[Case Report]

A Case of Rapid Exacerbation of Pulmonary *Mycobacterium Avium* Complex Infection Mimicking Pulmonary Aspergillosis

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Abstract **:** We herein report a case of pulmonary *Mycobacterium avium* complex (MAC) infection with pulmonary multiple nodules and the "halo sign" on chest computed tomography (CT) in which the patient showed rapid exacerbation seven years after undergoing bone marrow transplantation (BMT). A 68-year-old Japanese female visited our hospital due to a productive cough and dyspnea. She had undergone allogeneic BMT for acute myelocytic leukemia and received both prednisolone (2 mg/day) and cyclosporine (30 mg/day). Chest CT demonstrated no abnormal findings on admission; however, multiple pulmonary nodules and the "halo sign" were detected three weeks later. Although a fungal infection was initially suspected, a bronchoscopic examination revealed pulmonary MAC infection. In the present case, pulmonary MAC infection exhibited rapid progression with unique CT findings. Physicians should consider MAC infection in the differential diagnosis in patients who receive BMT and/or immunosuppressive agents, even if the clinical and radiological findings are atypical of the disease.

Keywords **:** Mycobacterium avium complex, bone marrow transplantation, multiple pulmonary nodules, halo sign.

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Introduction

Nontuberculous mycobacteriosis (NTM) is increasingly being diagnosed worldwide, and, to date, more than 150 species of *Mycobacterium* have been identified [1]. *Mycobacterium avium* complex (MAC) is the most common organism in patients with pulmonary NTM, while pulmonary MAC infection is usually slowly progressive, and affected patients often receive no treatment if their symptoms are trivial [1, 2].

Approximately 20 different mycobacterial species have been reported as causative pathogens of NTM in transplant recipients. In particular, the incidence of NTM after hematopoietic stem cell transplantation (HSCT) ranges from 0.4% to 4.9% [3]. Catheter-related infection followed by pulmonary disease, cutaneous and/or disseminated diseases is the most common manifestation in patients who develop NTM after HSCT [4].

We herein report a case of pulmonary MAC infection that showed rapid appearance and exacerbation within

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three weeks a total of seven years after bone marrow transplantation (BMT) in a patient with unique and characteristic findings on chest computed tomography (CT).

Clinical report

A 68-year-old Japanese female visited our hospital due to a productive cough and dyspnea lasting for a couple of days, as well as a low-grade fever of 37.6ºC. She had received allogeneic BMT as treatment for acute myelocytic leukemia at 61 years of age, followed by prednisolone (2 mg/day) and cyclosporine (30 mg/day) for chronic graft-versus-host disease. She was a never-smoker and had no medical or family history of chronic lung or allergic diseases.

On admission, her blood pressure was 118/72 mmHg, her pulse rate was 96 beats/min, her transcutaneous oxygen saturation was 89% (room air, rest), her body temperature was 36.9ºC and auscultation revealed no adventitious respiratory sounds. The laboratory findings on admission demonstrated a normal peripheral white blood cell count (8,100 /μ*l*), slight elevation of the serum C-reactive protein level (1.39 mg/d*l*) and a slightly decreased serum albumin level (3.6 g/d*l*). The immunoglobulin (Ig) G, IgA and IgM titers were 1,740 (normal range; 800-1,600), 219 (100-350), and 150 (60−250) mg/d*l*, respectively. A chest X-ray (Fig. 1A) and CT scans (Fig. 1D and G) obtained on admission showed no abnormal findings, whereas urinary cultivation identified *Escherichia coli*. A diagnosis of urinary infection was therefore initially considered, and treatment with meropenem at a dose of 1.0 g/day was started. Meropenem was then changed to micafungin sodium (MCFG) at a dose of 100 mg/day seven days after admission due to a possible fungal infection as a result of the patient's immunosuppression, although the β-D glucan titer was negative. However, gradual aggravation of oxygen desaturation was observed without a treatment effect. A second chest CT scan was performed 21 days after admission, which disclosed bilateral multiple pulmonary nodules with the "halo sign" (Fig. 1B, E and H). Pulmonary mycosis, particularly aspergillosis, was suspected, and the administration of amphotericin B (L-AMB) at a dose of 100 mg/day, instead of MCFG, was subsequently initiated 23 days after admission. On the same day, a bronchoalveolar washing specimen was obtained from the right lower lobe using fiberoptic bronchoscopy. Ziehl-Neelsen staining, mycobacterial cultivation and polymerase chain reaction (PCR) of MAC revealed positive findings, while nucleic acid identification of the *Mycobacterium* group identified *M. intracellulare* (Table 1 and Fig. 2). Additionally, expectorated sputum cultivation showed the same results. Based on these findings, the patient was eventually diagnosed with pulmonary MAC infection, and the treatment was changed to combined therapy with clarithromycin, rifampicin and ethambutol. Her clinical symptoms, laboratory data and chest radiological findings were promptly ameliorated (Fig. 1C, F and I), and the results of subsequent sputum mycobacterial cultivation remained negative for four months after the start of the anti-MAC treatment (Table 1).

Table 1. Changes in the clinical course and the results for acid-fast bacilli

	2013/7/24	2013/8/15	2013/8/19	2013/8/26	2013/9/9	2013/12/27
Body temperature	36.9	37.3	37.4	36.7	36.5	36.4
SpO_2	89	88	94	96	92	94
Oxygen content	room air	1*l*	2*l*	2*l*	1*l*	room air
CRP	1.39	2.76	N.A	4.68	1.34	0.37

	2013/7/24	2013/8/15	2013/8/19	2013/8/26	2013/9/9	2013/12/27
Sample	N.A	Bronchial specimen	sputum	sputum	sputum	sputum
Smear		1+ (G2)	± (G1)	2+ (G5)	(−)	(−)
Liquid culture		+ (2w)	+ (2w)	+ (1w)	+ (2w)	− (8w)
Ogawa culture		+ (4w)	+ (4w)	+ (2w)	+ (4w)	− (8w)
		⇧ Bronchofibrotic examination		⇧ Starting of administration (CAM/RFP/EB)		

SpO_2: pulse oximetry saturation, CRP: C-reactive protein, N.A: not analyzed, CAM: clarithromycin, RFP: rifampicin, EB: ethambutol, G: Gaffky scale, w: week

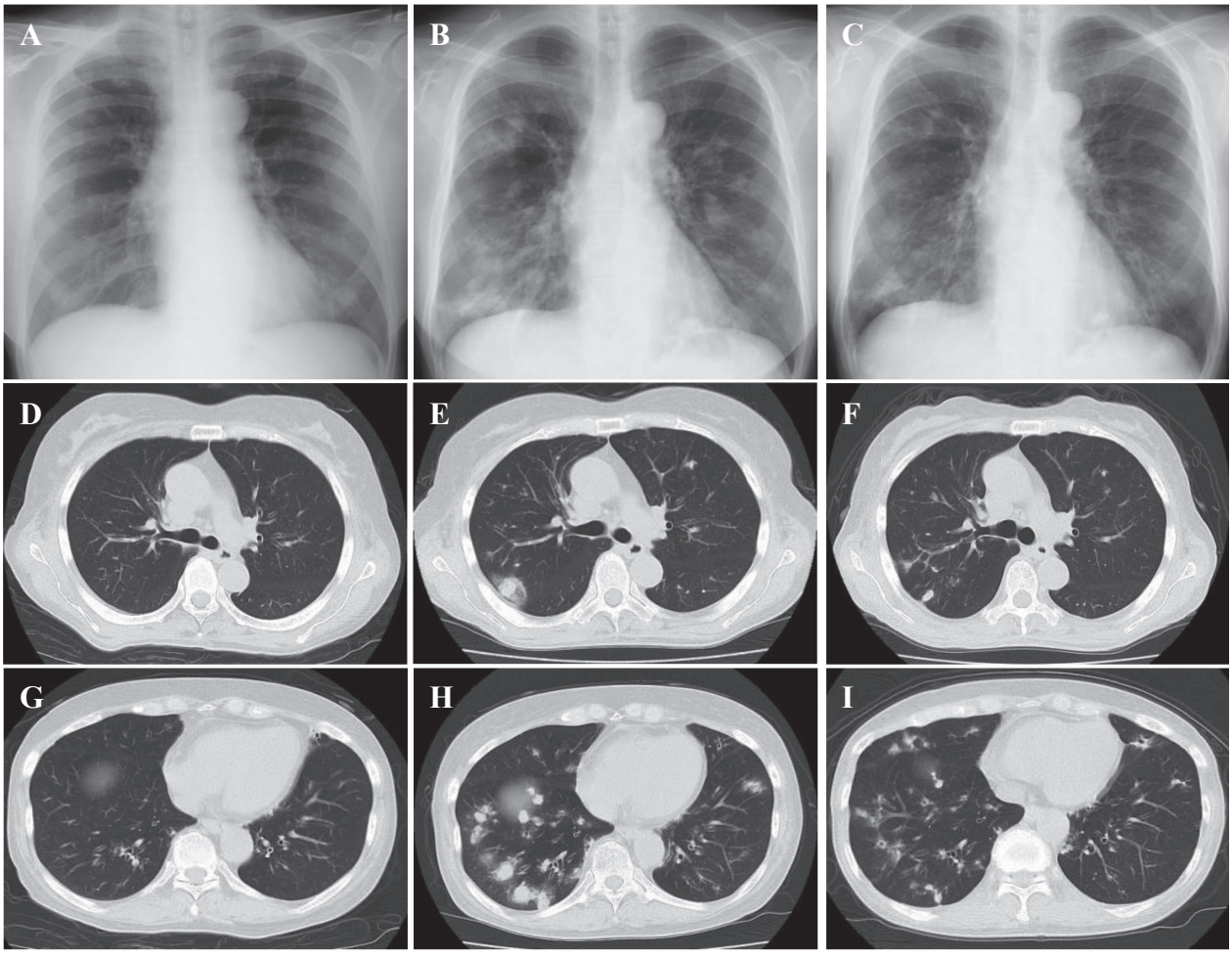

Fig. 1. Clinical course of Chest X-ray and computed tomography. A chest radiograph (A) and chest CT scans (D and G) obtained on admission showed normal findings. Images obtained on day 21 of admission demonstrated multiple bilateral nodules with the halo sign (R>L) (B, E and H). Six months after admission, these findings improved with combination therapy for *Mycobacterium avium* complex infection (C, F and I).

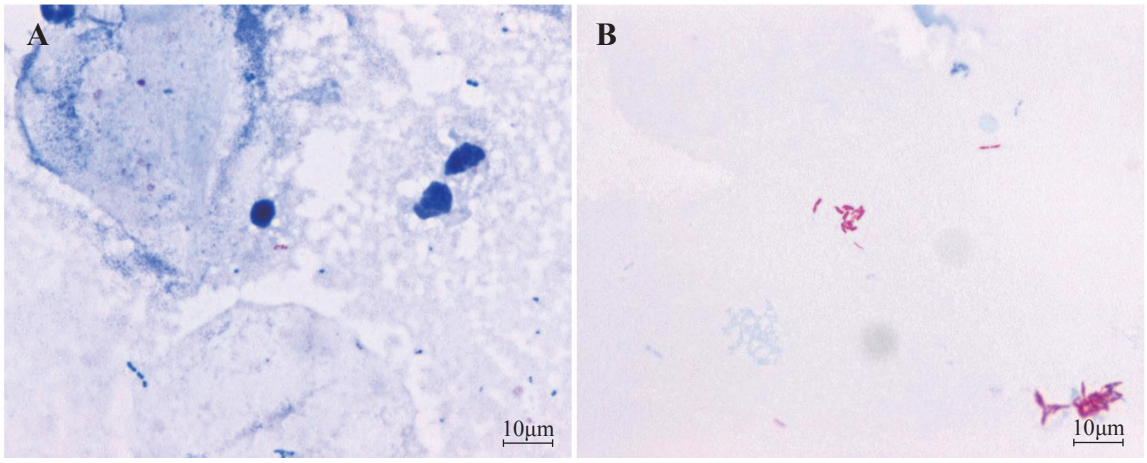

Fig. 2. Ziehl-Neelsen staining. Ziehl-Neelsen staining showed positive findings for acid-fast bacteria in liquid cultures of specimen obtained via bronchoscopy.

Discussion

The current patient suffered from rapid deterioration of pulmonary MAC infection, although the CT findings of bilateral multiple pulmonary nodules with the "halo sign" resembled those of pulmonary mycosis, especially aspergillosis, which usually occurs in immunocompromised hosts. The patient was finally diagnosed with pulmonary MAC infection according to the diagnostic criteria for NTM documented in the 2007 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines [5]. The interesting aspects of the present case are as follows: 1) the rapid exacerbation of pulmonary MAC infection in a patient with no history of chronic lung disease; 2) the presence of multiple nodules and the "halo sign" on chest CT; and 3) the onset of these pulmonary manifestations seven years after BMT.

Pulmonary MAC infection is usually slowly progressive; however, the current patient exhibited rapid aggravation of new areas of patchy bilateral opacity on chest CT within only three weeks. Okubo *et al* reported the rapid appearance of small nodular shadows of MAC infection on chest X-ray six weeks after starting the administration of methotrexate, sulfasalazine and infliximab in a patient with rheumatoid arthritis [2]. Lemense *et al* also reported the development of a nonproductive cough and multiple pulmonary small nodules of MAC infection, that had not been present two years earlier on chest X-ray, three months after initiating treatment with methotrexate for pityriasis rubra pilaris [6]. However, to our knowledge, the rapid progression of pulmonary MAC infection within a short period of time, such as three weeks, is very rare. The current patient's rapid clinical course and chest CT findings were suggestive of bacterial or fungal infection requiring treatment with antibiotic and antifungal therapies, whereas it was difficult to doubt the occurrence of pulmonary MAC infection due to the rapid appearance and exacerbation of the chest X-ray and CT findings after admission.

Pulmonary MAC infection is clinically important in patients with chronic lung diseases and immunocompromised conditions, such as acquired immunodeficiency syndrome (AIDS) [1]. Franquet *et al* reported mycobacterial infections in 24 (*M. tuberculosis*: 17, *M. kansasii*: 5, MAC: 2) of 78 immunocompromised patients, all of which with mycobacterial infections had AIDS [7]. The reported incidence of infection due to NTM ranges from 0.4% to 4.9% among HSCT recipients [4, 8-10], and the most common manifestation of NTM disease in this population is catheter-related infection [4]. Roy *et al* reported documenting pulmonary mycobacterial infections in two of 2,241 (0.09%) BMT recipients. Both of these patients were found to have *M. tuberculosis*, while two of the 2,241 (0.09%) patients, in whom MAC was detected, were identified to have extrapulmonary MAC infection [8]. Au *et al* also demonstrated an incidence of pulmonary NTM after HSCT of 1.16% (seven of 601 cases), with only one case of pulmonary MAC infection (0.17%) [9]. Therefore, pulmonary MAC infection is uncommon in HSCT recipients. With respect to the interval between HSCT and pulmonary NTM infection, Gaviria *et al* reported that pulmonary MAC infection is diagnosed approximately 250 days after HSCT [10], while Minamoto *et al* described a case of pulmonary MAC infection that developed three years after BMT [11]. Nevertheless, the onset of infection more than 100 days after transplantation is uncommon, as the immunological recovery after HSCT is usually achieved within 9-12 months [10]. As seven years had passed after BMT in the present case, the combined influence of BMT and long-term treatment with low-dose corticosteroids (2 mg/day) and cyclosporine may have been a risk factor for MAC infection [12].

Typical chest CT findings of NTM include bronchiectasis, small and large pulmonary nodules, branching centrilobular nodules, bronchial or peribronchial thickening and consolidation [13, 14]. The unique chest CT findings of pulmonary MAC infection observed in the present patient were the detection of multiple pulmonary nodules accompanied by the "halo sign" and ground-glass attenuation surrounding the circumference of the nodules or masses, which were histological findings suggesting the presence of pulmonary infarction and alveolar hemorrhage [15]. It has been reported that the "halo sign" is observed in 47-75% of patients with invasive pulmonary aspergillosis after allogeneic HSCT [15] and that large nodules and the "halo sign" are common findings of fungal pneumonia in patients with a history of BMT [16]. There are

few reports of mycobacterial infection with the "halo sign," and most such cases involved *M. tuberculosis*, with MAC infection being extremely rare [7, 17]. It has been reported that the histological findings in the acute active phase in patients with pulmonary NTM infection showed necrosis and the presence of acute inflammation, neutrophil infiltration [18] and strong inflammation due to the acute progression of progressive pulmonary NTM infection, which might have led to the atypical findings of a "halo sign" on the chest CT in the present patient. Although the incidence of pulmonary MAC infection as a differential diagnosis of the "halo sign" is low, physicians must consider this condition, in addition to pulmonary aspergillosis and other fungal infections, in patients with "halo sign" findings.

It is known that cellular immunity plays an important protective role in MAC infection, and allogeneic HSCT causes an impairment of cellular immunity. Mori *et al* reported that the use of systemic corticosteroids after allogeneic HSCT delays immune reconstitution [19, 20]; therefore, the immunosuppressive state might have contributed to the atypical clinical and radiological appearance and progression in this patient. In addition, this patient showed only pulmonary manifestations of NTM, but Yamazaki *et al* reported a case of NTM infection localized only in the small intestine after allogeneic BMT [20], and physicians should take into account the possibility of localized pulmonary or intestinal MAC infections in patients in an immunosuppressed state after BMT. However, an evaluation of the upper and lower intestinal tracts was not performed in the present study.

The criteria for NTM infection were fulfilled in the present case. Weinstock *et al* reported the survival of patients with definitive NTM infection is significantly better than that associated with probable or possible NTM infection after HSCT [21]. Therefore, it is important to suspect the possibility of NTM infection and make an effort to obtain a precise diagnosis.

In conclusion, although MAC infection usually exhibits a slowly progressive clinical course, the present case involved the rapid appearance and deterioration of pulmonary MAC infection within a short period of time. MAC infection should be considered in the differential diagnosis of clinical signs of infection (fever, coughing, hypoxia, *etc*.) in patients with an immunosuppressive state or history of HSCT, even if the radiological findings are normal or atypical for the disease.

Conflict of Interest

The authors declare that they have no conflict of interest.

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肺アスペルギルス症との鑑別に苦慮し，急性増悪をきたした肺*Mycobacterium avium* complex感染症の1例

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要　　旨：われわれは, 骨髄移植7年後に, 胸部CTにおいてハローサインを伴う多発結節を認め, 急性増悪をきたした, 肺*mycobacterium avium* complex（MAC）感染症の1例を経験したので報告する．症例は68歳, 女性．湿性咳嗽と呼吸困難を主訴に当院を受診した．既往として, 急性骨髄性白血病に対して同種骨髄移植が施行され, プレドニゾロン（2 mg/day）, シクロスポリン（30 mg/day）内服にて通院加療されていた．受診時の胸部CTでは明らかな異常陰影を認めなかったが, 入院3週間後のCTにてハローサインを伴う多発結節影を認めた．画像所見より真菌感染症が疑われたが, 気管支鏡検査の結果, 肺MAC症との診断に至った．本症例は急速な進行と非典型的な画像所見を示したことより, 臨床経過や画像所見がMAC症に非典型的であっても, 骨髄移植後, または, 免疫抑制剤使用後の患者では鑑別疾患の一つとして本疾患を考慮する必要があると考えられた．

キーワード：*mycobacterium avium* complex, 骨髄移植, 多発肺結節, ハローサイン．

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