Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4234-24
Intern Med 64: 1275-1279, 2025
http://internmed.jp

【 CASE REPORT 】

Disseminated Nontuberculous Mycobacterium Infection During Treatment of Multiple Myeloma: A Case Report and Review of the Literature

Takatoshi Kitazawa, Ai Yamamoto, Shin Nakayama, Kyotaro Kawase and Yoshitaka Wakabayashi

Abstract:
Multiple myeloma (MM) is a plasma B-cell malignancy characterized by immune dysfunction, with infection representing a major complication. Bacteria, including *Streptococcus pneumoniae*, are common pathogens in patients with MM, but reports on infections with nontuberculous mycobacteria (NTM) have been limited. We herein report a case of disseminated NTM infection in a patient with MM undergoing treatment with immunomodulatory drugs. At the diagnosis, the patient showed lymphocytopenia and was treated with clarithromycin, rifampicin, and ethambutol; however, culture positivity persisted, and the patient died. The possibility of NTM infection should be considered in cases of unexplained deterioration of the MM patient's general condition.

Key words: disseminated nontuberculous mycobacterium infection, multiple myeloma, immunomodulatory drug, elotuzumab, lymphocytopenia

(Intern Med 64: 1275-1279, 2025)
(DOI: 10.2169/internalmedicine.4234-24)

Introduction

Multiple myeloma (MM) is a plasma cell tumor characterized by the presence of clonal plasma cells that produce monoclonal immunoglobulins. Disease-related complications include extensive skeletal destruction with osteolytic lesions, hypercalcemia, renal impairment, and infections. Infection is the leading cause of death in patients with MM (1).

Gram-positive organisms, including *Streptococcus pneumoniae* and *Staphylococcus aureus* are common causative pathogens of MM (2). However, reports on nontuberculous mycobacterial infections, particularly disseminated nontuberculous mycobacterial infections, are limited.

We herein report a case of disseminated disease with nontuberculous mycobacteria (NTM) in a patient with MM who was receiving treatment with immunomodulatory drugs. We also reviewed the case reports of NTM infections in patients with MM.

Case Report

A 74-year-old man was transferred to our hospital because of a disseminated NTM infection. He had been diagnosed with MM four years earlier at a previous hospital. He had received one course of bortezomib and dexamethasone (VRd), which had been discontinued due to skin rash and liver dysfunction. He had subsequently been treated with 15 courses of lenalidomide and dexamethasone (Rd) followed by 41 courses of elotuzumab, lenalidomide, and dexamethasone (ERd). The immunoglobulin-free L-chain κ/λ ratio remained approximately 3.

Four months before admission, he had developed a fever of 38°C, diarrhea, anorexia, and fatigue. Leukocytopenia (3,900/μL), including mild lymphocytopenia (780/μL) was observed. Outpatient chemotherapy was stopped, and the patient was admitted to the previous hospital for a thorough examination. Colonoscopy revealed no abnormalities. Anemia and leukocytopenia progressed gradually over the three

Department of Medicine, Teikyo University, Japan
Received: June 4, 2024; Accepted: July 21, 2024; Advance Publication by J-STAGE: September 4, 2024
Correspondence to Dr. Takatoshi Kitazawa, tkitazaw@med.teikyo-u.ac.jp

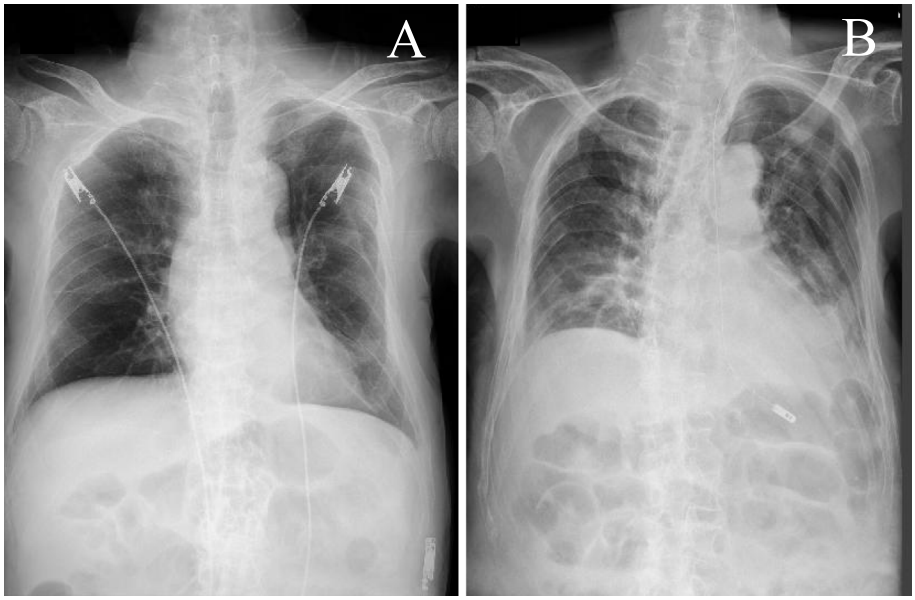

Figure 1. Chest radiographs during the clinical course. A) Chest radiography on admission shows decreased permeability of the left lower lung. B) Chest radiography on day 11 shows infiltration in the left and right lower lung fields.

months prior to admission. A bone marrow sample taken two weeks before admission showed positive results for an acid-fast smear, and polymerase chain reaction (PCR) testing showed positive results for *Mycobacterium avium* complex (MAC). The patient was diagnosed with disseminated NTM infection. Thrombocytopenia and severe lymphocytopenia were also present one week prior to admission.

On admission to our hospital, the patient was conscious and alert, body temperature was 37.5°C, blood pressure was 84/50 mmHg, heart rate was 98 beats/min, respiratory rate was 18 breaths/min, and peripheral oxygen saturation was 98% in room air. The conjunctivae were anemic and non-icteric. Breath sounds were clear. Neither the liver nor the spleen was palpable. No skin lesions were observed, and no superficial lymph nodes were palpated.

Laboratory testing revealed a leukocyte count of 800/μL, lymphocyte count of 80/μL, hemoglobin level of 7.8 g/dL, and platelet count of 114,000/μL, indicating pancytopenia. The serum total protein was 4.1 g/dL, albumin level was 1.6 g/dL, C-reactive protein was 8.55 mg/dL, and procalcitonin levels were 9.96 ng/mL. The CD4-positive lymphocyte count was 18/μL, but negative results were obtained for the anti-human immunodeficiency virus (HIV) antibody. Chest radiography on admission showed decreased permeability of the left lower lung (Fig. 1A). Chest computed tomography revealed a nodule in the dorsal region of the upper lobe of the left lung, consolidation in the lingular segment, and left pleural effusion (Fig. 2A). These findings matched the results from the previous hospitalization two months earlier but were exacerbated compared to the images obtained three years earlier (Fig. 2B).

Blood samples for mycobacterial culture were collected on admission. Treatment was initiated with rifampicin (450 mg/day), ethambutol (750 mg/day), and clarithromycin (800 mg/day). As the patient was found to have been in close contact with a patient with coronavirus disease 2019 on day 5, PCR testing for severe acute respiratory syndrome coronavirus 2 was performed. A positive result was obtained; therefore, 200 mg of intravenous remdesivir was administered, followed by 100 mg/day for 4 days. On day 6, a mycobacterium was isolated from the blood culture taken on admission and later identified as *M. avium* using a matrix-assisted laser desorption ionization Biotyper system on the VITEK-MS V3.2 database (bioMérieux, Tokyo, Japan). Minimum inhibitory concentration tests of clarithromycin using broth microdilution with BrothMIC NTM® (Kyokuto Pharmaceutical Industry, Tokyo, Japan) showed that the values for blood and sputum isolates were both 0.25 μg/mL, indicating susceptibility to clarithromycin. On day 11, chest radiography revealed infiltrative shadows in the right and left lower lung fields. Tazobactam/piperacillin was initiated on suspicion of hospital-acquired pneumonia. On day 15, infiltration was observed in both lungs (Fig. 1B). Despite continued treatment for disseminated MAC infection and hospital-acquired pneumonia, however, the patient showed no improvement in his respiratory condition and died on day 18.

Discussion

Infection is a major complication and the leading cause of death in patients with MM (1). The increased risk of infection is attributable to both multifactorial immunodeficiency caused by the MM itself and treatment regimens in place at various stages of therapy. Causative pathogens vary according to local epidemiology, but Gram-positive organisms ac-

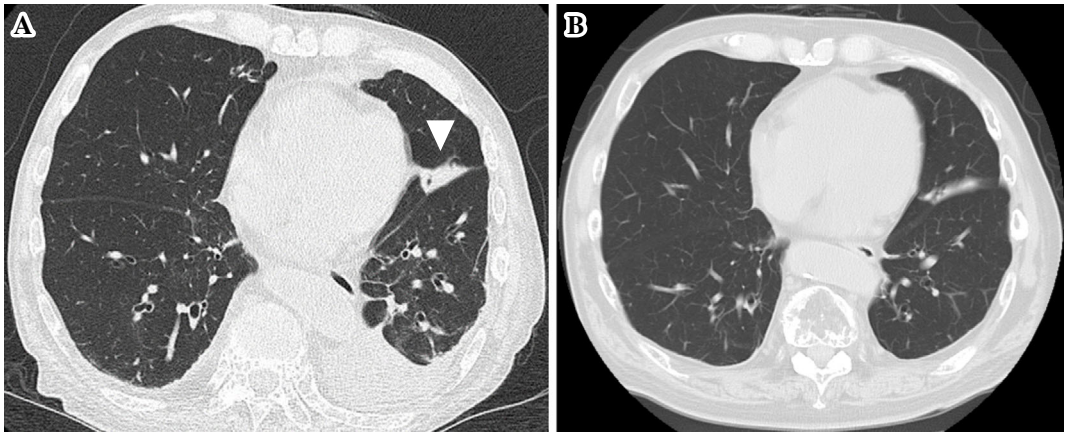

Figure 2. **A) Computed tomography of the chest on admission. Consolidation in the lingular segment (arrowhead) and left pleural effusion are observed. B) Computed tomography of the chest three years before admission. Consolidation in the lingular segment was smaller than that in A.**

Table. **Characteristics of Nontuberculous Mycobacterial Infections in Patients with Multiple Myeloma.**

Ref.	Year	Age (y)/ Sex	Comorbidities'	Treatment for MM	NTM species	Infection site	Samples collected	Treatment for NTM	Outcome
(4)	1998	73M	None	MP	*M. szulgai*	Lung	FNA	INH+IPM/CS+RFP	Cured
(5)	2000	33M	None	Melphalan, PBCST	*M. fortuitum*	Bone (disseminated)	Bone	CFX+AMK+CPFX	Cured
(6)	2005	74M	None	MP	*M. abscessus*	Lung	Sputum	EB+CAM+CPFX	Cured
(7)	2006	43M	n.d.	n.d.	*M. canariasense*	Bloodstream (disseminated)	Blood	CAZ+VCM+AMK	n.d.
(7)	2006	59M	n.d.	n.d.	*M. canariasense*	Bloodstream (disseminated)	Blood	AMK+IPM/CS	n.d.
(8)	2008	79M	COPD, HT	MP	*M. gastri*	Lung	Sputum	n.d.	Dead
(9)	2021	84M	DM, HT, DL	VRd	*M. abscessus*	Disseminated	Sputum, blood	IPM/CS	Dead
(10)	2023	85M	ESRD	n.d.	MAC	Peritoneum (disseminated)	Ascites	EB+AZM+RFP	n.d.
(11)	2023	n.d.	n.d.	n.d.	*M. scrofulaceum*	n.d.	n.d.	n.d.	n.d.
(12)	2024	53M	None	PAd, CHOP, BiRd, PBCST	*M. kansasii*	Intracranial surgical site (disseminated)	Cranial abscess	EB+INH+RFP+CAM	Cured
Present	2024	74M	None	Rd, ERd	MAC	Disseminated	BM, blood, sputum	EB+CAM+RFP	Dead

NTM: nontuberculous mycobacterium, MM: multiple myeloma, COPD: chronic obstructive pulmonary disease, HT: hypertension, DM: diabetes mellitus, DL: dyslipidemia, ESRD: end-stage renal disease, MP: melphalan and prednisolone, PBCST: peripheral blood stem cell transplantation, VRd: bortezomib, lenalidomide and dexamethasone, Rd: lenalidomide and dexamethasone, PAd: bortezomib, doxorubicin and dexamethasone, CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone, BiRd: clarithromycin, lenalidomide and dexamethasone, ERd: elotuzumab, lenalidomide and dexamethasone, MAC: *Mycobacterium avium* complex, FNA: fine-needle aspiration biopsy, BM: bone marrow, INH: isoniazid, IPM/CS: imipenem/cilastatin, RFP: rifampicin, CFX: cefoxitin, AMK: amikacin, CPFX: ciprofloxacin, EB: ethambutol, CAM: clarithromycin, CAZ: ceftazidime, VCM: vancomycin, AZM: azithromycin

count for more than 50% of such infections in most reports early after the diagnosis, with *Streptococcus pneumoniae* and *Staphylococcus aureus* being the most common pathogens. In addition, herpes zoster has become a frequent infection during the first few months of treatment in the era of immunomodulatory drug therapy (2). A retrospective study of mycobacterial infections in adult patients with hematological malignancies found NTM infection in 1 of 291 patients (0.3%) with MM, representing a lower incidence than that seen in other hematological diseases (3). A clinical study of 248 patients with MM who underwent fluorodeoxyglucose positron emission tomography for staging showed infections in 165 cases, with only 1 case of NTM (due to MAC) (4). A literature search for case reports also revealed a limited number of cases, with a PubMed search identifying 11 case reports of NTM infections in patients with MM, including the present case (Table) (4-12). As the causative NTM species, six cases involved rapidly growing mycobacteria (*M. szulgai*, *M. fortuitum*, *M. abscessus* and *M. canariasense*), and five cases involved slow-growing mycobac-

teria (*M. gastri*, MAC, *M. scrofulaceum* and *M. kansasii*). In addition to respiratory tract infections, four cases involved blood infections, one case involved bone infections, and seven cases were classified as disseminated infections. The outcome was cured in reports prior to 2005, but three deaths were described in four known reports after 2008; this adverse change may have been related to the influence of treatment for MM.

Based on this review, NTM infections in MM appear to be rare. However, the prevalence of NTM infections has increased in many countries in recent years (13, 14). Future studies should clarify whether or not NTM infections are increasing among MM-associated diseases.

In the present case, chemotherapy for MM was administered before the diagnosis of disseminated NTM infection. Elotuzumab is an immunomodulatory, humanized immunoglobulin G1 monoclonal antibody that targets signaling lymphocytic activation molecule family member 7 (SLAMF7), exerting antitumor effects through antibody-dependent cytotoxicity. SLAMF7 is highly expressed in malignant plasma cells but not in most normal tissues (15). In a randomized multicenter study of relapsed MM treated with ERd, lymphopenia was identified as a frequent adverse reaction to elotuzumab (21%), but its direct impact is difficult to assess in combination with other drugs (16). In a randomized control trial of elotuzumab combined with other drugs for MM, the overall incidence of infection did not differ markedly between the ERd group (81%) and Rd group (74%), but the incidence of herpes zoster increased (4.1 vs 2.2 episodes/100 person-years, respectively) (17). Our patient also showed grade 4 lymphocytopenia during NTM infection, which may have been a strong risk factor for complications of opportunistic infection associated with cellular immunodeficiency and may have triggered fatal disseminated NTM infection. The cause of pancytopenia in this case was not identified, although bone marrow biopsy findings performed during pancytopenia ruled out MM progression and hemophagocytic syndrome, which has been reported in previous cases (18). We speculate that the progression of disseminated NTM infection may have led to decreased myelopoiesis.

Disseminated infection due to NTM, particularly MAC, occurs primarily in severely immunocompromised patients, such as HIV-infected patients with CD4 lymphocyte counts below 25/μL (19), although disseminated NTM infection is uncommon among immunocompromised individuals not infected with HIV. There have been no reports on the CD4 count in the peripheral blood of patients with MM, although a reduced percentage of CD4 cells in the bone marrow has been reported (20). Disseminated NTM infection may complicate pulmonary or gastrointestinal disease through local multiplication and entry into the bloodstream with seeding of other organs (21). Disseminated NTM infection with non-HIV infection may delay a definitive diagnosis owing to its rarity. In a Taiwanese review of 15 cases of disseminated NTM infection among non-HIV-infected patients, the mean time from initial presentation to the initiation of anti-NTM therapy was 130 days (range, 9 days-17 months) (22). In the present case, the diagnosis was confirmed at the onset of NTM infection, approximately four months prior to the initiation of appropriate treatment. MAC was first isolated from bone marrow aspirate but was also detected in sputum and blood cultures at the time of treatment initiation. Although colonoscopy was performed to investigate the cause of the diarrhea, no culture specimens were collected from the gastrointestinal tract. We speculated that if mycobacterial cultures had been performed earlier, the introduction of appropriate treatment might have been accelerated.

A three-drug regimen of rifampicin, ethambutol, and clarithromycin was selected for the treatment of MAC in this case. For severe cases, the addition of aminoglycosides is advocated in the pulmonary MAC guidelines of international respiratory medicine and infectious disease societies (23). We considered the addition of amikacin during treatment, but the timing of the addition was ultimately missed because renal dysfunction was observed during COVID-19 treatment and antimicrobial therapy for nosocomial pneumonia, while the patient's general condition deteriorated.

In conclusion, we encountered a case of disseminated NTM infection during chemotherapy for MM. Although reports of patients developing disseminated NTM infection during the treatment of MM remain rare, immunomodulators can cause lymphocytopenia, which may exacerbate disseminated NTM infection. In patients showing deterioration of general condition during the treatment of MM, mycobacterial cultures from the respiratory or gastrointestinal tract may lead to an early diagnosis.

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

References

1. Nucci M, Anaissie E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. Clin Infect Dis **49**: 1211-1225, 2009.
2. Teh BW, Harrison SJ, Worth LJ, Spelman T, Thursky KA, Slavin MA. Risks, severity and timing of infections in patients with multiple myeloma: a longitudinal cohort study in the era of immunomodulatory drug therapy. Br J Haematol **171**: 100-108, 2015.
3. Chen CY, Sheng WH, Lai CC, et al. Mycobacterial infections in adult patients with hematological malignancy. Eur J Clin Microbiol Infect Dis **31**: 1059-1066, 2012.
4. Inoue Y, Ishii H, Hirakata Y, Maesaki S, Tomono K, Kohno S. [Pulmonary infection in the emphysematous bulla due to *Mycobacterium szulgai* diagnosed by percutaneus needle aspiration]. Kansenshogaku Zasshi (J Jpn Assoc Infect Dis) **72**: 1236-1241, 1998 (in Japanese).
5. Tejan-Sie SA, Avery RK, Mossad SB. *Mycobacterium fortuitum* osteomyelitis in a peripheral blood stem cell transplant recipient. Scand J Infect Dis **32**: 94-96, 2000.
6. Nishizawa Y, Fujimura M, Tagami A, et al. [Two cases of pulmonary infection by *Mycobacterium abscessus* in which drug susceptibility testing results conflicted with clinical courses]. Nihon Kokyuki Gakkai Zasshi (Ann Jpn Respir Soc) **43**: 241-246, 2005 (in

Japanese).

7. Campos-Herrero MI, García D, Figuerola A, Suárez P, Campo C, García MJ. Bacteremia caused by the novel species *Mycobacterium canariasense*. Eur J Clin Microbiol Infect Dis **25**: 58-60, 2006.
8. Guerra Laso J, Morán Blanco A, Lorenzana de la Varga R, Fernández Natal I. [Cavited pneumonia with *Mycobacterium gastri* positive culture smear]. Rev Clin Esp **208**: 237-238, 2008 (in Spanish).
9. Rodriguez JA, Bonnano C, Khatiwada P, Roa AA, Mayer D, Eckardt PA. COVID-19 coinfection with *Mycobacterium abscessus* in a patient with multiple myeloma. Case Rep Infect Dis **2021**: 8840536, 2021.
10. Ozgur SS, Ansari N, Patel D, Rahman R, Shih R. Rare case of *Mycobacterium Avium* complex peritonitis in a patient with multiple myeloma undergoing peritoneal dialysis. J Community Hosp Intern Med Perspect **14**: 54-56, 2024.
11. Riva E, Garrido D, Villano F, Bove V. Epidemiology and risk factors for the development of infectious complications in newly diagnosed multiple myeloma: a multicenter prospective cohort study in Uruguay. Hematol Transfus Cell Ther. Forthcoming.
12. Sekiguchi E, Kurosawa S, Iketani Y, Yoshimura Y, Nakazato T. Disseminated *Mycobacterium kansasii* infection due to surgical site infection following allogeneic hematopoietic stem cell transplantation: a case report and literature review. Int J Infect Dis 107123, 2024.
13. Winthrop KL, Marras TK, Adjemian J, Zhang H, Wang P, Zhang Q. Incidence and prevalence of nontuberculous mycobacterial lung disease in a large U.S. Managed Care Health Plan, 2008-2015. Ann Am Thorac Soc **17**: 178-185, 2020.
14. Schildkraut JA, Gallagher J, Morimoto K, et al. Epidemiology of nontuberculous mycobacterial pulmonary disease in Europe and Japan by Delphi estimation. Respir Med **173**: 106164, 2020.
15. Hsi ED, Steinle R, Balasa B, et al. CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma. Clin Cancer Res **14**: 2775-2784, 2008.
16. Richardson PG, Jagannath S, Moreau P, et al. Elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma: final phase 2 results from the randomised, open-label, phase 1b-2 dose-escalation study. The Lancet Haematol **2**: e516-e527, 2015.
17. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med **373**: 621-631, 2015.
18. Chou YH, Hsu MS, Sheng WH, Chang SC. Disseminated *Mycobacterium kansasii* infection associated with hemophagocytic syndrome. Int J Infect Dis **14**: e262-e264, 2010.
19. Fordham von Reyn C, Arbeit RD, Tosteson AN, et al. The international epidemiology of disseminated *Mycobacterium avium* complex infection in AIDS. International MAC Study Group. AIDS **10**: 1025-1032, 1996.
20. Redoglia V, Boccadoro M, Battaglio S, Dianzani U, Massaia M, Pileri A. Multiple myeloma: altered CD4/CD8 ratio in bone marrow. Haematologica **75**: 129-131, 1990.
21. Horsburgh CR Jr. The pathophysiology of disseminated *Mycobacterium avium* complex disease in AIDS. J Infect Dis **179 Suppl 3**: S461-S465, 1999.
22. Lai CC, Lee LN, Ding LW, Yu CJ, Hsueh PR, Yang PC. Emergence of disseminated infections due to nontuberculous mycobacteria in non-HIV-infected patients, including immunocompetent and immunocompromised patients in a university hospital in Taiwan. J Infect **53**: 77-84, 2006.
23. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Clin Infect Dis **71**: 905-913, 2020.