Pulmonary *Mycobacterium fortuitum* Infection with Cervical Lymphadenitis in a Patient Carrying Autoantibodies to Interferon-γ

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Abstract

A 74-year-old woman was referred to our hospital for an evaluation of unidentified pneumonia. She gradually developed a high-grade fever with a growing infiltrative shadow on chest CT and an enlarging bilateral cervical mass. She was diagnosed with a pulmonary *Mycobacterium fortuitum* (*M. fortuitum*) infection with cervical lymphadenitis based on the results of an open biopsy of the cervical lymph node. While the patient’s clinical condition resolved almost completely after treatment with multiple antibiotics, neutralizing autoantibodies to interferon-gamma (IFN-γ) were identified in her serum. The progression of disseminated *M. fortuitum* infection in immunocompetent patients may be affected by the presence of autoantibodies to IFN-γ.

Key words: nontuberculous mycobacterium, autoantibodies to interferon-gamma, human immunodeficiency virus


Introduction

*Mycobacterium fortuitum* (*M. fortuitum*) is a rapidly growing nontuberculous mycobacterium (NTM) that has been isolated from various environmental sources (e.g., soil and water) and is an infrequent human pathogen (1-3). The major types of disease caused by *M. fortuitum* include infections of postsurgical wounds, soft tissue, skin and lungs. In general, deep organ involvement and disseminated infections caused by *M. fortuitum*, which manifest both high mortality and morbidity, occur in immunocompromised patients or those with comorbid conditions (4, 5). The clinical and pathologic features of disseminated *M. fortuitum* infection in immunocompetent patients have not been well documented, although such patients usually experience limited infections associated with low mortality (4, 5). We herein report a case of non-human immunodeficiency virus (HIV) associated with disseminated *M. fortuitum* infection with pulmonary and bilateral cervical lymph node involvement in a patient in whom neutralizing autoantibodies to interferon-gamma (IFN-γ) were detected.

Case Report

A 74-year-old woman presented with a six-month history of a dry cough and intermittent low-grade fever. She had never smoked and had an unremarkable family and past medical history. A radiograph of the chest revealed consolidation in the right upper lobe. She was initially treated with oral antibiotics (cefditoren pivoxil and faropenem) for presumed community-acquired pneumonia at a previous hospital; however, her symptoms and radiological findings did not improve. Therefore, she was referred to our hospital in November 2010 for a further evaluation of unidentified pneumonia.

Upon presentation, the patient was afebrile, and her vital signs were normal. The regional lymph nodes were not palpable, and the results of a physical examination were normal. The levels of peripheral white blood cells, including...
The patient’s clinical course with respect to the radiological findings on X-ray and CT scans, the peripheral white blood cell count and C-reactive protein level and the degree of neck lymph node swelling following treatment with multiple antibiotic therapy. WBC: peripheral white blood cell count, CRP: serum C-reactive protein level, IPM/CS: imipenem/cilastatin, AMK: amikacin, LVFX: levofloxacin, CAM: clarithromycin

neutrophils and lymphocytes, as well as platelets, C-reactive protein, HbA1c and other routine biochemical parameters were normal. A chest CT scan revealed an infiltrative shadow and centrilobular small nodules in the right S2 region. Repeated sputum cultures did not detect any specific bacteria or acid-fast bacilli. Ten days of treatment with levofloxacin (LVFX) did not improve the patient’s clinical condition or radiological findings. She gradually developed a high-grade fever with a growing infiltrative shadow on chest CT in addition to an enlarging bilateral cervical mass (Figure). An enhanced CT scan of the neck demonstrated multiple bilateral lesions of lymphadenopathy extending from the high to low internal jugular lymph node chains and around the salivary glands (Figure). Additional laboratory data revealed negative findings for HIV and human T-cell leukemia virus type 1 (HTLV1). Mildly elevated levels of soluble interleukin receptor 2 (767 U/dL) and gamma globulin (IgG, 2,355 mg/dL; IgA, 868 mg/dL) were observed in the serum associated with inflammation presumed to be due to the infection; however, no specific hematological diseases or abnormalities were identified. Neither bone marrow aspiration nor a biopsy were conducted due to the patient’s refusal.

Although bronchoscopy with a transbronchial biopsy of the infiltrative shadow in the right upper lobe was performed, a culture for bacteria, including acid-fast bacilli, was negative (i.e., normal bacterial flora) and no granuloma formation was observed. Therefore, an open biopsy of the right cervical lymph node was undertaken. Beaded bacilli were identified on staining for acid-fast bacilli. On the third hospital day, the culture was positive for acid-fast bacilli, which were identified to be *M. fortuitum* according to the DNA-DNA hybridization method. The histological findings showed a mixed suppurative response with focal neutrophils and monocyte infiltration without granuloma formation. No organisms were detected on Ziehl-Neelsen staining of the lymph node tissue. The patient was diagnosed with pulmonary disease associated with cervical lymphadenitis caused by *M. fortuitum* infection.

Following admission to our hospital, treatment with imipenem/cilastatin (IPM/CS) plus amikacin (AMK) for two weeks and LVFX plus clarithromycin (CAM) for 15 months was initiated. Later, antimicrobial susceptibility tests showed the *M. fortuitum* to be susceptible to CAM (minimum inhibitory concentration (MIC): 0.5 mg/L), LVFX (MIC: 0.5 mg/L), AMK (MIC: 1 mg/L) and IPM/CS (MIC: 1 mg/L). After eight days of therapy, the patient’s high-grade fever and C-reactive protein level improved (Figure). After one month of therapy, the consolidative shadow began to improve. After three months of antibiotics, the cervical adenitis resolved almost completely. This clinical response to antibiotic treatment strongly suggested that the lung lesions were caused by *M. fortuitum* infection, and it may be safely concluded that the patient had a disseminated *M. fortuitum* infection.

Although the present patient seemed to be immunocompetent, the possibility of adult-onset immunodeficiency was suspected. However, no inherited disorders of the immune
system or specific acquired immune deficiencies, such as those due to viral infection (e.g., HIV, HTLV1 or Epstein-Barr virus), hematological disease, malignancy or collagen-vascular disease, were identified in the present case. Additionally, the patient had never used immunosuppressive agents, such as steroids or anti-tumor necrosis factor-alpha drugs. Therefore, the titer of neutralizing anti-IFN-\(\gamma\) auto-antibodies was measured at Niigata University Medical and Dental Hospital six months after treatment. A high titer of autoantibodies to IFN-\(\gamma\) (concentration of anti-IFN-\(\gamma\): 54 E.U., control 18 E.U.; STAT1 phosphorylation index: 47, control 407) was identified in the serum using an enzyme-linked immunosorbent assay (ELISA), although the trigger for the production of anti-IFN-\(\gamma\) autoantibodies remains unidentified. While the antibody titers may decrease in association with the amelioration of disease, it has also been reported that elevated titers can persist for years (6).

**Discussion**

The clinical and pathological features of *M. fortuitum* infection, including the development of cervical lymphadenitis in 11 acquired immune deficiency syndrome (AIDS) patients, are well documented (7). Cervical lymphadenitis, in particular, is the most common initial sign of *M. fortuitum* infection in reported series. On the other hand, a large case series demonstrated that *M. fortuitum* usually causes colonization or transient infection, rather than progressive pulmonary disease, in immunocompetent patients (3). Additionally, in the absence of HIV infection in adult patients, cervical lymphadenitis is rarely caused by *M. fortuitum* infection (8). In contrast to these previous reports, the present patient, who lacked identified pulmonary or immune disease, exhibited a clinical course characterized by prolonged pneumonia leading to cervical lymphadenitis.

Recently, an increasing number of disseminated NTM infections has been reported in Asia (9), especially those involving *Mycobacterium avium complex* (10, 11), in patients expressing autoantibodies to IFN-\(\gamma\). These case reports demonstrated that several adult non-HIV patients with unexplained disseminated NTM infection (e.g., bone marrow, muscle, lymph nodes, pleural effusion) were found to have autoantibodies to IFN-\(\gamma\). In a large study of adult-onset immunodeficiency conducted in Thailand and Taiwan, 42 of 52 adult immunocompetent patients with disseminated and rapidly or slowly growing NTM mycobacterial infections were found to have high titers of anti-IFN-\(\gamma\) autoantibodies (12). Therefore, we suspect that the presence of anti-IFN-\(\gamma\) autoantibodies may have been one mechanism impairing the patient’s mycobacterial defense in the present case. The presence of autoantibodies to IFN-\(\gamma\), whose primary regulatory pathway is interleukin-12-dependent in cell-mediated immunity (13), could have predisposed the patient to disseminated infection with *M. fortuitum*, although one single mechanism, such as the appearance of autoantibodies to IFN-\(\gamma\), cannot fully explain the pathogenesis of adult-onset immunodeficiency.

The diagnostic procedure of an open biopsy of the neck mass was performed in the present case because other investigations did not reveal any specific pathogens. A possible reason as to why the repeated testing of bronchial material, including bronchial lavage fluid, did not provide a diagnosis of pulmonary *M. fortuitum* infection was that isolating and detecting the rapidly growing mycobacterium from the bronchial material was relatively difficult due to the sputum decontamination procedure using NaOH (14) compared to the procedure used for the surgical material, which was not subjected to decontamination. Additionally, since the long-term treatment with multidrug antibacterial therapy for *M. fortuitum*, but not the treatment with antibiotic monotherapy before admission to our hospital, resolved the pulmonary disease and cervical lymphadenitis (Figure), we concluded that the present patient had pulmonary *M. fortuitum* infection with cervical lymphadenitis. The histologic evaluation performed in the present case demonstrated the presence of mixed supplicative abscesses without granuloma formation. The lack of granuloma formation in the disease material observed in the present case also suggests a potentially lower immune response to *M. fortuitum* infection, in which the dysfunction of IFN-\(\gamma\) may have played a role.

In conclusion, we experienced the case of a non-HIV-infected patient who carried autoantibodies to IFN-\(\gamma\) and developed progressive pulmonary disease with cervical lymphadenitis caused by *M. fortuitum* infection. This report indicates that clinicians should consider the presence of autoantibodies to IFN-\(\gamma\) in immunocompetent patients with disseminated *M. fortuitum* infection.

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

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**References**