Central nervous system infection with non-tuberculous mycobacteria: A report of that infection in two patients with AIDS

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1. Introduction

Non-tuberculous mycobacteria (NTM) are organisms that typically live free in the environment in soil, water, milk, food, aerosols, and wild and domestic animals. NTM are Mycobacterium species but do not include the M. tuberculosis complex (M. tuberculosis, M. africanum, M. bovis, M. microti, M. canetti, and M. leprae). However, NTM include Mycobacterium avium complex (MAC), M. kansasii, rapidly growing mycobacteria (RGM), M. flavescent, M. scrofulaceum, M. szulgai, and M. gordonae. NTM can cause a wide variety of infections, including pulmonary, lymphatic, skin, soft tissue, skeletal, and catheter-related infections (1).

NTM infections are relatively common in patients with acquired immune deficiency syndrome (AIDS) and especially is those with a CD4 T lymphocyte cell count < 50 cells/μL. Although NTM can cause serious pulmonary and disseminated infection in some patients (2), central nervous system (CNS) infections with brain lesions are rare. Moreover, there are no reports in China of patients infected with HIV who have developed meningitis due to NTM.
and urinary retention occurred. Consequently, a lumbar puncture was performed again on the 6th day after admission. The results of CSF analysis are shown in Table 1. Based on the results of CSF analysis, tubercular meningitis was diagnosed again: low glucose levels, low chlorine levels, and smears positive for acid-fast bacilli. However, T-SPOT.TB test results were negative, suggesting the infection was not tuberculosis. The same anti-tuberculosis regimen was maintained. On the 14th day after admission, muscle strength is the patient's lower limbs was grade 0. The patient lost confidence in the treatment and voluntarily discharged himself from the hospital.

Nine days after discharge, the first CSF culture revealed NTM. The patient's family was informed of the results so that the patient could receive anti-NTM treatment rather than anti-tuberculosis treatment. Unfortunately, the patient had died 7 days after discharge.

Table 1. Results of laboratory tests of blood and CSF from two patients

| Sample                  | Test                                                                 | Case 1  | Case 2  |
|-------------------------|-----------------------------------------------------------------------|---------|---------|
| Blood                   | Glucose (mmol/L) (the same time as the 1st lumbar puncture)           | 8.36    | 4.9     |
|                         | CD4 count (/μL)                                                       | 2       | 4       |
|                         | CD8 count (/μL)                                                       | 75      | 122     |
|                         | T-SPOT.TB                                                             | N       | NA      |
| CSF                     | Pressure (mmH₂O)                                                      | 150     | 160     |
| The 1st lumbar puncture | Total leukocyte count (/μL)                                           | 124     | 2       |
|                         | Multinucleated cells (%)                                             | 90      | NA      |
|                         | Lymphocytes (%)                                                       | 10      | NA      |
|                         | Pandy test                                                           | WP      | N       |
|                         | Chloride (mmol/L)                                                    | 113     | 116     |
|                         | Glucose (mmol/L)                                                     | 2.15    | 2.02    |
|                         | Protein (mg/L)                                                       | 428     | 314     |
| Blood                   | Glucose (mmol/L) (the same time as the 2nd lumbar puncture)           | 6.67    | 5.54    |
| CSF                     | Pressure (mmH₂O)                                                      | 55      | 120     |
| The 2nd lumbar puncture | Total leukocyte count (/μL)                                           | 300     | 24      |
|                         | Multinucleated cells (%)                                             | 90      | NA      |
|                         | Lymphocytes (%)                                                       | 10      | NA      |
|                         | Pandy test                                                           | P       | WP      |
|                         | Chloride (mmol/L)                                                    | 110     | 118     |
|                         | Glucose (mmol/L)                                                     | 1.99    | 2.54    |
|                         | Protein (mg/L)                                                       | 2314    | 514     |

NA, not available; N, negative; P, positive; WP, weakly positive.
2.2. Case 2

A 27-year-old man had symptoms of a dry cough and fever for 6 months and progressive dyspnea for 10 days that went without treatment prior to admission. The man was in a coma for 4 days and he was taken to another hospital. Chest CT scans revealed extensive interstitial hyperplasia, fibrosis, and exudate in both lungs. There were nodular shadows from the posterior segment in the upper lobe of the right lung and as well as pleural thickening. Brain CT scans revealed atrophied frontal and temporal lobes. The preliminary diagnosis was a lung infection. The therapeutic regimen included tracheal intubation with a ventilator, imipenem and cilastatin sodium, norvancomycin, azithromycin, sulfamethoxazole (SMZ), caspofungin, and nutritional support.

The man was admitted to this Hospital because he tested positive for HIV. The preliminary diagnoses were AIDS, a lung infection, and type 1 respiratory failure.

Because the pathogenic microorganism had not been identified, medications included SMZ and caspofungin for Pneumocystis carinii, the anti-viral oseltamivir, norvancomycin for Gram-positive bacteria, imipenem and cilastatin sodium for Gram-negative bacteria, azithromycin for mycoplasma, and gamma globulin to improve immunity.

In the first 2 days after admission, CD4 T and CD8 T cell counts were determined (Table 1). On the 3rd day after admission, the patient recovered consciousness. An acid-fast bacilli sputum smear was positive, so tuberculosis infection was considered. Isoniazid, rifampicin, ethambutol, and pyrazinamide were administered as anti-tuberculosis therapy. On the 8th day after admission, anti-retroviral treatment (ART) was begun with tenofovir, lamivudine, and efavirenz. A bedside chest radiograph revealed diffuse inflammation in the lungs with no significant changes. Therefore, tigecycline and amikacin were substituted for norvancomycin. A tracheotomy was performed and the patient was placed on a ventilator. On the 10th day after admission, results of a sputum culture revealed Acinetobacter baumannii that was highly drug-resistant. On the 12th day after admission, HIV RNA was 102,000.00 copies/mL. However, caspofungin treatment was sufficient and thus stopped. Fluconazole was used as an anti-fungal agent. Seventeen days after admission, the lung lesions improved and voriconazole was stopped. On the 57th day after admission, the patient developed dysphagia, which may have been due to encephalopathy associated with HIV infection. Lopinavir and ritonavir tablets, which readily penetrated into the central nervous system, were substituted for efavirenz. Rifabutin was also used instead of rifampin. A lumbar puncture was performed again (Table 1). A subsequent brain MRI is shown in Figure 1C. A chest CT scan revealed that the pulmonary lesions had improved slightly. Sixty-eight days after admission, the first CSF culture revealed NTM. The diagnosis of NTM meningitis was clear and anti-NTM therapy was continued. On day 74, convulsions manifested and the patient lost consciousness. Sodium valproate and carbamazepine were used to control the convulsions. The patient's parents refused use of a ventilator, and 76 days after admission the patient died.

3. Discussion

Saritsiri et al. studied 71 patients infected with HIV who were subsequently infected with NTM (3). They noted MAC in 62% of those patients, *M. kansasii* in 15.5%, and RGM in 8.4%. None of the HIV-infected patients they studied had meningitis due to NTM. This finding suggests that MAC infection may constitute the primary form of NTM infection. Medication given to the two patients described here followed the treatment for MAC because there are no guidelines for treatment of meningitis due to NTM. Meningitis due to NTM is rare but often fatal (4).

The two patients reported here presented with weight loss, a chronic cough, a prolonged fever, and nervous system disorders. Biochemical analysis of CSF revealed normal CSF pressure, low levels of chloride and glucose, and high levels of protein. The patient in Case 1 had muscle strength in his lower limbs and he was diagnosed with tubercular meningitis. Anti-tuberculosis treatment was administered until hospital treatment was sufficient and thus stopped.
discharge although the results of the T-SPOT.TB test, a moderately specific and sensitive test for the diagnosis of tuberculosis (5,6), were negative. The patient in Case 2 presented with a severe pulmonary infection including bacteria, fungi, and NTM. Anti-NTM treatment was started before the emergence of new nervous system symptoms and before the definitive diagnosis of NTM meningitis. However, the patient died after 55 days of anti-NTM treatment. The species of NTM was not identified further. The therapeutic regimen was based on treatment of MAC, the most common species of NTM (7). Drug options for treating disseminated MAC disease include clarithromycin or azithromycin, rifabutin, ethambutol, amikacin or streptomycin, and levofloxacin or moxifloxacin (2). Azithromycin, ethambutol, amikacin, and moxifloxacin were selected and rifampin was used initially but was switched to rifabutin. Rifampicin, rifabutin, and moxifloxacin are readily able to permeate the blood-brain barrier. Ethambutol has moderate ability to permeate the blood-brain barrier in patients with meningitis. Azithromycin and amikacin have limited ability to permeate the blood-brain barrier. Limited drug selection and time-consuming procedures to diagnose NTM meningitis might be factors for the high mortality rate of NTM meningitis. In a study of 15 patients with MAC meningitis and AIDS, Jacob et al. found that the in-hospital mortality rate was 67% (8). However, some of those patients were lost to follow-up.

Recent studies (since 2000) regarding NTM meningitis are predominantly case reports. Dickerman et al. reported isolated intracranial MAC infection in a patient (9). The patient was initially treated with a cocktail of anti-MAC medications, including clarithromycin, ethambutol, and rifampin, for 4 months. However, the CNS lesions in the right aspect of the cerebellum continued to grow. Surgery to clear the lesion was successful and the patient remained free of recurrent disease for longer than 2 years. The authors recommended a conventional systemic antibiotic regimen as the first-line treatment for intracranial infections and suggested neurosurgical intervention in cases of medically refractory intracranial infections. However, the patient in that report did not have AIDS. Sharma et al. reported that PCR was able to detect co-infection of TB and MAC in CSF from two AIDS patients with meningitis (10). However, neither of the patients received prompt anti-NTM treatment and both died. These previous studies indicate that MAC meningitis is a terminal event in the clinical evolution of AIDS.

Based on previous reports and the two patients reported here, treatment of NTM meningitis requires a rapid and accurate method of its diagnosis (e.g. PCR) and various methods of treatment (e.g. neurosurgery). If a patient tests positive for acid-fast bacilli but the T-SPOT. TB test is negative, NTM infection should be suspected.

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