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Case Report

Disseminated Nocardiosis Coinfection with Extrapulmonary Tuberculosis in a Patient with Metastatic Thymoma: A Case Report and Literature Review

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Abstract

Patients with metastatic thymoma postintensive chemotherapy and radiotherapy are prone to opportunistic infectious diseases. Disseminated nocardiosis is a rare disease; however, its incidence has increased in recent years due to the growing population of immunocompromised hosts. We present the first report of *Nocardia beijingensis* infection with extrapulmonary tuberculosis coinfection causing muscular and brain abscesses in a patient with metastatic thymoma postintensive chemotherapy and radiotherapy. This case illustrates the possibility of coinfection with two pathogens and the difficulty in establishing a rapid diagnosis. Awareness of opportunistic infections and the early initiation of appropriate antibiotic therapy are important for the treatment of immunocompromised patients with infectious diseases.

Keywords: Nocardiosis, thymoma, tuberculosis

Introduction

Two-third of thymomas are encapsulated and benign, and most are the round epithelial or spindle cell type.[1] Chemotherapy is considered the standard therapy for metastatic thymoma, followed by radiotherapy or thymectomy. However, intensive chemotherapy or radiotherapy may impair the patient's immunity, which makes them more vulnerable to opportunistic infections. *Nocardia* species belong to the aerobic actinomycetes group of bacteria, which are Gram-positive bacilli with mildly acid-fast features. These saprophytic bacteria are often found in soil and water.[2] Inhalation (pulmonary nocardiosis-pneumonia, lung abscess, and cavitary lesions) or contact with the bacteria via a cut or skin abrasion (cutaneous nocardiosis-cellulitis and ulcers) may result in human infection with *Nocardia*.[3] *Nocardia* species are capable of causing disseminated diseases that can readily enter the bloodstream and spread throughout the body, including the skin, lungs, central nervous system,

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and abdominal organs.[4] Tan *et al*. reported that the major types of nocardial infection were cutaneous (56.6%), pulmonary (33.6%), and disseminated (7.1%) infections. In developing countries, more than 60% of cases of human nocardiosis occur in immunocompromised individuals, and more frequently in males than females.[5] *Nocardia farcinica* or *Nocardia asteroides* have been shown to more frequently cause disseminated nocardial infection.[6] Herein, we report a rare coinfection with disseminated nocardiosis and extrapulmonary tuberculosis in a patient with metastatic thymoma.

Case Report

A 52-year-old male presented with Masaoka stage IV malignant thymoma with metastases of the left lung, pleura, and neck lymph nodes [Figure 1a]. He received six courses of systemic chemotherapy with the ADOC regimen (doxorubicin, cisplatin, vincristine, and cyclophosphamide), followed by radiotherapy to targeted sites of the neck and mediastinal region with 33 fractions, with a total 6600 cGy, and he exhibited a partial treatment response [Figure 1b]. He had been well except for grade 3 radiotherapy-related mucositis and one episode of neutropenia (white blood cell: 2986 per microliter, absolute neutrophil count: 1346/μL). Six weeks later, he experienced a progressive night cough and low-grade fever. He did not have any travel history or contact with drugs, insects, animals, or soil and water during the follow-up period. Chest computed tomography (CT) revealed a residual thymoma, bilateral multiple (newly developed) pulmonary nodules, and pleural effusion [Figure 1c]. Under the impression of thymoma progression, he was admitted to our hospital for salvage chemotherapy.

On admission, he was afebrile with an intermittent dry cough. However, no significant abnormalities were observed during a physical examination, except for the presence of rales in the right lung field. Pulmonary sputum and pleural effusion samples were collected for infectious pathogen screening, which revealed negative findings for *Mycobacterium tuberculosis*, fungi, and viral infections.

Three days later, he complained of a painful sensation at the left thigh, which was accompanied by a regional erythematous change. CT of the left leg demonstrated abscess formation [Figure 2a]. Abscess drainage was subsequently performed, and the pus was collected for pathogen identification, including aerobic and anaerobic bacteria, fungi, and *Mycobacterium tuberculosis* (TB) [Figure 2b]. A polymerase chain reaction and sputum culture reported positive findings of TB pathogen. Empiric antibiotics including piperacillin/tazobactam and fluconazole were administered; however, a tender and swollen cutaneous mass developed at the left shoulder region 7 days later [Figure 2c]. Soft tissue sonography also revealed a deep muscle abscess, and tubal drainage was repeatedly performed. Both abscess culture results yielded *Nocardia beijingensis* infection. In addition, he had a sudden onset of conscious disturbance and delirium. Magnetic resonance imaging (MRI) of the brain revealed a nodular lesion over the left thalamus, which was considered to be focal abscess formation [Figure 3a]. Disseminated *N. beijingensis* infection with muscular and brain abscesses was suspected, and antibiotics including intravenous trimethoprim/sulfamethoxazole (TMP/SM × 10 mg/kg/day) and imipenem were administered. He recovered after the muscle abscess had been drained, and his psychological condition improved after the antibiotic therapy. The brain lesion totally disappeared as revealed in subsequent MRI of the brain [Figure 3b]. Three weeks later, *M. tuberculosis* was cultured from the pus but not from sputum specimens, leading to the diagnosis of *N. beijingensis* infection with coinfection of extrapulmonary TB. Antituberculosis medication including rifampin, isoniazid, pyrazinamide, and ethambutol was prescribed, and he recovered well after completing 6 months of TMP-SMX and 9 months of anti-TB therapy.

Discussion

Two-third of thymomas are encapsulated and benign, and most are round epithelial or spindle cell type.[1,7] The standard therapy for metastatic thymoma is adjuvant chemotherapy and salvage radiotherapy or thymectomy.

Radiation therapy of the mediastinum causes a rapid decrease in circulating B- and T-lymphocytes. While the acute decrease in lymphocytes postprocedure is short lived, most patients show a modest chronic depression in both numbers and function of circulating lymphocytes.[8,9] CD4 + lymphocyte recovery after dose-intense chemotherapy is constrained in adults both by a limited thymic regenerative capacity, as well

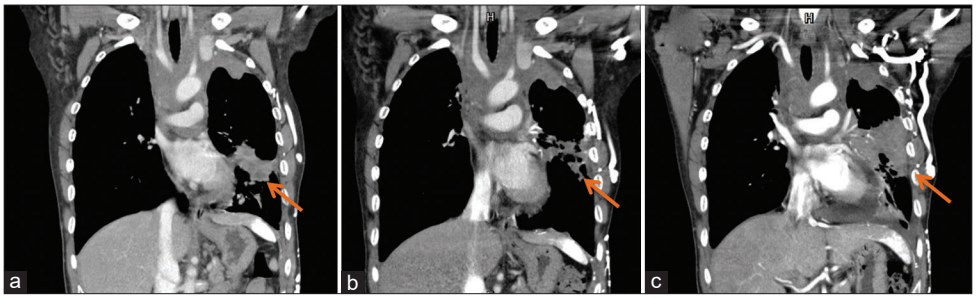

Figure 1: (a) Computed tomography of the chest, before concurrent chemotherapy and radiotherapy. (b) Computed tomography of the chest, during concurrent chemotherapy and radiotherapy. (c) Computed tomography of the chest, after concurrent chemotherapy and radiotherapy

Table 1: Case reports of *Nocardia Beijingensis* infection

Author/year	Region	Patient	Year/ gender	Symptoms	Predisposing factor	Infection sites	Treatment regimen	Outcome
Kageyama *et al*., 2004[25]	Thailand and Japan	NA	70/male	NA	NA	Pulmonary nocardiosis	TMP/SMX, MEPM and levofloxacin	Recovery
Chu *et al*., 2008[26]	China	Systemic lupus erythematosus	13/ female	Fever, dyspnea	High-dose PSL, MMF	Pulmonary nocardiosis with massive lung abscess	IV MEPM for 4 weeks, shifted to oral TMP/ SMX for 1 year	Recovery
Takayanagi *et al*., 2008[27]	Japan	Interstitial pneumonia	60/ female	Dry cough	NA	Pulmonary nocardiosis	TMP/SMX, MEPM and levofloxacin	Died
Ohmori *et al*., 2011[28]	Japan	Prostate cancer with multiple bone metastases	79/male	Refractory skin eruption on left forearm	C/T with docetaxel, PSL	Cutaneous nocardiosis, left forearm	Oral garenoxacin 400 mg/day for 2 weeks	Recovery
Martinaud *et al*., 2011[29]	France	Human immunodeficiency virus infection	47/male	BW loss (5 kg)	HIV (47,833 copies/ml), CD4 (39/mm^3)	Pulmonary nocardiosis with abscess	IMPM and AMKI for 3 weeks, shift to oral TMP/SMX for 3 months	Recovery
Ogawa *et al*., 2011[30]	Japan	Living kidney transplant	48/male	Cough, fever	MMF, PSL, FK506	Pulmonary nocardiosis	IV IMPM 0.5 g/Q12H for 30 days, shifted to ceftriaxone 2 g/ QD for 12 days, shifted to oral minocycline for 3 months	Recovery
Derancourt *et al*., 2012[31]	France	Immunocompetent	42/ female	Small, crusted ulcerations, painless skin lesion	NA	Cutaneous nocardiosis, lower left leg	Oral TMP/ SMX Q4H for 2 months	Recovery
Arunachalam *et al*., 2014[32]	Italy	Renal transplant	47/male	Scratched by a bush. Red slightly painful lesion of right thigh	Cyclosporine, MMF, PSL	Cutaneous nocardiosis, right thigh	Oral ciprofloxacin, garenoxacin (400 mg/day) for 3 weeks	Recovery
Aragaki-Nakahodo *et al*., 2014[33]	USA	Kidney and pancreas transplant	50/ female	Dry cough	MMF, PSL, FK506	Pulmonary nocardiosis	High dose oral TMP/SMX for 6 months	Recovery
Crozier *et al*., 2014[34]	USA	Immunocompetent	48/male	Dry cough, fever, drenching night sweats, BW loss	NA	Pulmonary nocardiosis	IV ceftriaxone for 6 weeks, shifted to oral TMP/SMX for 6 months	Recovery
Rigotti *et al*., 2015[35]	Italy	Immunocompetent	75/male	Fever, abdominal pain, constipation, low back pain	NA	Isolated subfascial lumbar spine nocardiosis	IMPM and AMKI for 2 weeks, shifted to oral TMP/ SMX for 3 weeks	Recovery
Palavutitotai *et al*., 2015[36]	Thailand	Cadaveric renal transplant	58/male	Fever, fatigue, BW loss (7 kg), left groin pain	MMF, PSL, FK506	Psoas muscle abscess	Percutaneous drainage and IV TMP/SMX and IMPM for 2 weeks, shifted to IV TMP/SMX for 4 weeks, shifted to oral TMP/SMX for 4 weeks	Recovery

Contd...

Table 1: Contd...

Author/year	Region	Patient	Year/ gender	Symptoms	Predisposing factor	Infection sites	Treatment regimen	Outcome
Abdel-Rahman *et al*., 2015[37]	Israel	Immunocompetent (breast cancer s/p OP)	55/ female	Fever, cough, hemoptysis, BW loss (5 kg)	NA	Endobronchial pulmonary nocardiosis	IV ceftriaxone for 1 month, shifted to oral TMP-SMX for 3 months	Recovery
Richards *et al*., 2015[38]	Australian	Syphilis, HBV, bony metastases	80/male	Arthralgia, fever, headaches, visual hallucinations, deteriorating left vision	NA	Disseminated nocardiosis (bilateral subretinal abscesses and cerebral abscesses)	IV MEPM for 1 week and shifted to AMKI	Recovery
Sheikh-Taha and Corman, 2017[39]	USA	Multiple sclerosis	50/ female	Cough, dyspnea, fever, BW loss (5 kg)	Alemtuzumab (12 mg/m^2)	Pulmonary nocardiosis with sepsis	IV MEPM 1 g/ q8h for 4 weeks	Recovery

NA: Not available, BW: Body weight, MMF: Mycophenolate mofetil, PSL: Prednisolone, TMP: Trimethoprim, SMX: Sulfamethoxazole, IMPM: Imipenem, AMKI: Amikacin, MEPM: Meropenem

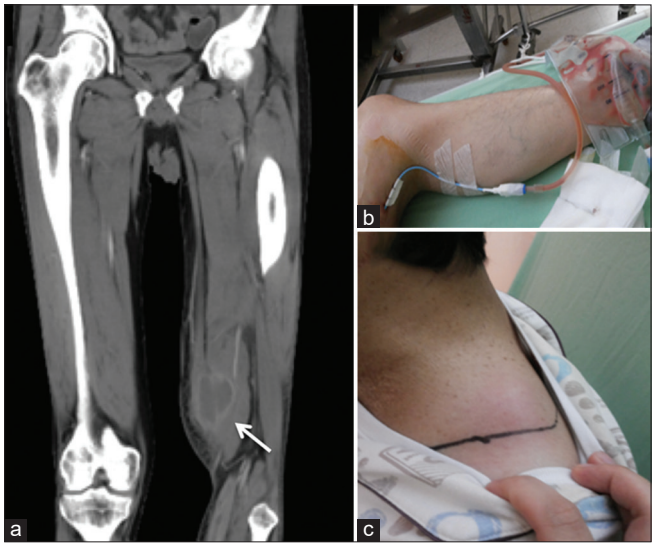

Figure 2: (a) Computed tomography of the lower legs, white arrow demonstrates abscess formation in the left thigh. (b) Tubal drainage of the left thigh abscess. (c) A tender and swollen cutaneous mass in the left shoulder region

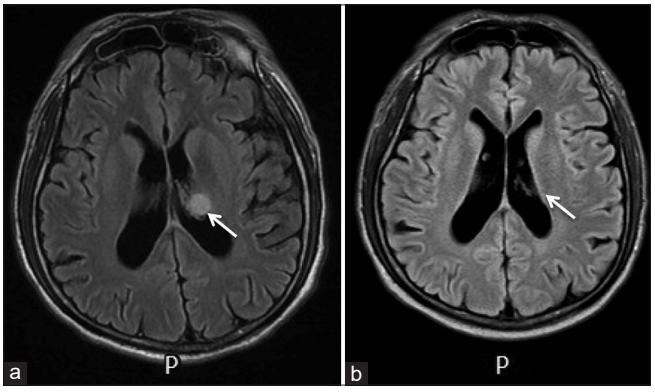

Figure 3: (a) T1-weighted magnetic resonance imaging of the brain showed a nodular lesion over the left thalamus, which was considered to be focal abscess formation. (b) T1-weighted magnetic resonance imaging of the brain demonstrated total resolution of the focal abscess after trimethoprim/sulfamethoxazole treatment

as an increased susceptibility to apoptosis within the expanding peripheral CD4+ population.[10,11] Radiation-induced T-cell deficiency in patients may be irreversible.[12]

Infections which are thought to be due to defects in humoral immunity include XLA and CVID.[13,14] Recurrent sinopulmonary infections are the most commonly reported, often resulting in bronchiectasis.[13,15] Other infections including bone, joint, skin, and central nervous system infections have also been reported.[13,15,16]

Nocardia infection is attributed to suppression of cell-mediated immunity. In Ekrami *et al*., study, the coincidence of pulmonary TB and nocardiosis was 1% for the entire study population and 6.25% among HIV-infected patients.[17] In addition, Alnaum *et al*. reported that 3% of HIV-infected patients with suspected pulmonary TB had pulmonary nocardiosis.[18] Severe disseminated nocardial infections are mostly caused by *N. farcinica* or *N. asteroides*; however *N. beijingensis* is a very rare *Nocardia* species.[5] Furthermore, infections with opportunistic agents such as *Nocardia* have been associated with suppression of cell-mediated immunity.[19]

According to a large cohort study,[20] the incidence of TB is about 0.2 cases per 1000 new cancer diagnoses, and extrapulmonary TB cases account for 15% of all TB infections.[21] Malignant thymomas have an overall incidence of only 0.15 per 100,000 person/years,[22] and thus, disseminated *N. beijingensis* coinfection with extrapulmonary infection in a patient with metastatic thymoma is considered to be extremely rare.

To the best of our knowledge, there are no previous reports on extrapulmonary TB with nocardiosis coinfection. Our patient had received intensive chemotherapy and radiotherapy, and so he may have had a compromised immune status

and acquired rare opportunistic infections. *N. beijingensis* infection is less severe and has a good response to antibiotic therapy. Its treatment includes intravenous carbapenem or TMP/SMX as the first-line therapy, which is maintained with oral TMP/SMX with a duration of 2 weeks to 1 year depending on clinical symptoms and signs.[23,24] In our case, the clinical symptoms were improved after 1 month of antibiotic treatment. The patient completed 6 months of TMP-SMX and 9 months of anti-TB therapy without the recurrence of *N. beijingensis* infection.

We systematically searched PubMed and Embase for published cases of *N. beijingensis* infection, and only 15 case reports were found. Of these cases, 66.7% had underlying immunocompromised diseases or were taking immunosuppression medications. Most of the patients (73.3%) had clinical symptoms including cough, fever, or body weight loss, and others (20%) had cutaneous lesions. The major types of *N. beijingensis* infection were pulmonary nocardiosis (60.0%), cutaneous nocardiosis (20.0%), isolated local infection (13.3%), and disseminated subretinal and cerebral abscess (6.7%). *N. beijingensis* is less severe and has a good response to antibiotic therapy. Most patients received intravenous imipenem, meropenem, amikacin, or TMP/SMX as the first-line therapy and were maintained by oral TMP/SMX with a duration from 2 weeks to 1 years depending on the clinical symptoms and signs [Table 1]. In the present case, the clinical symptoms improved after 1 month of antibiotics treatment. He completed 6 months of TMP-SMX and 9 months of anti-TB therapy without recurrence of *N. beijingensis* infection. In conclusion, the present study is the first report on disseminated *N. beijingensis* infection with the coinfection of extrapulmonary TB in a patient with metastatic thymoma postintensive chemotherapy and radiotherapy. Disseminated nocardiosis is a rare disease; however, its incidence has increased in recent years due to the growing population of immunocompromised hosts. This case illustrates the possibility of coinfection with two pathogens and the difficulty in establishing a rapid diagnosis. Awareness of opportunistic infections and the early initiation of appropriate antibiotic therapy are important for the treatment of immunocompromised patients with infectious diseases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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