CASE REPORT

Successful treatment of non-tuberculous mycobacterial pleurisy with acute fever by antimycobacterial therapy

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SUMMARY

We report two cases of pleurisy caused by non-tuberculous mycobacteria followed by pneumothorax. The onset of pleurisy was accompanied by acute fever. Cultured samples of the pleural effusions from the two patients, an 80-year-old man and an 87-year-old woman, were ultimately found to contain *Mycobacterium intracellulare* and *Mycobacterium kansasii*, respectively. Both patients were initially administered antibiotics, but their fevers persisted. Therefore, different combinations of antimycobacterial drugs were used, which reduced the fever in a few days. In these patients, pleurisy caused by non-tuberculous mycobacteria followed by pneumothorax was characterised by acute fever and improvement in the fever after administration of antimycobacterial drugs; however, the aetiology remains to be clarified.

BACKGROUND

Non-tuberculous mycobacterial lung disease (NTM lung disease) exhibits the following three clinical phenotypes: nodular bronchiectasis, a tuberculosis-like pattern and hypersensitivity pneumonitis. Of these, nodular bronchiectasis is a common phenotype, which can cause cough, fatigue, dyspnoea, low-grade fever and weight loss over the chronic course of months to years. The radiological pulmonary findings in NTM disease typically show nodules and bronchiectasis.¹ Although case reports of pleurisy caused by non-tuberculous mycobacteria (NTM) have recently increased, few have described associated fevers.^{2–8} We herein report two cases of pleurisy with acute fever caused by NTM that were successfully treated with antimycobacterial drugs.

CASE PRESENTATION

Case 1

An 80-year-old male ex-smoker (seven packs/year) presented to our hospital complaining of fever for the past several days. He received medication for hypertension but did not have a history of an immunodeficiency disorder. His temperature was 38.0 °C. He did not present with any respiratory symptoms including cough, sputum or dyspnoea. Furthermore, he was not experiencing any chest pain. His weight had not fluctuated significantly for the past several years. Seven years prior, NTM disease was suspected from the results of chest CT, which showed scattered nodules and mild

bronchiectasis in the right middle and lower lobes. At that time, mycobacteria were not detected in his sputum. Auscultation revealed diminished breath sounds in the left lung.

Case 2

An 87-year-old woman with no smoking history presented with a chief complaint of fever and right-side chest pain for a few days. She had a medical history of NTM disease caused by *Mycobacterium kansasii*. She had been observed without therapeutic intervention because she was advanced in age, asymptomatic and had NTM disease with a seemingly indolent course. She also had a history of mild cerebral infarction, but had no disability. She received medication for hypertension. Her temperature was 38.2 °C and her resting oxygen saturation was 94% on room air. Physical examination revealed diminished breath sounds in the left lung.

INVESTIGATIONS

Case 1

This patient's white blood cell count was 8.7×10^9 cells/L and C-reactive protein level was 14.2 mg/dL. A chest X-ray and CT scan showed left pneumothorax, scattered small nodules in the right middle lobe and a moderate amount of pleural effusion and infiltration in the lingula of the left upper lobe (figure 1). The results of an acid-fast stain and mycobacterial culture of the patient's sputum were negative for mycobacteria. Bacterial culture of the sputum yielded only normal flora. His pleural effusion was slightly cloudy and yellow in colour, and analysis revealed an exudate of predominantly lymphocytes (lymphocytes 76%, neutrophils 24%), no increase in levels of adenosine deaminase (25.3 U/L), the presence of acid-fast bacilli and positive PCR results for *Mycobacterium intracellulare*. *M. intracellulare* was isolated from the effusion after an incubation period of 14 days.

Case 2

Laboratory findings showed a white blood cell count of 15.4×10^9 /L and a C-reactive protein level of 14.2 mg/dL. Furthermore, laboratory tests revealed normal levels of haemoglobin, platelets and serum electrolytes, along with normal renal function and urinalysis results. A chest X-ray revealed increased interstitial reticular markings in

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Figure 1 Case 1: chest CT image after drain insertion showing left pneumothorax with pleural effusion and infiltration in the right middle lobe and the lingula of the left upper lobe.

the lungs bilaterally. A CT scan revealed right pneumothorax with a small amount of pleural effusion, infiltration and bronchiectasis in the right middle lobe (figure 2). As a result, thoracentesis was performed. The fluid obtained was slightly cloudy and yellow-coloured. Analysis revealed an exudate of predominantly lymphocytes (lymphocytes 88%, neutrophils 8%, eosinophils 4%) and increased concentration of adenosine deaminase (130.1 U/L). Furthermore, the exudate was negative for acid-fast

Figure 2 Case 2: chest CT image showing right pneumothorax with a small amount of pleural effusion, infiltration and bronchiectasis in the right middle lobe.

bacilli. *Mycobacterium* species was isolated after 14 days of incubation. Later, it was identified as *M. kansasii*.

DIFFERENTIAL DIAGNOSIS

Both patients were suspected to have developed bacterial pleurisy because of the acute onset, which is an unlikely clinical course of NTM lung disease.

TREATMENT

Case 1

He was admitted to our hospital and underwent thoracic drainage, along with administration of tazobactam/piperacillin (TAZ/PIPC) because we suspected that his high fever was caused by bacterial pleurisy. However, his high-grade fever persisted over the initial 3 days of TAZ/PIPC treatment and over the subsequent 5 days of meropenem (MEPM) treatment (TAZ/PIPC treatment was discontinued for this subsequent treatment). On day 9 of hospitalisation, we switched from MEPM to levofloxacin because we suspected a possibility that his pleurisy was caused by *M. intracellulare*. The patient's fever subsided by the next day and, thus, therapy was focused in *M. intracellulare*; we administered an antimycobacterial therapy of clarithromycin, rifampicin (RFP) and ethambutol (EB) to limit the target organism to *M. intracellulare* on day 11.

Case 2

The patient was diagnosed with bacterial pleurisy and administered a combination of sulbactam/ampicillin. However, high fever continued for 11 days after admission. We suspected that the pleurisy was caused by *M. kansasii* infection because white blood cells in the effusion included predominantly lymphocytes, and she had a history of NTM disease by *M. kansasii*. She was ultimately administered an antimycobacterial therapy of isoniazid, RFP and EB.

OUTCOME AND FOLLOW-UP

Case 1

The patient recovered from both conditions of pleurisy and pneumothorax. Consequently, he was discharged on day 32 of hospitalisation and continued treatment for 2 years. There has been no recurrence of either pleurisy or pneumothorax to present time. Figure 3 shows the clinical course of Case 1.

Case 2

The patient's fever subsided 2 days after the start of therapy. Her pleurisy and pneumothorax improved, and she was discharged on day 23 of hospitalisation (figure 4). She was administered

Figure 3 Clinical course of Case 1. CAM, clarithromycin; EB, ethambutol; LVFX, levofloxacin; MEPM, meropenem; PIPC, piperacillin; RFP, rifampicin; TAZ, tazobactam.

Figure 4 Clinical course of Case 2. ABPC, ampicillin; EB, ethambutol; INH, isoniazid; RFP, rifampicin; SBT, sulbactam.

medications for 12 months. To date, there has been no recurrence of either pleurisy or pneumothorax.

DISCUSSION

The number of patients with NTM lung disease continues to increase worldwide.⁹ Especially in Japan, NTM lung disease has increased dramatically over the past decade.¹⁰ Although NTM lung disease rarely causes pneumothorax and pleurisy, recent cases of both pneumothorax and pleurisy have been reported in succession.^{4 5 7 8 11} We reported two cases of pleurisy caused by NTM, which were likely to have developed as a result of pneumothorax. Both cases were accompanied by acute fever. Both patients expressed a phenotype of nodular bronchiectasis and had no symptoms prior to the development of pneumothorax. Pleural effusions were isolated and used to culture the NTM. Previously, there have been two reported mechanisms on how pleurisy is potentially caused by NTM.³ First, one potential mechanism is the spread of inflammation through the pleura caused by a subpleural pulmonary lesion. This may be accompanied by the spreading of infiltrative lesions in the periphery of the lung. Alternatively, the spread of NTM could be caused by the anatomical rupture of the pleura caused by pneumothorax. Pulmonary lesions, such as a cavity and fibrosis caused by underlying NTM disease, can lead to pleural rupture. As a result, direct spreading of NTM to the thoracic cavity is possible. We speculate that the abrupt spreading of NTM to the thoracic cavity is associated with acute fever, although the pathophysiology of this mechanism remains unclear. Pneumothorax may occur with a higher frequency in patients with NTM lung disease than previously believed.^{11–13}

When our patients with NTM disease presented with high fevers, we suspected that they had developed superimposed bacterial infections (because high fevers caused by NTM disease are rare). Few previous reports have described, in detail, fevers caused by NTM. The high fevers of our patients did not subside despite treatment with antibiotics for bacterial pleurisy for over a week. Notably, no other infectious foci were discovered. After

Learning points

- ▶ Pleurisy and pneumothorax by non-tuberculous mycobacteria (NTM) are likely to increase in association with an increasing prevalence of NTM lung disease.
- ▶ NTM can subsequently cause pleurisy with acute fever mimicking bacterial infection after pneumothorax.
- ▶ Antimycobacterial drugs can improve the pleurisy caused by NTM.

switching to antimycobacterial drugs, their fevers subsided in a few days. The pleurisy, which was caused by NTM followed by pneumothorax, was suspected to have caused acute fever, mimicking bacterial pleurisy. However, antimycobacterial drugs could improve the pleurisy with acute fever caused by NTM.

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