentration in the plasma. We were planning to increase the dose of DTG from 50 mg/day to 100 mg/day if the virus was still sensitive to DTG and DTG concentration was low. On the day that sample was submitted for examination, CMV retinitis supervened. While treating CMV retinitis with oral valganciclovir (1800 mg/day) and intravitreal ganciclovir, the serum creatinine level increased from 0.99 mg/dL to 1.29 mg/dL, suggesting the nephrotoxicity of these drugs. We delayed the increase of the dose of DTG, because the result of the serum DTG assay had not been reported at that time and because increasing

the dose of DTG can further increase the creatinine level, making it difficult to measure the renal function. If creatinine level increases, it will complicate the ART regimen, perhaps required a decrease in the dose of 3TC. Fifty-eight days after we submitted the sample for DTG concentration, the DTG concentration was reported as 0.4 μg/mL. This concentration was relatively low, because the median concentration of DTG in a study of 107 Japanese individuals was 1.06 μg/mL [4]. Following receipt of the DTG assay report, we increased the dose of DTG from 50 mg/day to 100 mg/day.

Regarding the etiology of persistent high HIV RNA in the plasma after initiating ART, possible causes include MAC-induced inflammation, a very large HIV reservoir, poor adherence to ART, and pharmacokinetic-pharmacodynamic factors. The adherence to ART was confirmed to be 100% during his hospitalization. After his discharge, the adherence to ART was evaluated by self-report; however, the patient's report of remaining medication at the time of outpatient consultation was completely correct, and the trough value of DTG concentration, which was relatively low but was still in effective concentration, convinced us of his complete adherence to treatment. Because the high HIV RNA plasma concentration persisted until the inflammation due to dNTM abated, it is reasonable to think that the very large HIV reservoir size and MAC-induced inflammation were the main reasons for the persistent viremia.

DTG resistance imposes a high fitness cost on HIV and appeared to maintain the sensitivity of the virus to ART in this patient. In the presence of such a prolonged high HIV RNA plasma concentration, we could have selected darunavir (DRV) with ritonavir instead of DTG, to avoid the emergence of resistance. However, when using DRV, RFB should be administered 300 mg 3 times weekly or 150 mg daily. We selected DTG (100 mg/day), to simplify the administration because this patient presented many complications, and it was possible that another opportunistic infection such as a fungal infection might occur. This case suggests that DTG is useful in such situations.

Although the diagnosis of immune reconstitution syndrome should be considered in cases of prolonged inflammation [5], our case suggests that severe recurrent self-limiting inflammation can accompany the treatment of dNTM infection in HIV-infected individuals. Prompt diagnosis and persistent therapy for mycobacterial infection are important for the treatment of dNTM in HIV-infected patients.

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Conflict of Interest: None

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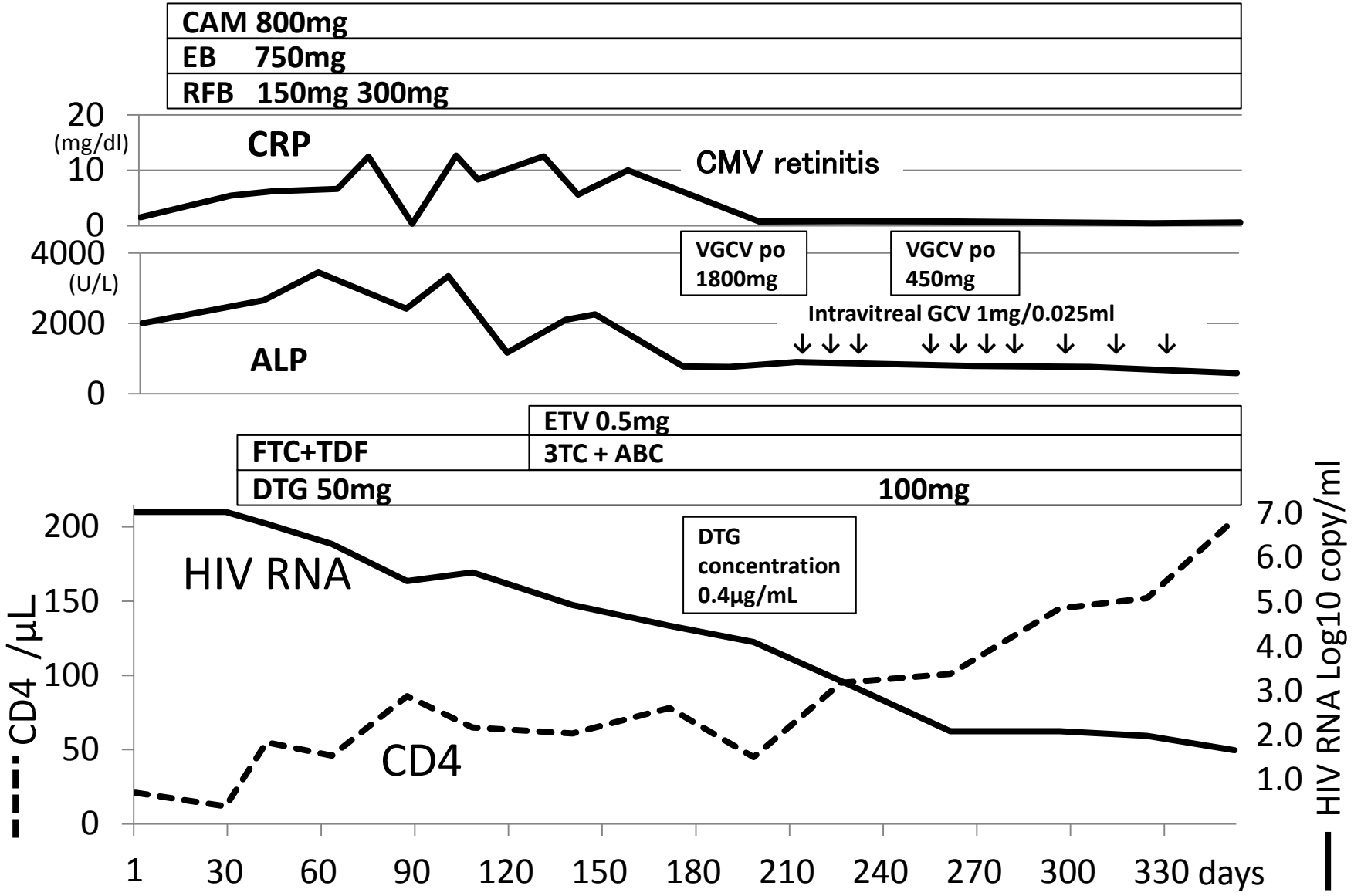
Figure Legends:

Clinical course of disseminated *Mycobacterium avium* bacteremia with HIV infection.

The patient experienced recurrent inflammatory episodes with a high ALP and high CRP, but the episodes spontaneously resolved each time without change in medication.

CAM Clarithromycin, EB Ethambutol, RFB Rifabutin, CRP C reactive protein, ALP alkaline phosphatase, VGCV po Valganciclovir per os, GCV ganciclovir, ETV Entecavir, FTC Emtricitabine, TDF Tenofovir, 3TC Lamivudine, ABC Abacavir, DTG Dolutegravir

Figure


CAM 800mg
EB 750mg
RFB 150mg 300mg
20
(mg/dl)
10
0
CRP
CMV retinitis
4000
(U/L)
2000
0
ALP
VGCV po 1800mg
VGCV po 450mg
Intravitreal GCV 1mg/0.025ml
ETV 0.5mg
FTC+TDF
3TC + ABC
DTG 50mg
100mg
DTG concentration 0.4μg/mL
HIV RNA
CD4
200
150
100
50
0
CD4 /μL
7.0
6.0
5.0
4.0
3.0
2.0
1.0
HIV RNA Log10 copy/ml
1
30
60
90
120
150
180
210
240
270
300
330 days