A 66-year-old man with human immunodeficiency virus (HIV) infection was admitted for treatment of Pneumocystis pneumonia. Upon admission, a tumor mass adjacent to the thoracic descending aorta was revealed on computed tomography. Histology revealed an exudative granuloma with histiocytes packed with numerous acid-fast bacilli. Mycobacterium avium was isolated from the tissue. A genetic examination of the isolates demonstrated this strain to be located in the cluster consisting of strains that cause systemic infection. The patient's baseline CD4 cell count was 9/μL and the HIV-RNA viral load was 43,800 copies/mL. This case suggests the possibility of a localized onset of disseminated M. avium infection.

Key words: HIV, disseminated mycobacteriosis, Mycobacterium avium, immune reconstitution inflammatory syndrome

(Intern Med 51: 3089-3094, 2012)
(DOI: 10.2169/internalmedicine.51.8232)
A 66-year-old man with HIV infection was admitted for treatment of *Pneumocystis* pneumonia (PcP) and further evaluation of other AIDS-related complications. Upon admission, his HIV-RNA level was \(6.18 \times 10^4\) copies/mL and his CD4+ cell count was 4/μL (Fig. 1). Trimethoprim-sulfamethoxazole was administered at 720 mg/day-3,600 mg/day for eight days from admission and then was changed to pentamidine 150 mg/day for the following 13 days (Fig. 1). Prednisolone was also administered at 80 mg/day from day 1 to day 3 and at 40 mg/day from days 4 to 6. Anti-PcP: treatment for *Pneumocystis* pneumonia, ART: antiretroviral therapy, BT: body temperature, CAM: clarithromycin, CT/Ga: computed tomography/gallium-scintigraphy, EB: ethambutol, ESR: erythrocyte sedimentation rate, IRIS: immune-reconstitution inflammatory syndrome, MAC: *Mycobacterium avium* complex, MFLX: moxifloxacin, RAL: raltegravir, RFB: rifabutin, S: steroid (prednisolone), TVD: tenofovir/emtricitabine

**Figure 1.** The clinical course of an AIDS patient diagnosed with disseminated *M. avium* infection. The non-filled red arrow indicates the culture duration. Prednisolone was administered at 80 mg/day from days 1 to 3 and at 40 mg/day from days 4 to 6. Anti-PcP: treatment for *Pneumocystis* pneumonia, ART: antiretroviral therapy, BT: body temperature, CAM: clarithromycin, CT/Ga: computed tomography/gallium-scintigraphy, EB: ethambutol, ESR: erythrocyte sedimentation rate, IRIS: immune-reconstitution inflammatory syndrome, MAC: *Mycobacterium avium* complex, MFLX: moxifloxacin, RAL: raltegravir, RFB: rifabutin, S: steroid (prednisolone), TVD: tenofovir/emtricitabine.

**Case Report**

A 66-year-old man with HIV infection was admitted for treatment of *Pneumocystis* pneumonia (PcP) and further evaluation of other AIDS-related complications. Upon admission, his HIV-RNA level was \(6.18 \times 10^4\) copies/mL and his CD4+ cell count was 4/μL (Fig. 1). Trimethoprim-sulfamethoxazole was administered at 720 mg/day-3,600 mg/day for eight days from admission and then was changed to pentamidine 150 mg/day for the following 13 days (Fig. 1). Prednisolone was also administered at 80 mg/day from day 1 to day 3 and at 40 mg/day from days 4 to 6 (Fig. 1). During a thorough examination for HIV infection, a tumor mass adjacent to the thoracic descending aorta (at the transitional level of the thoracic spine 10) in the mediastinum was revealed on thoracoabdominal computed tomography (CT) (Fig. 2). However, the mass did not show an uptake of gallium-67 on gallium-scintigraphy upon initial investigation (Fig. 3). No other abnormal findings, such as enlarged lymph nodes on CT, were detected. A biopsy was performed on the mass under video-assisted thoracoscopic surgery. The histological characteristics of the mass showed exudative granulomas with histiocytes packed with many acid fast bacilli (AFB) (Fig. 4A, B). We confirmed the presence of AFB with an immunohistochemical assay using a mycobacterium antibody (rabbit polyclonal to *Mycobacterium tuberculosis*, ab 905 with 1/200 dilution, Abcam PLC, Cambridge, UK) (data not shown). Additionally, the histiocytes showed a positive response to an antibody against human CD68 (Fig. 4C). Subsequently, *Mycobacterium avium* was confirmed using polymerase chain reaction (PCR) amplification of the biopsied tissue. The mycobacterial organism was isolated from this tissue, yet all blood cultures remained negative. Therefore, this thoracic mass was considered to have been caused by an *M. avium* infection. The following genetic examination of the isolates with a variable-number tandem-repeat (VNTR) typing method using the *M. avium* tandem repeat (MATR) loci demonstrated this strain to be located in clusters consisting of HIV strains and pig strains that are composed of Mah (Fig. 5). Subsequently, a liquid culture of blood samples obtained on day 14 yielded *M. avium* after seven weeks of culture. In addition, a blood sample taken on day 43 yielded mycobacteria after three weeks of culture (Fig. 1). Anti-mycobacterial therapy began with the administration of clarithromycin (800 mg/day) and ethambutol (750 mg/day) combined with rifabutin [RFB (300 mg/day)] on day 44 according to the guidelines (8). During the administration of the anti-mycobacterial therapy, the administration of RFB was stopped at the onset of anorexia on day 60 and moxifloxacin (MFLX) was administered at 400 mg/day as an alternative. However, MFLX was again changed to RFB at 150 mg/day on day 65 following an improvement in the patient’s anorexia. The patient’s clinical symptoms and the radiographic findings gradually improved following this treatment. After anti-mycobacterial chemotherapy was administered for three weeks, antiretroviral therapy (ART), consisting of tenofovir/emtricitabine (TVD) and raltegravir (RAL), was initiated. Before treatment, the patient’s CD4+ cell count was 9/μL and the
HIV-RNA viral load was 43,800 copies/mL. The onset of fever and elevations in the levels of inflammatory markers were observed 25 days post-ART initiation (92 days in the hospital) (Fig. 1). The previous thoracic episode of *M. avium* infection was exacerbated and an enlarged mass with an uptake of gallium was confirmed on a thoracic CT image and gallium scintigraphy (Figs. 2, 3). At that time, the CD4+ cell count was 11/μL and the HIV-RNA viral load was 40 copies/mL. We considered this event to be an episode of immune reconstitution inflammatory syndrome (IRIS). Thereafter, a mild enlargement of both sub-clavicular lymph nodes was confirmed. The lesions gradually improved without an interruption of ART or anti-mycobacterial therapy. The previous CD4+ cell count increased to 35/μL and the HIV-RNA viral load was maintained below a detectable quantity. The patient’s clinical status remained stable, and he was therefore discharged after 117 days in the hospital. A lymphadenopathy adjacent to the thoracic descending aorta remains, and swollen lymph nodes in the para-aortic region became apparent approximately 13 months post-discharge. The CD4 cell count has been closely monitored since discharge and has remained under 50/μL. Additionally, the HIV-RNA level
The present patient with advanced HIV disease developed an isolated lesion with bacteremia of *M. avium* prior to the initiation of ART. The mechanisms underlying the formation of isolated lesions have not yet been previously discussed. However, transient bacteremia caused by *M. avium* has been previously reported (9). Aberg et al. (2002) suggested that localized mycobacterial infections can occur with intermittent bacteremia before disseminated seeding to other organs (10). Furthermore, after evaluating autopsy cases, Torigian et al. (1996) concluded that detectable histological involvement is related to the duration of bacteremia (3). In addition, mycobacterial lesions in the abdominal lymph nodes of patients with disseminated MAC infection are not always detectable. Nyberg et al. reported that mycobacterial abdominal lymphatic lesions were detected in 14 of 17 cases of disseminated MAC infection (11). These findings suggest that the isolated lesion observed in this case was possibly a consequence of transient bacteremia occurring prior to antimycobacterial treatment.

In the present case, aggregated histiocytes with many AFB and moderate amounts of lymphocytes were detected in the mediastinal lymph nodes. The presence of unorganized granulomas composed of foamy histiocytes packed with numerous AFB has been reported to represent the typical histological characteristics of disseminated lesions caused by *M. avium* infection (3, 12). In contrast, previous studies have shown that most localized pulmonary lesions developing after the initiation of ART display organized granulomas with scarce AFB (6). Therefore, the histological findings in the present case were compatible with those of disseminated MAC disease rather than those of typical lesions. However, the histological characteristics of localized lesions before the initiation of ART have not yet been systematically studied. In addition, it has been reported that non-caseating granulomas with numerous AFB are observed in cases of MAC-related IRIS (6). Therefore, we cannot conclude that this case was a consequence of systemic infection based on the histological characteristics alone.

According to previous genetic analyses of clinical *M. avium* strains isolated in Japan, the strains can be divided into two main clusters using MATR-VNTR (13). When we added this patient’s strain to a part of the dendrogram, this strain fit into the cluster composed of pig strains and HIV strains. Since Mah strains isolated from the blood of HIV patients have been reported to result in highly infective enterocytes (14-16), the clinical strains that cause systemic infection might thus have strong infectivity for enterocytes (17). In addition, Ichikawa et al. (2009) reported that the insertion sequence IS*Mah*6 is related to the pathogenicity of Mah, and IS*Mab*6 is frequently found in strains that cause pulmonary infections in HIV-negative patients, unlike strains that cause systemic infections in HIV-positive patients (18). These studies suggest that the phenotypic characteristics differ between strains that cause pulmonary infections and strains that cause systemic infections. Using a MATR-VNTR analysis, the strain isolated from this patient was classified as a strain that causes systemic infection rather than localized pulmonary infection. Therefore, we consider this strain to be a strain that causes dissemination as a consequence of intestinal mucosa invasion.

In the present case, the reactivation of the mediastinal lesion occurred after the initiation of ART. This clinical condition was compatible with the definition of IRIS (5). However, the mechanisms underlying IRIS have not yet been fully determined. In a previously reported case, it was demonstrated that *M. avium* was isolated from the patient’s sputum before the initiation of ART while the patient was asymptomatic, and IRIS-related hilar lymphadenopathy subsequently occurred without bacteremia after the initiation of ART.
ART (6). Additionally, the strain isolated from a case of pulmonary MAC-related IRIS without bacteremia that we previously reported (19) was classified into the cluster composed of strains that cause localized pulmonary infection in HIV-negative patients (Fig. 5). It has also been demonstrated that, in patients with prior disseminated MAC diseases, the enlargement of the abdominal lymph nodes is frequently observed with or without enlarged thoracic lymph nodes in MAC-related IRIS (5). Therefore, we should consider two transmission mechanisms in HIV-positive patients: the IRIS-related infectious focus that is formed locally as the result of infection through the respiratory tract and the infectious focus that is formed locally and/or systematically due to prior systemic dissemination. In the present case, since an enlargement of the mediastinal lymph nodes was observed without extrathoracic involvement, extension to the mediastinal lymph nodes may have been achieved through a respiratory tract infection. However, the strain isolated from the lesion was determined to be analogous to isolates from pigs that are generally enterically-transmitted rather than those from HIV-negative patients with pulmonary diseases (13). Therefore, although the primary infectious site was un-
known, the lesion in the present case seemed to be formed as a result of a systemic infection.

It has been reported that abnormal accumulations of gallium are observed in patients with disseminated MAC disease or MAC-related IRIS (20, 21). In the present case, although the accumulation of gallium-67 was not observed on initial gallium scintigraphy, a positive reaction was observed at the onset of IRIS. Activated lymphocytes or polymorphonuclear leukocytes may have been responsible for the gallium-67 concentration in the lesion, although the mechanisms underlying the accumulation of gallium in the inflammatory foci are still debatable (22-24). In this patient, prednisolone (80 mg/day for three days followed by 40 mg/day for three days) was used to treat PEP at the time of the first scintigraphy; however, steroids were not administered at the time of the second gallium-scintigraphy. It has been reported that the use of steroids can suppress the gallium uptake (25).

Therefore, we believe that the first gallium scintigraphy showed no-uptake of gallium due to an inhibitory effect induced by steroids.

To the best of our knowledge, this is the first report to speculate a localized onset of disseminated *M. avium* infection based on the histological characteristics and genetic typing of the isolated strain.

The authors state that they have no Conflict of Interest (COI).

References