

CMEARTICLE

Clinics in diagnostic imaging (212)

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Fig. 1 Initial CT image of the thorax obtained in 2014.

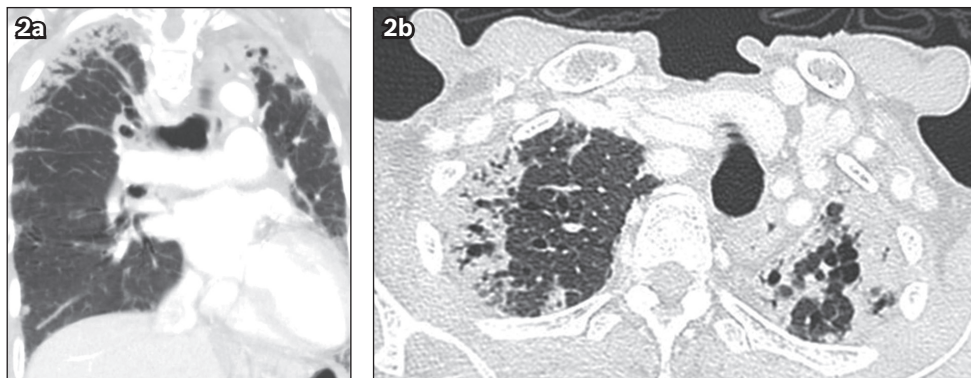


Fig. 2 Subsequent (a) coronal and (b) axial CT images of the thorax obtained in 2019.

CASE PRESENTATION

A 75-year-old woman presented in 2014 with a non-resolving left lower lobe consolidation. Initial less invasive attempts at biopsy of the left lower lobe consolidation failed to obtain a definitive diagnosis, and the patient underwent a left lower lobectomy and lymph node dissection. Histology revealed adenocarcinoma with no lymphovascular invasion, and she was diagnosed with Stage IIA lung adenocarcinoma. She did not require radiotherapy and declined adjuvant chemotherapy.

Upper lung changes on initial preoperative computed tomography (CT) of the thorax performed in 2014 (Fig. 1) were originally interpreted to be due to benign post-infectious scarring. The patient subsequently underwent surveillance CT of the thorax over a period of time until 2020. She had no chronic

cough, sputum production or worsening exertional dyspnoea over the years. She was a non-smoker and her body mass index (BMI) was 12.6 kg/m² on her latest review. Her oxygen saturation was 98% on room air, and physical examination revealed reduced breath sounds over the left lung, with bilateral fine crepitations. There were no signs suggestive of a connective tissue disease. An autoimmune screen comprising anti-nuclear antibody, rheumatoid factor and anti-cyclic citrullinated peptide tests was negative, and the patient was unable to produce sputum to screen for acid-fast bacilli. She held multiple jobs previously, including dishwashing, cleaning and being a kitchen helper.

What do the initial CT done in 2014 (Fig. 1) and subsequent CT done in 2019 (Fig. 2) show? What is the diagnosis?

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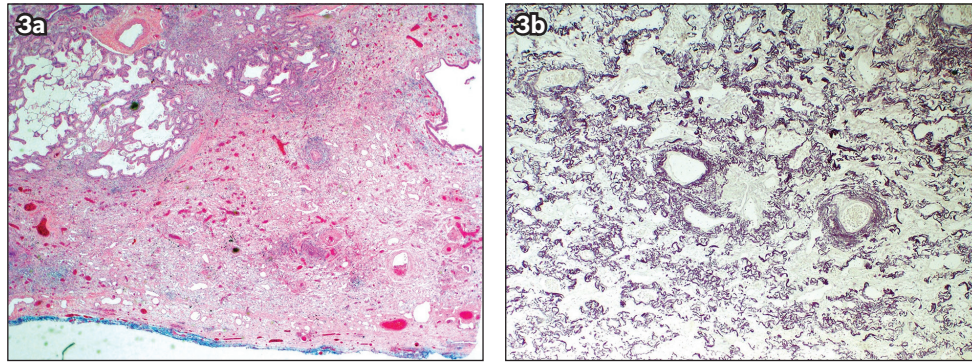


Fig. 3 (a) Photomicrograph in low-power view shows thickened pleura surface in the resected specimen (Haematoxylin & eosin, original magnification $\times 40$). (b) Photomicrograph in medium-power view shows abundant elastic fibres in the thickened portion of the pleura (elastic van Gieson, original magnification $\times 100$).

IMAGE INTERPRETATION

Coronal CT of the thorax performed in 2014 (Fig. 1) demonstrated bilateral upper lobe subpleural consolidation with reticular thickening and traction bronchiectasis. There was relative sparing of the lower lobes.

Follow-up CT of the thorax performed in 2019 (Fig. 2a) depicted worsening of subpleural consolidation, traction bronchiectasis, bilateral apical pleural thickening and volume loss in the upper lobes. The axial CT image (Fig. 2b) of the lung apices demonstrated bilateral subpleural consolidation and reticulation with associated traction bronchiectasis. Note the presence of a deep suprasternal notch, commonly seen with platythorax.

DIAGNOSIS

Pleuroparenchymal fibroelastosis (PPFE).

CLINICAL COURSE

The patient was referred to the interstitial lung disease (ILD) clinic and the case was discussed at the ILD multidisciplinary team meeting. Histology from the left lower lobectomy demonstrated thickening of the pleura as the result of a fibrosing process that was elastotic in nature (Figs. 3a & b). In conjunction with the upper lobe imaging findings, a diagnosis of PPFE was established. The patient has remained clinically well with minimal respiratory symptoms over the six years that she had been followed up at the time of writing.

DISCUSSION

PPFE is a fibrosing process that affects the pleura and the adjacent lung parenchyma, with a predilection for the upper lobes. Since the initial reports by Amitani et al in 1992,⁽¹⁾ several other corroborative case series have been added through the years, describing its unique clinical, radiological and pathological features that are distinct from other idiopathic interstitial pneumonias (IIPs). This culminated in the recognition of idiopathic PPFE (IPPF) as a rare IIP in the 2013 joint American Thoracic Society/European Respiratory Society IIP classification.⁽²⁾

Although PPFE is classified as a rare IIP, owing to greater awareness since the publication of the IIP classification guidelines and proposal of various diagnostic criteria,^(3,4) the incidence and prevalence of PPFE are not as uncommon as once



Fig. 4 A 79-year-old man had pleuroparenchymal fibroelastosis with co-existent idiopathic pulmonary fibrosis. Coronal CT image shows bilateral upper lobe subpleural fibrosis and wedge-shaped subpleural consolidation, with honeycombing at the lung bases. Spirometry showed a forced vital capacity of 37% predicted and raised residual volume/total lung capacity ratio of 128%. The body mass index of the patient was 14.6 kg/m². He died two months after his diagnosis.

thought. For instance, PPFE accounts for 7.7% of consecutive IIP cases evaluated in a single centre over a ten-year period.⁽⁵⁾ The exact pathogenesis of PPFE is poorly understood, although acute and sub-acute lung injury have been proposed to be triggers for this disease. Common aetiologies associated with PPFE include haematopoietic stem cell, bone marrow and lung transplantation.⁽⁶⁾ Other associations include allergens and exposure to occupational dust (asbestos, aluminium), connective tissue diseases (scleroderma, rheumatoid arthritis) or exposure to drugs (chemotherapeutic agents, dapsone and daptomycin).^(3,7-9) Familial associations have also been reported.⁽³⁾ Of note, over half of the patients had a history of recurrent pulmonary infections.⁽³⁾ In the absence of any known associations, the term IPPFE is used.

PPFE affects patients of a wide age range. The median age at presentation is in the fifth decade of life, and the age distribution is likely to be bimodal, peaking at the third and sixth decade.^(6,10) It does not have any gender preponderance. Common presenting symptoms include insidious onset of progressive dyspnoea, cough and weight loss. With progression of PPFE or when it co-exists with other fibrotic lung diseases, lung auscultation

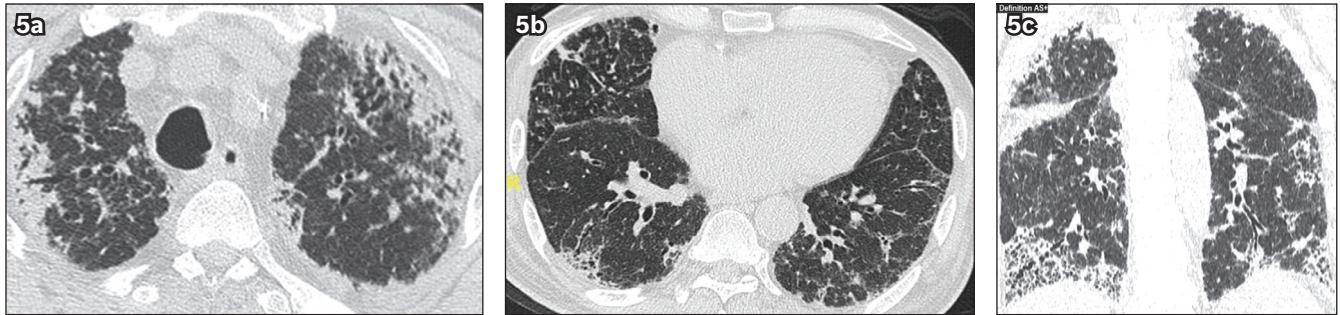


Fig. 5 CT images of a 71-year-old man with pleuroparenchymal fibroelastosis show (a) bilateral subpleural fibrotic changes with traction bronchiectasis in the upper lobes; (b) ‘free-standing’ bronchiectasis, which may reflect recurrent aspiration, in the middle lobe; and (c) a typical interstitial pneumonia pattern with subpleural reticulation, traction bronchiectasis and honeycombing in the lung bases.

may reveal inspiratory crackles. One peculiar sign of PPFE is the development of platythorax, also called the ‘flattened thoracic cage’ appearance, due to upper lobe contraction and reduced chest wall bulk.^(7,11)

Imaging is often the first step in the diagnosis of PPFE. In the early stages, chest radiography shows bilateral upper zone pleural thickening, which may sometimes be asymmetrical. With progression of fibrosis, there is lobar volume loss, often accompanied by hilar elevation.⁽¹²⁾ On high-resolution CT images of the chest, Reddy et al defined ‘definite PPFE’ as upper lobe pleural thickening with associated subpleural fibrosis, with absent or minimal involvement of the lower lobes.⁽³⁾ The fibrosis is manifested as architectural distortion and traction bronchiectasis. Other ancillary CT findings include anteroposterior flattening of the chest (platythorax), ‘free-standing’ bronchiectasis and mosaic attenuation of the lung parenchyma.^(7,11) Other patterns of lung fibrosis can co-exist with PPFE, most frequently usual interstitial pneumonia, non-specific interstitial pneumonia or hypersensitivity pneumonitis.⁽⁷⁾ Figs. 4 and 5 depict cases of PPFE that were found to be co-existent with other fibrotic lung diseases in our institution. Importantly, pneumothorax and pneumomediastinum may develop over the course of the disease, and clinicians need to be mindful of this complication if there is acute worsening of respiratory symptoms (Fig. 6).

Several differential diagnoses should be considered when evaluating patients with upper zone fibrosis. Benign pathologies such as apical pleural caps are often incidental findings on imaging in asymptomatic elderly smokers. Unlike PPFE, they are typically localised at the uppermost 5 mm of the lung apices. Differentiating PPFE from active pulmonary tuberculosis (TB) is usually straightforward, as the latter presents with asymmetrical upper lobe centrilobular nodules, consolidation or cavities. However, differentiating PPFE from sequelae of past tuberculous pleurisy is more challenging, as the resultant pleural thickening and calcification from TB may mimic the findings of PPFE (Fig. 7), and histology may be needed to establish the diagnosis. Other radiological differentials include ankylosing spondylitis, progressive massive fibrosis, fibrotic hypersensitivity pneumonitis and fibrotic sarcoidosis.⁽¹¹⁾ Additional clinical information such as a previous history of TB, occupational history, systemic symptoms, autoimmune serologies and previous imaging may be helpful in establishing the diagnosis.

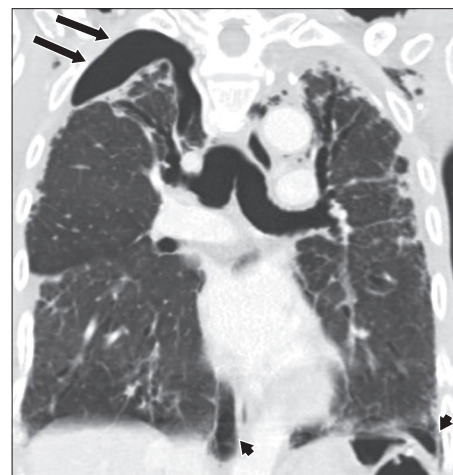


Fig. 6 Pleuroparenchymal fibroelastosis was observed in a 63-year-old man who presented with a five-day history of dyspnoea. Coronal CT image of the thorax shows a right apical pneumothorax (arrows) and at both lung bases (arrowheads).

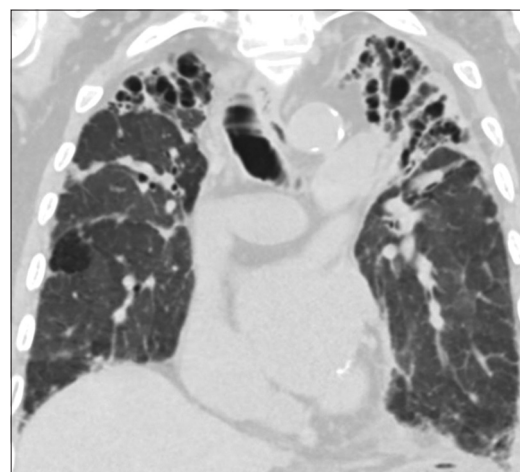


Fig. 7 An 82-year-old man had a history of pulmonary tuberculosis diagnosed and treated more than 30 years ago. Coronal CT image of the thorax shows bilateral, symmetrical upper lobe fibrosis, volume loss with associated severe traction bronchiectasis and biapical pleural thickening. Sequelae of prior tuberculosis is a common mimic of pleuroparenchymal fibroelastosis in the local context and can pose a challenge in diagnosis.

A surgical lung biopsy is required to secure the diagnosis of PPFE. Histologically, PPFE demonstrates intense visceral pleural fibrosis, and prominent and homogenous subpleural intra-alveolar fibrosis with alveolar septal elastosis that is best visualised with an elastin van Gieson stain. The alveolar septal elastosis

sparing the lung parenchyma away from the pleura, with scanty lymphoplasmacytic infiltrates and small numbers of fibroblastic foci at most.⁽¹²⁾ There could be some degree of temporal continuity from early interstitial inflammation and fibrosis to the eventual development of PPFE as well as the possibility of co-existent ILDs.⁽¹³⁾

As surgical lung biopsies may result in postoperative complications such as pneumothoraces and prolonged air leaks, IPPFE diagnostic criteria without the need for histology were proposed recently by Watanabe et al. Using imaging, clinical and physiological features, patients were labelled as 'radiologically possible IPPFE', 'radiologically probable IPPFE', or 'radiologically and physiologically probable IPPFE'.⁽⁴⁾ 'Radiologically possible IPPFE' included early imaging features of upper lobe subpleural airspace consolidation with traction bronchiectasis, while 'radiologically probable IPPFE' required additional progressive features of upper lobe volume loss or bilateral upward shift of hilar structures to be present, together with clinical features such as dry cough or exertional dyspnoea. 'Radiologically and physiologically probable IPPFE' further included physiological parameters such as the percentage predicted value of the residual volume/total lung capacity ratio as well as the BMI of the patient. However, none of these classifications have been validated in other studies.

No treatment has been shown to be effective in PPFE, except for lung transplantation. The long-term prognosis of PPFE varies from an insidious course over 10–20 years to a more progressive respiratory decline, with a median survival of less than five years.⁽⁷⁾ Transplant-associated PPFE may portend a poorer prognosis,⁽⁶⁾ and patients with PPFE co-existing with idiopathic pulmonary fibrosis have more frequent complications and poorer survival.⁽¹⁴⁾

This case highlights several learning points. Firstly, given the various associations with PPFE, obtaining a detailed history is important when evaluating a patient presenting with radiological features suggestive of PPFE. As TB is prevalent in this region, eliciting symptoms such as chronic cough, haemoptysis and constitutional symptoms, or a previous history of TB may prompt

the clinician to obtain sputum for microbiological correlation. Secondly, even though PPFE is described as predominantly affecting the upper lobes, it can also involve the lower lobes, although the changes may be more subtle. Finally, it is important to relook and consider alternative diagnoses, especially when the patient's clinical behaviour is not in keeping with expected disease trajectory, as demonstrated by this case.

In conclusion, greater awareness of PPFE has enabled more in-depth understanding of its pathogenesis, temporal evolution with time and longitudinal disease course. Establishing universally accepted diagnostic criteria may help to facilitate studies in a more uniform cohort to better understand this disease.

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME (Code SMJ 202202B)

Question 1. Common aetiologies associated with pleuroparenchymal fibroelastosis (PPFE) are:

- (a) Connective tissue diseases
- (b) Dapsone
- (c) Malignancy
- (d) Post-haematopoietic stem cell transplant

True False

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Question 2. Which of the following statements are relevant to the presentation of PPFE?

- (a) PPFE tends to affect females more than males.
- (b) PPFE usually presents insidiously with progressive dyspnoea, cough and weight loss.
- (c) PPFE may present with bilateral pneumothoraces and pneumomediastinum.
- (d) PPFE is one of the sequelae of pulmonary tuberculosis.

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Question 3. Imaging features of PPFE include:

- (a) Bilateral symmetrical hilar lymphadenopathy
- (b) Platythorax
- (c) Upper lobe-predominant pleural thickening with subpleural fibrosis
- (d) Widespread bronchial wall thickening, mucus plugging and tree-in-bud opacities

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Question 4. Regarding diagnosis of PPFE:

- (a) A definite diagnosis of PPFE requires a surgical lung biopsy.
- (b) Patients with PPFE who undergo surgical lung biopsies may be at increased risk of postoperative complications such as prolonged air leaks from a pneumothorax.
- (c) Revised diagnostic criteria without the need for histology have been widely accepted to diagnose PPFE.
- (d) Histological features of PPFE include visceral pleural fibrosis and subpleural intra-alveolar fibrosis with alveolar septal elastosis that spares the lung parenchyma away from the pleura.

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Question 5. The following treatments have been shown to be effective in PPFE:

- (a) Methotrexate
- (b) Lung transplant
- (c) Chronic antibiotic therapy
- (d) Bronchodilator therapy

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RESULTS:

- (1) Answers will be published online in the SMJ April 2022 issue.
- (2) The MCR numbers of successful candidates will be posted online at the SMJ website by 29 April 2022.
- (3) Passing mark is 60%. No mark will be deducted for incorrect answers.
- (4) The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council.
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- (6) SMC credits CME points according to the month of publication of the CME article (i.e. points awarded for a quiz published in the December 2021 issue will be credited for the month of December 2021, even if the deadline is in February 2022).

Deadline for submission (February 2022 SMJ 3B CME programme): 12 noon, 22 April 2022.