Case Report

RESPIRATORY AND ENTERAL TRANSEPITHELIAL INFECTIONS OF *MYCOBACTERIUM AVIUM* COMPLEX IN A PATIENT WITH ADVANCED HIV INFECTION

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Abstract Pulmonary manifestation of *Mycobacterium avium* complex (MAC) disease is an unusual event in patients with advanced HIV infection. Here, we present a case of disseminated MAC disease in a 29-year-old acquired immune deficiency syndrome (AIDS) patient that had both pulmonary and enteral involvement. The mycobacteria isolated from the pulmonary and enteral lesions were genetically identical. Based on a dendrogram analysis with variable-number tandem-repeat typing, the isolate appears to cluster with *M.avium* subsp. *avium* and *M.avium* subsp. *paratuberculosis*. Biopsies of both the pulmonary lesion and the enteral lesion were conducted; the resulting histology showed infections of the epithelia, implicating both sites as being the source of the transepithelial infection. The patient was then treated with anti-mycobacterial therapy, and anti-retroviral therapy for the treatment of AIDS was introduced on the 13th day. The patient's general condition improved, so he was discharged on the 69th day. To our knowledge, this is the first case report of a MAC transepithelial infection through the airways in the lung of a patient with advanced human immunodeficiency virus infection. However, the information collected in the present study is insufficient to determine the mechanism by which the enteral lesion developed. Further study will be required to determine whether or not the specificity of the isolates is related with the mechanism of lesion development.

Key words: *Mycobacterium avium* complex, AIDS, Pulmonary involvement

INTRODUCTION

Mycobacterium avium complex (MAC) contains two genetically distinct species: *Mycobacterium intracellulare* and *M. avium*[1]. *M.intracellulare* is more common among immunocompetent individuals. Although *M.avium* also occasionally infects immunocompetent individuals, it typically invades patients with human immunodeficiency virus (HIV) infection[1)2)]. In immunocompetent subjects, pulmonary MAC disease is caused by airborne infection. In contrast, MAC disseminated disease is generally caused through enteral invasion in patients with HIV infection[2)]. Additionally, pulmonary involvement during MAC disease is an unusual event in patients with HIV infection; the percentage of pulmonary involvement is reported to be 0%–22% in these patients[3)~5)]. It is generally thought that these pulmonary lesions are formed following bacteremia[2)]. However, it was previously unknown if airborne infection could occur in patients with advanced HIV infection. In this report, we present a case of disseminated MAC disease in a patient with HIV infection. This case had dual pulmonary involvement and enteral involvement, and both sites were histologically suggested as being the transepithelial infection. This is the first reported case demonstrating diverse infectious routes (airborne and enteral) in the same individual.

CASE REPORT

(1) Clinical presentation

A 29-year-old homosexual man with herpes zoster consulted the ophthalmologic department at the University of the Ryukyus Hospital with the complaint of an unpleasant sensation in his right eye (Fig. 1). Based on the results of an ophthalmologic screening test, cytomegalovirus retinitis was diagnosed, and a subsequent hematological examination detected the presence of anti-HIV antibodies. Based on these findings, he was admitted to our department, the Department of Infectious, Respiratory, and Digestive Medicine. Upon admission, the patient's level of HIV RNA was 1.57×10^5 copies/mL, and his $CD4^+$ T cell count was 7 cells/μL, so he was diagnosed as having AIDS. The patient had a history of sex with men over the last nine years but no history of drug

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abuse. At the initial visit, no clinical findings were observed that suggested liver dysfunction, nor did the patient's medical history include the occurrence of gastroesophageal reflux disease (GERD).

During the examination for HIV infection, a chest x-ray showed a nodular shadow in the lower lung field (Fig. 2A). The subsequent chest computed tomography (CT) scan revealed nodules in the middle lobe, as well as in the lingular lobe (Fig. 2B, C), in addition to a right mediastinal lymphadenopathy (Fig. 2D). The results of positron-emission tomography/thoracic CT showed an accumulation of fluorine-18 deoxyglucose in the mediastinal lymph nodes (Fig. 2E). To further investigate these findings, video-assisted thoracoscopic surgery (VATS) was conducted on the left upper lobe.

An abdominal CT scan revealed a tumor mass adjacent to the abdominal descending aorta and mesenteric artery (Fig. 3A), but no abnormal liver findings were observed on the image. The results of positron-emission tomography/abdominal CT showed an accumulation of fluorine-18 deoxyglucose in the abdominal lymph nodes (Fig. 3B). Esophagogastroduodenoscopy was conducted for further evaluation; the endoscopic examination showed that the color of the duodenum mucosa was faded and the microvilli were destroyed. To investigate the cause of these changes, the lesion was biopsied.

Mycobacteria were isolated from the lung specimen, duodenum specimen, feces, and blood. These bacteria were all genetically identified as *M.avium*, so we diagnosed the patient with disseminated MAC disease (Fig. 1). Clarithromycin, ethambutol, and rifabutin were then administered as antimycobacterial therapy. On the 13th day after introducing antimycobacterial therapy, anti-retroviral therapy with tenofovir, lamivudine, and raltegravir was introduced for the treatment of AIDS. On the 23rd day after the introduction of anti-retroviral therapy, the administration of tenofovir was discontinued due to kidney dysfunction. Abacavir with 3TC was then administered as a replacement for tenofovir, while the lamivudine and raltegravir were administered continuously. The patient's general condition improved, so he was discharged on the 69th day.

(2) Pathological observation

Histological examinations of the specimens obtained by the VATS and duodenum biopsy were conducted. The results from the VATS samples showed an organized proliferative granuloma that was extended along the submucosa of the peripheral bronchiole to the alveoli (Fig. 4A). Additionally, foamy cells with necrosis were observed extensively in the alveolar areas (Fig. 4B), and phagocytized bacilli inside alveolar macrophages were positively stained by anti-mycobacterial antibody (Fig. 5A). The results for a specimen from the duodenum biopsy showed that acid-fast bacilli had invaded into the mucosal epithelial cells and that the lamina propria was filled with histiocytes packed with acid-fast bacilli (Fig. 5B, C and Fig. 6A, B). The histiocytes containing the acid-fast bacilli were positively stained with anti-CD68 antibody (Fig. 6C).

(3) Genetic tests of the isolates

PCR assays detected *M.avium* DNA from fecal, bone marrow, and lung tissue specimens but did not detect *M. avium* DNA in the sputum. Cultures of peripheral blood, bone marrow, feces, urine, and lung tissue each resulted in

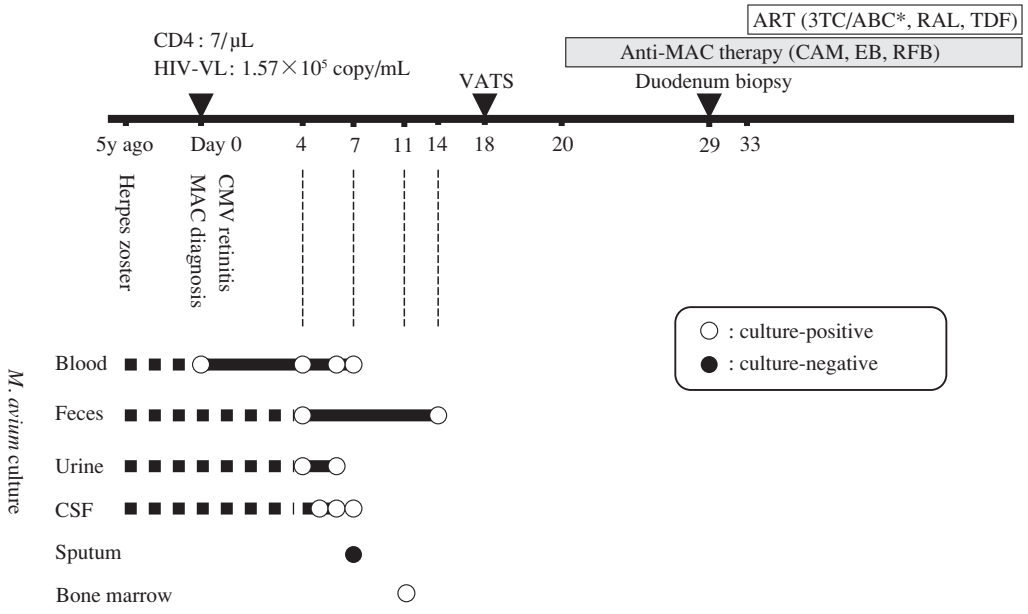


Fig. 1 Clinical course of the patient. Schematic illustrating the clinical course of the patient.
ART: anti-retroviral therapy, ABC: abacavir, CAM: clarithromycin, CMV: cytomegalovirus, CSF: cerebral spinal fluid, EB: ethambutol, MAC: *Mycobacterium avium* complex, RAL: raltegravir, RFB: rifabutin, TDF: tenofovir disoproxil fumarate, VATS: video-assisted thoracic surgery, VL: viral load, 3TC: lamivudine.
*TDF treatment was replaced with ABC treatment due to kidney dysfunction on the 56th day.

the growth of *M.avium*. Genotyping of these isolates was performed using the pulsed-field gel electrophoresis method[6]. Interestingly, the genotyping patterns of all the isolates from this patient were identical (Fig. 7A, B). Dendrogram analyses were conducted on the results of a variable-number tandem-repeat typing using the *M.avium* tandem repeat loci for the isolates from this case along with other reference strains[7]. We found that the isolates from our patient formed a cluster with *M.avium* subsp. *avium* (MAA; K-10) and *M.avium* subsp. *paratuberculosis* (MAP; ATCC25291) (Fig. 8).

DISCUSSION

(1) Primary infection of *M. avium*

Primary complex is the commonly accepted morphological evidence of primary *Mycobacterium tuberculosis* infection. It consists of a small peripheral focus of infection with regional lymph node involvement[8)9)]. MAC also causes respiratory tract infections and contributes to the development of granulomatous lesions in alveolar areas and bronchioles in immunocompetent subjects[6]. In our previous work, we demonstrated that the mechanism involved in the progression of pulmonary *M.avium* infection from a pulmonary focus to the regional lymph nodes occurred via the lymphatic vessels in a case with HIV-infection[6]. In the present case, the pulmonary lesions were localized to the middle lobe and the lingular lobe. The granulomatous lesion was distributed in the submucosa of the

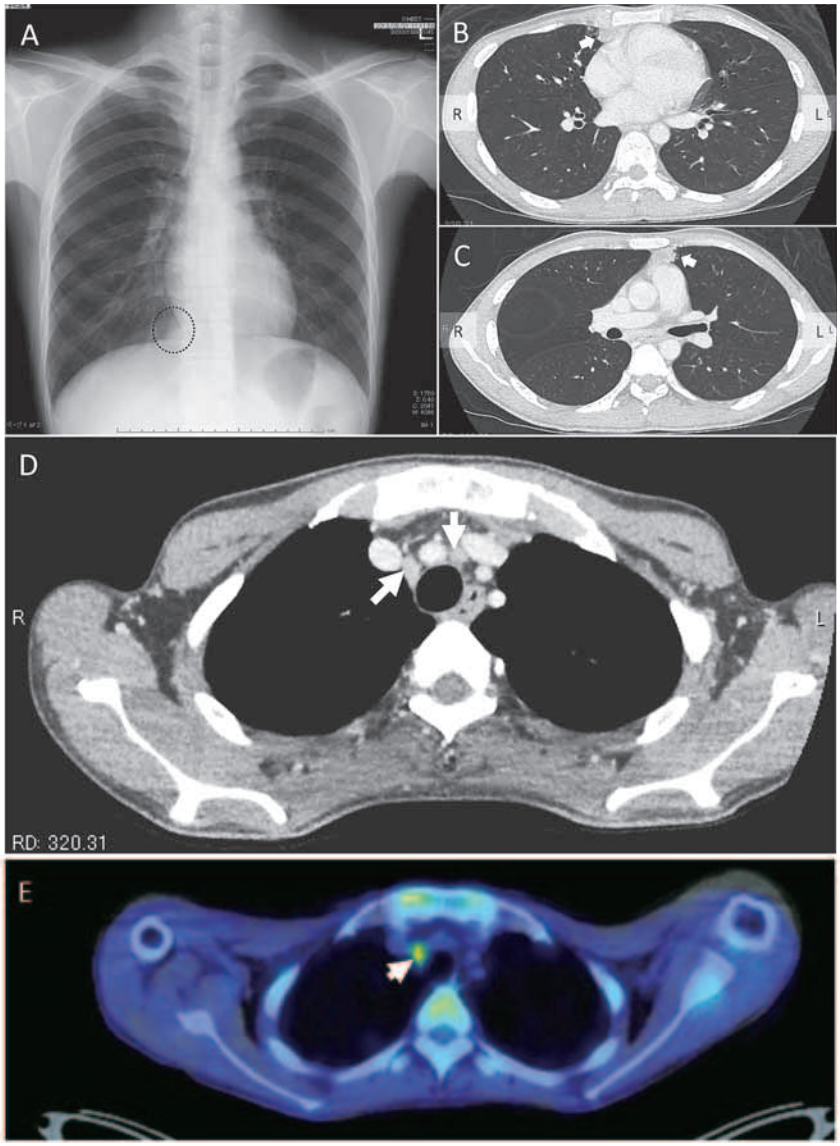


Fig. 2 Radiologic findings of the patient's pulmonary lesions.
A) Image from the patient's chest x-ray. Encircled area indicates a nodular shadow in the lower lung field. B−D) Images from the patient's chest computed tomography scan. Arrows indicate small nodules in the middle lobe (B), a nodule in the lingular lobe (C), or a right mediastinal lymphadenopathy (D). E) Image from the patient's positron-emission tomography/thoracic computed tomography scan. Arrow head indicates accumulations of fluorine-18 deoxyglucose in the right mediastinal lymph nodes.

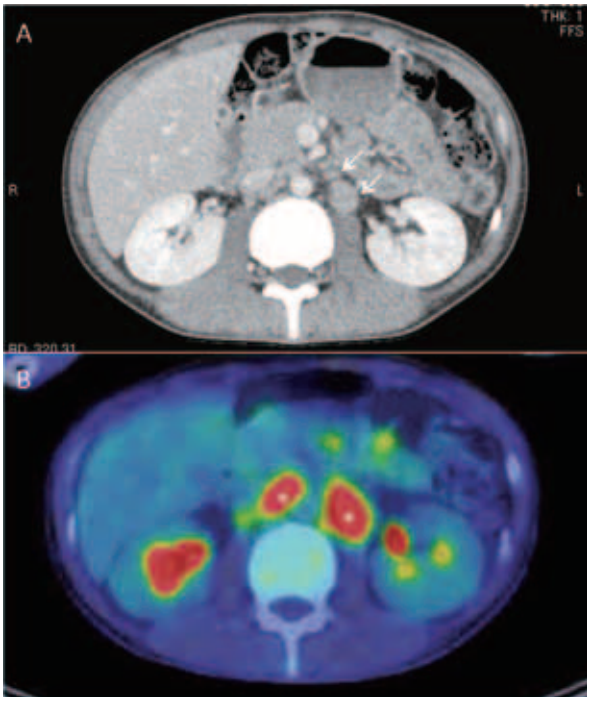
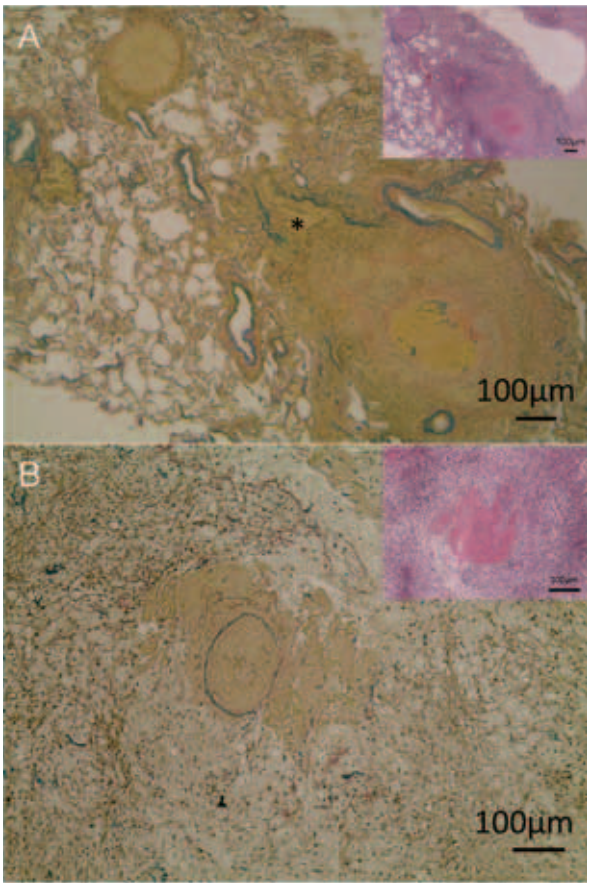


Fig. 3 Radiologic findings of the patient's abdominal lesions. A) Images from the patient's abdominal computed tomography scan. Arrows indicate lymph node swellings around the aorta and mesenteric artery. B) Images from the patient's positron-emission tomography/abdominal computed tomography scan. Asterisks indicate accumulations of fluorine-18 deoxyglucose in the abdominal lymph nodes.



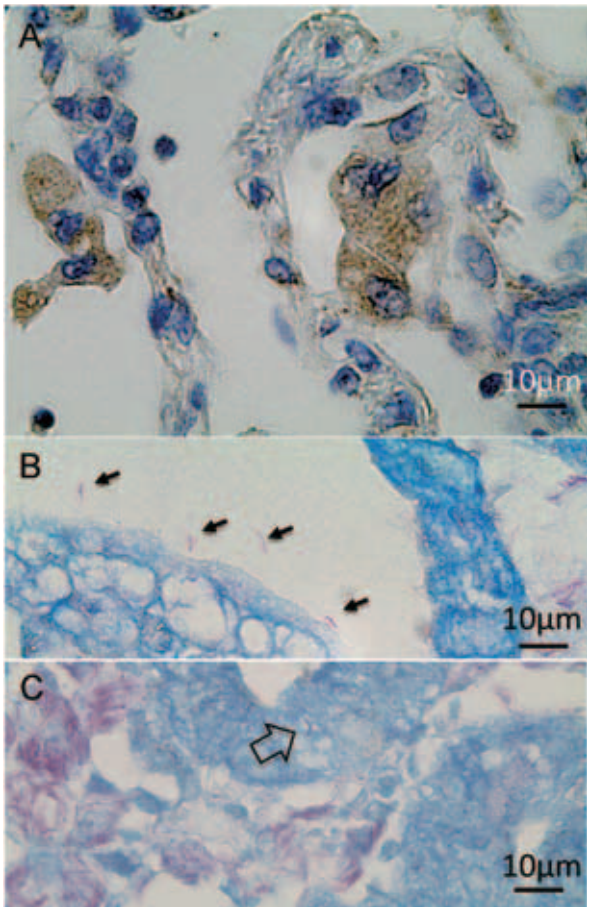


Fig. 5 Transepithelial infection in the lung and the intestine. A) Image of immunohistochemical staining for mycobacterial antigen (color), performed as previously described[6], in a lung sample. B, C) Images of the duodenum lumen (B) and the intestinal epithelium (C) stained with Fite-Faraco staining (color) to mark the acid-fast bacilli (arrows). Scale bars indicate 10 μm.

Fig. 4 Distribution of granulomatous lesions in the lung. Two representative histology images from the video-assisted thoracic surgery sample stained with Victoria Blue van Gieson staining (A, B) and hematoxylin eosin staining (the insets). A) The asterisk in the top image shows an organized proliferative granuloma in the submucosa of the peripheral bronchiole. Green indicates elastic fibers, red indicates collagen fibers, and yellow indicates the cell cytoplasm, muscle fibers, and caseous necrotic matter. B) Abundant foamy cells occupy alveoli around necrotic matter. Scale bars indicate 100 μm.

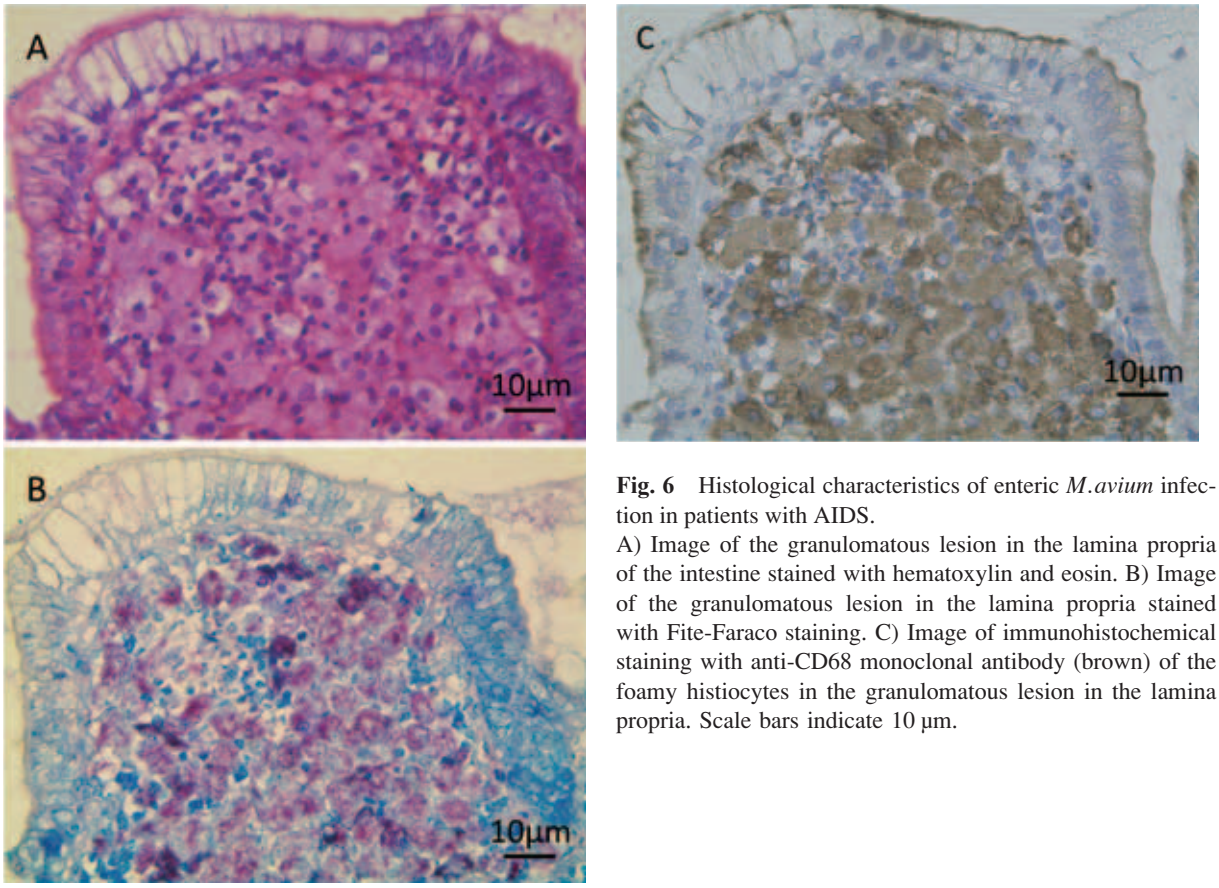


Fig. 6 Histological characteristics of enteric *M.avium* infection in patients with AIDS.
A) Image of the granulomatous lesion in the lamina propria of the intestine stained with hematoxylin and eosin. B) Image of the granulomatous lesion in the lamina propria stained with Fite-Faraco staining. C) Image of immunohistochemical staining with anti-CD68 monoclonal antibody (brown) of the foamy histiocytes in the granulomatous lesion in the lamina propria. Scale bars indicate 10 μm.

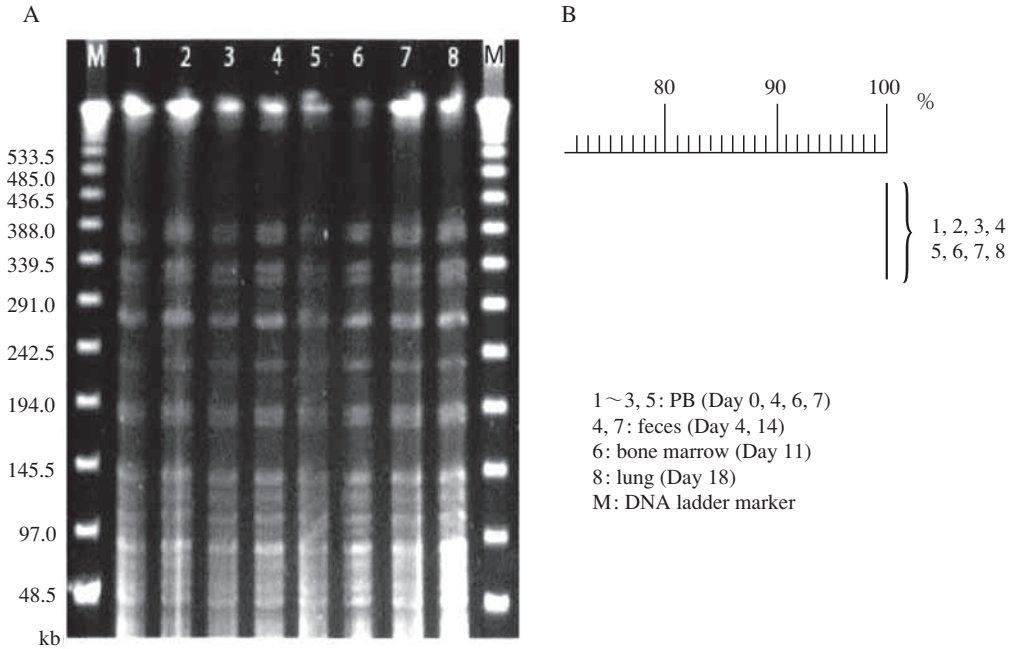


Fig. 7 Pulsed-field gel electrophoresis patterns of isolates from various samples.
The pulsed-field gel electrophoresis pattern of isolates from the peripheral blood, the feces, the bone marrow, and the pulmonary lesions (A) and a schematic diagram showing the differences (B).
PB: peripheral blood.

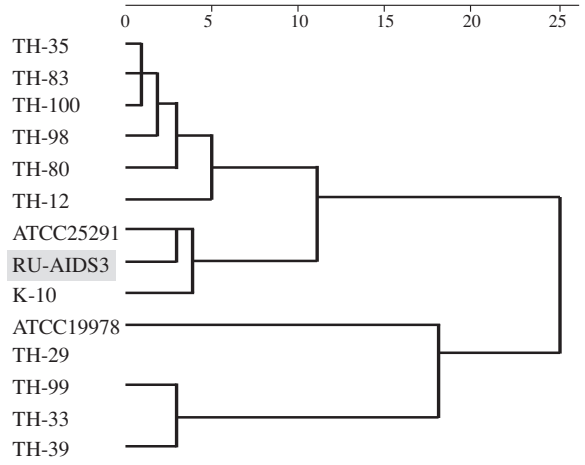


Fig. 8 Dendrogram of isolates from the present case.
A dendrogram caused by the Ward's method and based on the results of *M.avium* tandem repeat -variable number tandem repeat (MATR-VNTR) typing. TH: strainers isolated from patients with pulmonary disease. The MATR-VNTR profile data of TH strains carry a quotation from the study by Inagaki et al.[24]. All of the TH-strains are *M.avium* subsp. *hominissuis*[24]. ATCC25291: *Mycobacterium avium* subsp. *avium*, K-10: *Mycobacterium avium* subsp. *paratuberculosis*.

peripheral bronchiole, and an exudative lesion was observed in the alveolar areas. Additionally, the patient showed mediastinal lymphadenopathy. These findings indicate that this pathological condition is similar to the primary complex of tuberculosis. However, the hematogenous dissemination that typically occurs as multiple well-defined small nodular lesions spread over the entire surface of the affected organ[10)11)] was not observed. Notably, the present case also showed a localized duodenum lesion in the submucosal layer with regional lymphadenopathy. Aggregated histiocytes with acid-fast bacilli were focally distributed in the lamina propria of the duodenum, indicating that the pathogenic organisms had penetrated into the mucosal epithelial cells. These findings may suggest a primary enteral infection of MAC[12)].

(2) Potential mechanisms for the development of the *M.avium* enteral infection.

In the present case, the pulmonary lesions formed a proliferative granuloma, whereas the enteral lesion was an immature granuloma. This suggests that either the pulmonary lesions began developing first or the pulmonary granuloma grew at a faster rate than the enteral granuloma (Fig. 9). Notably, both the pulmonary lesion and the intestinal lesion were still in an active infectious state and were also relatively localized when we observed them. Even in AIDS patients

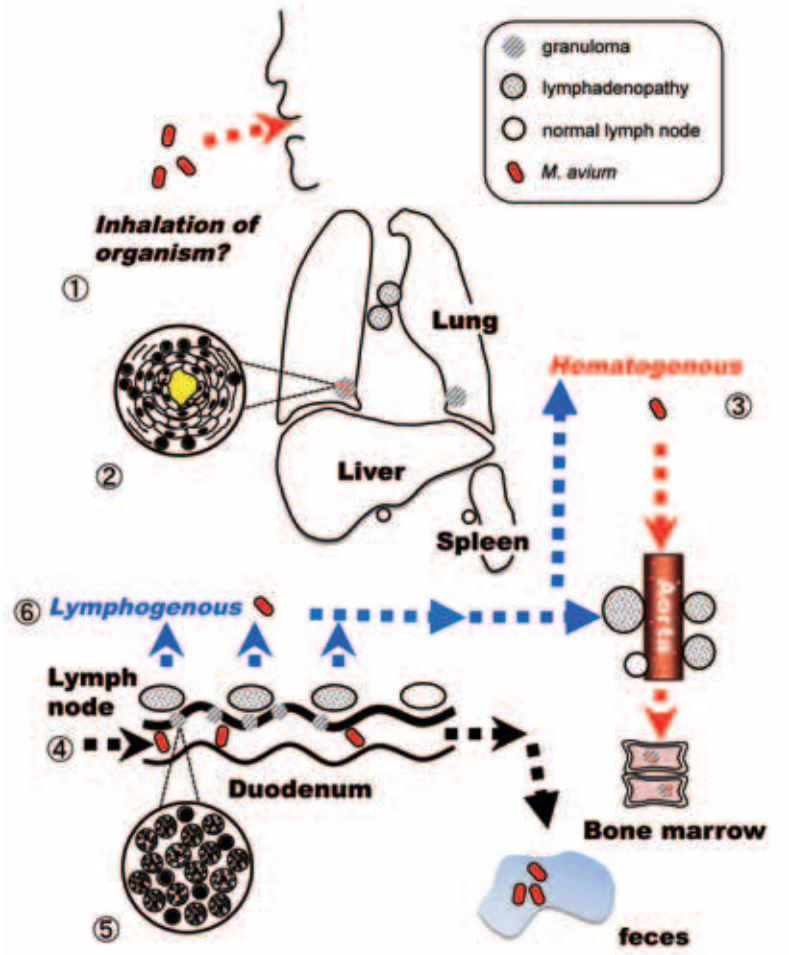


Fig. 9 Proposed mechanism for the dissemination of *Mycobacterium avium* infection in the present case. Airborne infection might first occur (①), then granulomatous lesion formed in the lower lung field (②). Subsequently, mediastinal lymphadenopathy occurred. Then, the organism may spread through the blood circulation to reticuloendothelial organs such as the bone marrow (③). Meanwhile, the organism reaches the intestinal mucosa after ingestion of the organism (④). The organism may then infect epithelial cells and may be transported to mesenteric lymph nodes by phagocytic cells (⑤). Further spread through the lymphatic system to the superior deep lymph nodes may occur (⑥).

receiving highly active antiretroviral therapy (HAART), the gastrointestinal tract, which is a major site for early viral replication and $CD4^+$ T-cell destruction, may be a major viral reservoir of human immunodeficiency virus (HIV)[13]. This suggests that there is a difference in the immune responsiveness into mucosal membranes between the intestine and lung. In light of this difference, despite the lesions in the lung and the intestine being different sizes and maturities when detected, these lesions may have begun forming at similar times. Based on previous work, there is a small chance that the enteral lesion in this case was formed via the swallowing of infected sputum from the pulmonary lesion[14]. Alternately, previous studies have found that GERD can contribute to the development of pulmonary lesions[15][16]; however, the present case did not have history of GERD so this is unlikely to have been the cause of the pulmonary lesions in this case. At present, it is not possible to prove that there was a time lag between the airborne infection and enteral infection of *M.avium* in this case.

(3) Potential portals of entry for the bacteria

Genetically identical strains were isolated from the duodenum, lung, bone marrow, and peripheral blood in the present case. Therefore, hematogenous dissemination must have taken place from either the pulmonary lesions or duodenum lesion (Fig. 9). It is well known that *M.avium* predominantly disseminates via the bowel mucosa to the mesenteric lymph nodes and the superior lymphatic system in patients with advanced AIDS[17][18]. The distribution of lesions in the present case appears to be compatible with this pathogenesis; however, 80% of cases in which the bacteremia originated from the gastrointestinal tract have liver involvement[4], and liver involvement was not clinically observed in the present case.

Mazurek et al. (1997) reported that *M.avium* can be isolated from respiratory secretions before the detection of bacteremia and that the same strain can be recovered latterly from the stool in some cases with advanced HIV-infection[19]. This evidence indicates that pulmonary lesions are developed initially and the respiratory tracts are entry portals from which *M.avium* can disseminate. Interestingly, non-HIV cases with primary or secondary immunodeficiency states often show MAC dissemination with lung involvement[20]~[22]. O'Connell et al. (2012) reported that the characteristic radiographic findings in patients with non-HIV disseminated non-tuberculous mycobacterial disease with lung involvement were miliary nodules, which were diffusely scattered throughout the lung parenchyma without aggregation around the airways[20]. Song et al. (2006) described a healthy pregnant woman with MAC dissemination who presented placenta and pulmonary involvement[21]. Myojo et al. (2003) reported a case who presented multiple osteomyelitis and pulmonary *M. avium* disease with infiltration in the right lower lobe of the lung, with pleural effusion[23]. Notably, none of the patients in these cases had a known underlying immunological disease.

The mechanism of MAC development in an immunocompetent host may be different from that in a patient with an AIDS-related MAC infection[22]. Immunocompromised hosts with comparatively high cellular immunity show relatively restricted MAC infection with bone marrow involvement, but AIDS patients show systemic infection over a relatively wide range in the abdomen[22]. Thus, the present case may have acquired *M.avium* through the airway passage in a stage of AIDS with a relatively higher cellular immunity, and the lung may have been the portal of entry for the bacteria.

(4) Characteristics of the isolates

Based on the results of variable-number tandem-repeat typing using the *M.avium* tandem repeat loci, the isolates from the present case formed a cluster with MAA and MAP. Until now, isolates from AIDS patients have always formed a cluster distinct from the isolates from patients with pulmonary MAC disease or MAA/MAP[24]~[28]. To our knowledge, no *M.avium* subsp. *hominissuis* (MAH) isolated from an AIDS patient have previously formed a cluster with MAA/MAP[25][26]. If there is such a cluster, it is unclear what conclusions can be drawn from its existence.

The infectiveness and pathogenicity of MAP in humans are uncertain[29]. Most mycobacteria isolated from patients with HIV-infection are MAH, but MAA is occasionally observed in HIV-infected patients[30]~[34]. It has been reported that Th-1 cytokine responses are higher in human blood mononuclear cells after *in vitro* stimulation with MAA than they are after stimulation with MAH[34]. MAH-infected pigs had an unvarying level of specific antibodies and showed low cell-mediated immunity, whereas MAA infection induced a significant increase in both types of immune responses in pigs[35]. In addition, MAA also replicates intracellularly to a greater extent than does MAH[36]. Furthermore, the results of restriction fragment length polymorphism for the insertion sequences IS*1245* and IS*901* indicate that MAA and MAH have different genetic patterns[37].

It is not obvious whether or not the findings from these previous studies apply to the isolates from the case presented here because the currently available data do not show if MAP or MAA share genetically homology with the present isolates. Further investigation is needed to determine how the uniqueness in the present case relates to the immunological diversity and/or genetic diversity between the newly identified cluster formed among MAA isolates and the isolates from this case and the conventional clusters that include MAH isolated from AIDS patients.

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Conflicts of interest: None to declare.

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RESPIRATORY AND ENTERAL TRANSEPITHELIAL INFECTIONS OF *MYCOBACTERIUM AVIUM* COMPLEX IN A PATIENT WITH ADVANCED HIV INFECTION

（進行したHIV感染者における*Mycobacterium avium* complexの経気道および経腸感染）

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要旨：進行したHIV感染者の播種性MAC症において，経気道感染は稀な現象である。われわれは29歳のHIV感染者で肺感染と消化器感染を同時に合併した播種性MAC症の1例を経験したので報告する。患者の腸感染病巣と肺感染病巣から分離された抗酸菌は遺伝子学的に同一のものであり，VNTR解析によれば*M.avium* subsp. *avium*および*M.avium* subsp. *paratuberculosis*と同一のクラスターを形成した。病理組織学的所見から両病巣は共に上皮感染を示唆するものであった。すなわち経気道感染および経腸感染が生じたことを意味している。しかし，経腸感染のメカニズムは今回の結果だけからは明らかでない。本報告は，進行したHIV感染者における肺と腸の経上皮感染を病理学的に示した最初の報告である。

キーワーズ：*Mycobacterium avium* complex，エイズ，肺感染