

Pulmonary alveolar proteinosis diagnosis after re-evaluation for chronic cough unresponsive to empirical antituberculosis therapy

TO THE EDITOR: Tuberculosis (TB) is a common cause of chronic cough in South Africa (SA). Empirical anti-TB therapy is often initiated in the absence of a microbiological diagnosis. We report on a patient who initially commenced treatment for TB despite negative sputum results and on re-evaluation was diagnosed with pulmonary alveolar proteinosis (PAP), which is a rare cause of chronic cough. This case report emphasises the need for microbiological diagnosis of pulmonary TB to justify the long-term use of potentially toxic medications, and also shows that rare diseases may present with common TB-like symptoms.

A 29-year-old black African woman had a 12-month history of dry cough, weight loss, intermittent wheezing and progressive dyspnoea. She was HIV negative and had no constitutional symptoms such as anorexia, fever or night sweats, and no joint pains or stiffness. She had never smoked, and had no exposure to organic or inorganic dust. She had been commenced on empirical treatment for TB at a peripheral hospital before transfer to Nelson Mandela Academic Hospital, Mthatha, for re-evaluation because she continued to deteriorate clinically despite 4 months of TB treatment, which had been started based on findings on the chest radiograph of bilateral diffuse infiltrates not responding to antibiotics.

Physical examination revealed grade 4 digital clubbing with peripheral and central cyanosis. She had tachypnoea (32 breaths per minute) with oxygen saturation of 70% in room air and 88 - 90% on a non-rebreather oxygen mask at 15 L/min. Chest examination revealed Velcro-like crepitation most pronounced in the lung bases. The rest of the clinical examination was unremarkable.

Laboratory results revealed a normal white cell count of $10.9 \times 10^9/L$ (normal range 3.9 - 12.6), polycythaemia (haemoglobin concentration 15.6 g/dL, normal range 12.0 - 15.0), and a normal platelet count of $358 \times 10^9/L$ (normal range 186 - 454). Connective tissue screening including antinuclear antibodies, antineutrophil cytoplasmic antibodies and the serum angiotensin-converting enzyme level was negative. The results of renal and liver function tests were normal, and the erythrocyte sedimentation rate was slightly elevated at 38 mm/h. Sputum GeneXpert MTB/RIF Ultra was negative for *Mycobacterium tuberculosis*, and microscopy showed normal flora. A polymerase chain reaction test for COVID-19 was also negative. A chest radiograph revealed bilateral diffuse alveolar infiltrates. A high-resolution computed tomography (HRCT) scan of the chest showed a bilateral ground-glass appearance with septal thickening consistent with a crazy-paving pattern.

The patient went on to have bronchoscopy, which revealed copious amounts of milky fluid (Fig. 1), and a small-volume lavage was done. Specimens were sent for periodic acid-Schiff (PAS) staining, GeneXpert MTB/RIF Ultra, and cytological, bacterial and fungal studies. Unfortunately, our laboratory could not perform PAS staining on the sample, but GeneXpert MTB/RIF Ultra was negative for TB.

A clinical diagnosis of PAP was made and TB treatment was discontinued. The patient was referred to Groote Schuur Hospital

in Cape Town, where whole-lung lavage was performed with marked improvement in her clinical state. She no longer required supplemental oxygen and had an oxygen saturation of 99% in room air. She is being followed up at the pulmonology clinic at Nelson Mandela Academic Hospital.

PAP is a rare cause of interstitial lung disease caused by alveolar accumulation of lipoproteinaceous material in the alveoli due to disordered surfactant homeostasis.^[1] The rarity of the disease is underscored by the findings in an Israeli study in which only 15 cases were identified in the entire country over the 22-year period from 1976 to 1998.^[2] China, with a population of more than billion, reported only 241 cases of PAP over four decades from 1965 to 2006.^[3] PAP has also rarely been reported in SA, and we found only 2 reports.^[4,5]

There are three types of PAP: primary PAP due to autoimmune and hereditary disease, secondary PAP and congenital PAP.^[6] Our patient probably has the autoimmune type, which constitutes 90% of all cases. Although we were unable to perform PAS staining on the bronchoalveolar lavage (BAL) fluid or to measure serum granulocyte macrophage-colony stimulating factor (GM-CSF) antibody, the diagnosis of PAP was made on the basis of clinical findings and imaging. The characteristic milky fluid noted on BAL further strengthened the likelihood of the diagnosis. Although there is a high prevalence of TB in our environment,^[7] this case highlights the need for restraint in initiating TB therapy without microbiological evidence of TB. An alternative diagnosis was considered in our patient because she did not improve on empirical TB therapy and was profoundly hypoxic, which is unusual in TB. The differential diagnosis of PAP includes pulmonary infections such as COVID-19, TB and *Pneumocystis jirovecii* pneumonia, interstitial lung disease from connective tissue disease, sarcoidosis, pulmonary oedema, bronchoalveolar carcinoma, hypersensitivity pneumonitis and cryptogenic organising pneumonia.



Fig. 1. Milky fluid from bronchoalveolar lavage in 50 mL specimen containers.

The National Department of Health in SA provides algorithms for TB diagnosis that advise additional investigations when initial sputum smear microscopy or GeneXpert MTB/RIF Ultra for TB are negative and individuals under investigation are co-infected with HIV. These algorithms recommend that clinicians commence TB treatment for HIV-positive individuals when two sputum smear microscopy tests or a single sputum GeneXpert are negative for *M. tuberculosis*, chest radiographic findings are compatible with TB, and symptoms do not respond to broad-spectrum antibiotics.

In our case, the recognition of a crazy-paving pattern on the HRCT scan that was suggestive of PAP prompted bronchoscopy and alveolar lavage, which revealed the characteristically milky fluid associated with this diagnosis. Whole-lung lavage at Groote Schuur Hospital was then offered to our patient, with dramatic resolution in her symptoms. Treatment for PAP is not required for patients with mild symptoms. In patients with troubling dyspnoea, whole-lung lavage is done under general anaesthesia with a double-lumen endotracheal tube. Lavage of one lung is done up to 15 times with 1 - 2 L saline while the other lung is ventilated. The process is then reversed.

Systemic corticosteroids play no role in the management of PAP and may increase the risk of secondary infection. The role of GM-CSF (inhalation or subcutaneous) in management remains to be determined. Lung transplantation is not often done, because the disorder may recur in the transplanted lung. PAP may remit spontaneously in up to 10% of patients. When patients are treated with whole-lung lavage, the 5-year survival rate is 95%. Secondary bacterial pulmonary infections occasionally develop because of impaired macrophage function, and require treatment.

Our case report is limited by our inability to perform PAS staining of the alveolar fluid or measurement of serum alveolar macrophage colony-stimulating factor antibody. Spirometry was not done because the patient was severely hypoxaemic at presentation. We do not have facilities to measure diffusion capacity of the lung for carbon monoxide (DLCO) in our institution. Pulmonary function testing is of limited usefulness in diagnosing the severity of PAP. An increased alveolar-arterial oxygen gradient correlates better with disease severity. Forced vital capacity (FVC) and forced expiratory volume in 1 second are generally within normal limits, although some patients show decreased FVC consistent with restrictive physiology. DLCO is frequently reduced and correlates with disease severity.

This study extends the reports of PAP in SA, in this case a 29-year-old HIV-negative black African woman with no history of smoking. Patients with respiratory symptoms who are microbiologically negative for TB should be carefully evaluated for an alternative diagnosis.

H Ghammo, FCP (SA), Cert Pulmonology (SA); **M Tau**, FCP (SA); **B Th mas MD**

Department of Medicine, Faculty of Health Sciences, Walter Sisulu University and Nelson Mandela Academic Hospital, Mthatha, South Africa

T Fathuse, MBBS

Department of Medicine, Nelson Mandela Academic Hospital, Mthatha, South Africa

C Ekpebeigh, FMCP 

Department of Medicine, Faculty of Health Sciences, Walter Sisulu University and Nelson Mandela Academic Hospital, Mthatha, South Africa
chuksekpebeigh@yahoo.com

T Dubula, FCP (SA); **N Ndlovu**, PhD

Cardiometabolic Research Niche, Walter Sisulu University, Mthatha, South Africa

Corresponding author: C Ekpebeigh (chuksekpebeigh@yahoo.com)

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