Reminder of important clinical lesson

Multidrug-resistant tuberculosis that required 2 years for diagnosis

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Isoniazid (H) or rifampicin (R) mono-resistant disease can be treated easily and effectively with first-line drugs, while combined H and R resistance (ie, multidrug-resistant tuberculosis (MDRTB)) requires treatment with at least four agents, including a quinolone and an injectable agent. Drug-resistant *Mycobacterium tuberculosis* strains are reported to be extremely difficult to cultivate invitro. The authors report a case of MDRTB that required 2 years for diagnosis, and was detected only in sputum culture on solid medium. Physicians should consider MDRTB if TB is suspected but pathogens are not detected.

BACKGROUND

If physicians suspect *M tuberculosis* but can not cultivate pathogens, the possibility of multidrug-resistant tuberculosis (MDRTB) should be considered.

CASE PRESENTATION

A 38-year-old man was referred to our hospital in November 2006 by a local doctor for further examination of an abnormal shadow seen on chest imaging. There was no history of allergy, previous major illness, or risk factors for immunodeficiency. The patient had no smoking history. On admission, haematological and biochemical examinations did not show any abnormal findings. Routine bacteriological, fungal and mycobacterial cultures of sputum were negative. A transbronchial biopsy specimen from the right B¹ showed epithelioid cell granuloma without caseous necrosis. As the sputum and bronchial washing fluid did not show any bacteria, fungi,

or mycobacteria in the smear or culture on solid or liquid medium, we could not establish a diagnosis. PCR examinations of sputum and bronchial washing fluid were also negative for *M tuberculosis* and *M avium* complex (MAC). The patient was followed in our outpatient clinic every 6 months. After 1 year, he admitted to our hospital to perform (figure 1) fiberoptic bronchoscope again. However, sputum and bronchial washing fluid obtained during that admission did not show any pathogens with only granulomatous tissue in the transbronchial lung biopsy specimen. One year after the second admission, he was admitted to our hospital on 28 September 2009, because the right upper lesion had gradually progressed compared to findings observed in 2008 (figure 2). CT of the chest showed progression of the right upper infiltration surrounding the cavity. Although the smear of sputum was negative for *M tuberculosis* in November, culture showed eight colonies of *M tuberculosis* only on solid medium.

Figure 1 (a) Chest CT showing centrilobular nodules or branching linear structure ('tree in bud') in 2007. (b) Chest CT showing a small thick-walled cavity with surrounding opacity.

Figure 2 (a) Chest CT in 2009 showing progression of centrilobular nodules. (b) Chest CT in 2009 showing progression of centrilobular nodules surrounding a small cavity.

INVESTIGATIONS

The colony was transferred to Mycobroth (Kyokuto Pharmaceutical Industrial Co., Ltd, Japan) for culture and after 3 days, fluid from the culture added to Broth MIC MTB-1 (Kyokuto Pharmaceutical Industrial Co., Ltd, Japan). After 4 days, MDRTB was detected in the culture.

As smear of the sputum obtained on 16 November was positive, he was admitted to our tuberculosis ward. Quantiferon-TB-2G (Nihon BCG Inc., Japan) was positive with early secretory antigenic target-6 of 0.68 IU/ml and culture filtrate protein-10 of 0.57 IU/ml. After we investigated sensitivity to drugs using Wellpack media S (Japan BCG Laboratory, Japan), the medication was changed to pyrazinamide (PZA), streptomycin (S), levofloxacin and para aminosalicylate on 24 December.

DIFFERENTIAL DIAGNOSIS

The radiographic findings were thought to be compatible with *M tuberculosis* and the transbronchial lung biopsy specimen showed epithelioid cell granuloma without caseous necrosis. However, we could not establish the diagnosis, because we did not detect *M tuberculosis* in the smear or culture of sputum or bronchial washing fluid on either solid or liquid medium. Centrilobular nodules or branching linear structure ('tree in bud') with or without bronchial wall thickening, lobular consolidation, cavity formation, bronchiectasis and/or fibrotic changes have been reported as characteristic findings of TB. In this case, CT showed a small cavity with surrounding branching tree in bud opacities and centrilobular nodules from the first admission of our hospital. However, we could not establish the diagnosis despite performing fiberoptic bronchoscopy twice. We suspected non-tuberculous mycobacterium other than *M tuberculosis*, MAC, or fungal diseases.

TREATMENT

Medication contained PZA, S, levofloxacin and para aminosalicylate.

OUTCOME AND FOLLOW-UP

We expect to treat this patient for a total of 2 years.

DISCUSSION

It took 2 years to diagnose this patient as having MDRTB, even though fiberoptic bronchoscope was performed totally three times. The radiographic findings were thought to be compatible with *M tuberculosis* and the transbronchial lung biopsy specimen showed epithelioid cell granuloma without caseous necrosis.^{1 2} Although unpublished experience has shown that some MDRTB strains are extremely difficult to cultivate in vitro,³ we did not know similar case required 2 years for diagnosis. We do not know why *M tuberculosis* in the sputum could only be detected by solid medium culture on the third admission despite negative smear of the bronchial washing fluid specimen, or why we could not cultivate the MDRTB from many previous specimens.

In any case, if we suspect MDRTB, we should investigate drug sensitivity and treat the disease according to the result of sensitivity. Surgery for detection of the pathogen may be preferable in a case like this.

Learning points

- MDRTB strains are extremely difficult to cultivate.
- Required 2 years for diagnosis in MDRTB.
- If physicians suspect *M tuberculosis* but can not cultivate pathogens, the possibility of MDRTB should be considered.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Yano S, Kobayashi K, Ikeda T. Multidrug-resistant tuberculosis that required 2 years for diagnosis. *BMJ Case Reports* 2012; 10.1136/bcr.02.2010.2775, Published XXX

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