Tuberculous pleural effusion and low pleural fluid adenosine deaminase level: a case report

Wai Chen, MB BS (HK), FHKAM (Medicine); Chi-Fai Ko, MB BS (HK), FHKAM (Medicine), FRCP (Edin & Glasg)

ABSTRACT
We describe an 87-year-old woman with bilateral pleural effusion who presented with low pleural fluid adenosine deaminase level. The patient was treated as having tuberculous pleural effusion, with a combination of isoniazid, rifampicin, and pyrazinamide. The patient responded promptly to the anti-tuberculous therapy. After completion of the 6-month treatment course, she had complete resolution of the pleural effusion.

Key words: Tuberculous pleural effusion; Adenosine deaminase

CASE PRESENTATION
In July 2018, an 87-year-old woman presented to the medical ward of North Lantau Hospital with fever, chest pain, and cough with scanty sputum. The patient was a non-smoker and had hypertension and beta-thalassaemia trait. On admission to the hospital, the patient was dyspnoeic with a respiratory rate of 22 per minute and a peripheral capillary oxygen saturation of 95% on 2 L/min O₂. The patient’s body temperature was 37.8°C and she had no ankle oedema. The patient’s breath sound was diminished on both lower zones. Her blood pressure was 160/90 mmHg and pulse rate was 100 per minute. Nonetheless, the patient’s cardiovascular system examination and abdominal examination results were normal. Chest radiographs showed bilateral pleural effusion. Complete blood test results showed leucocytosis. The patient was diagnosed as having community-acquired pneumonia and treated with intravenous antibiotics (amoxicillin-clavulanate). However, the patient had persistent fever and sepsis, with little clinical improvement. The antibiotic regimen was switched to intravenous meropenem in the second week of treatment. Further blood test results showed leucocytosis and raised C-reactive protein level. Liver function test results were unremarkable. The patient’s serum creatinine level was 127 µmol/L and serial cardiac enzyme levels were normal. Electrocardiography showed sinus tachycardia. Chest radiographs showed bilateral pleural effusion (Figure). Echocardiogram showed satisfactory left ventricular function. Sputum, urine, and blood cultures were all negative for bacterial growth. Sputum was smear-negative for acid-fast bacilli. Computed tomographic scan of the thorax confirmed bilateral pleural effusion. There was no empyema formation or pericardial effusion.

Diagnostic thoracentesis was performed. Biochemical results of the pleural fluid showed a total protein level of 44 g/L, lactate dehydrogenase level of 331 U/L, and adenosine deaminase level of 16 U/L (≥30 U/L is suggestive of tuberculous pleurisy with 82% sensitivity and 91% specificity). The patient’s serum protein and lactate dehydrogenase levels were 70 g/L and 130 U/L, respectively. Gram staining and bacterial culture of the pleural fluid were both negative. Acid-fast bacilli were not seen, and real-time polymerase chain reaction for Mycobacterium tuberculosis was negative. Cytological examination results showed a moderate number of polymorphs and lymphocytes but no malignant cells. The patient refused pleural biopsy.

Despite intravenous meropenem, the patient had
worsened functional status and required personal assistance for toileting and bathing. In view of the exudative pleural sepsis, the patient was treated as having tuberculous pleural effusion, and a therapeutic trial of isoniazid 300 mg daily, rifampicin 450 mg daily, and pyrazinamide 1 g daily was commenced.

The patient responded promptly to the anti-tuberculous therapy. She became afebrile and was weaned off supplemental oxygen. Follow-up blood tests results showed improvement of leucocytosis. Chest radiographs showed gradual resolution of pleural effusion. The patient was discharged 2 weeks later and was referred to a chest clinic for follow-up. The pleural fluid culture showed no growth of *Mycobacterium* species after 6 weeks of incubation. After completion of the 6-month anti-tuberculous treatment course, chest radiographs showed complete resolution of the pleural effusion (Figure). Her activities of daily living returned to her baseline level.

**DISCUSSION**

The gold standard for the diagnosis of tuberculous pleural effusion is detection of *M tuberculosis* in the sputum, pleural fluid, or pleural biopsy specimens, or histological demonstration of caseating granulomas in the pleura along with acid-fast bacilli. However, examination of pleural fluid can detect acid-fast bacilli in <10% of cases. Pleural biopsy is an invasive procedure and mycobacterial culture takes at least 6 weeks; newer modalities of non-invasive serological testing for tuberculosis are established for earlier diagnosis.

Tuberculous pleural effusion is a result of delayed hypersensitivity reaction to the proteins of *M tuberculosis*. The inflammatory response is initiated by macrophages, neutrophils, and subsequently by interferon-γ-producing CD4 T-lymphocytes against the mycobacterium antigens in the pleural space. This immune reaction is accompanied by the increased release of the enzyme adenosine deaminase (ADA) into the pleural space. Pleural fluid ADA level of 35 U/L was reported to be the optimal cut-off to detect tuberculous pleural effusion, yielding a sensitivity of 93% and specificity of 90%.

Although our patient presented with fever and bilateral exudative pleural effusion and yet relatively low pleural ADA level (16 IU/L), she responded rapidly to anti-tuberculous therapy. Pleural fluid ADA production decreases with age. In patients with tuberculous pleural effusion, those aged >55 years had significantly lower pleural ADA levels than those aged ≤55 years (26 IU/L vs 72 IU/L). In addition, those with a low ADA level (<40 IU/L) were significantly older than those with a high ADA level (≥40 IU/L). Thus, the use of a lower ADA cut-off can reduce the number of false-negative results.
The ageing immune system is characterised by a decline in stem cells, alterations in T-lymphocyte production, blunting of the B-cell associated antibody response and reduced phagocytic activity of neutrophils, macrophages, and natural killer cells. There is also an age-related decrease in T-lymphocyte function. Pleural fluid ADA production by various immune cells therefore decreases with age. This may increase the number of false negative results if a ‘standard’ ADA cut-off level is used in older people. Further clinical studies are required to determine the optimal cut-off value for older people.

CONCLUSION

Pleural fluid ADA level is valuable in making the diagnosis of tuberculous pleural effusion. Patients with lymphocytic predominant exudative pleural effusion and increased pleural fluid ADA level are usually justified with such a diagnosis and anti-tuberculous treatment, especially in tuberculosis prevalent regions. However, physicians must be cautious when interpreting the ADA level in older adults, because pleural fluid ADA production decreases with age.

DECLARATION

The authors have no conflict of interest to disclose.

REFERENCES