Bilateral mediastinal lymphadenopathy with cough and shortness of breath

Antoniya Kamenova[1], Tara Sathyamoorthy[1], Gillian Bain[2], Patrizia Viola[3] and George A. Margaritopoulos[1,4]

[1]Interstitial Lung Disease Unit, London North West University Healthcare NHS Trust, London, UK. [2]Radiology Department, London North West University Healthcare NHS Trust, London, UK. [3]Histopathology Department, Imperial College Hospital, London, UK. [4]Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK.

Corresponding author: George A. Margaritopoulos (georgios.margaritopoulos@nhs.net)

Shareable abstract (@ERSpublications)
Silicosis and sarcoidosis have very similar radiological appearances and a thorough occupational history may be the only clue to the diagnosis https://bit.ly/3Usxcj7

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Presenting complaint

A 48-year-old male was referred to the respiratory clinic with a few months' history of a persistent dry cough and mild breathlessness but no haemoptysis or constitutional symptoms. There were no joint pains or rash. He had no past medical history and was not on any regular medications. He was an ex-smoker with a smoking history of 20 pack-years, having quit smoking 3 years prior to the presentation. He had been working as a delivery driver for 1 year.

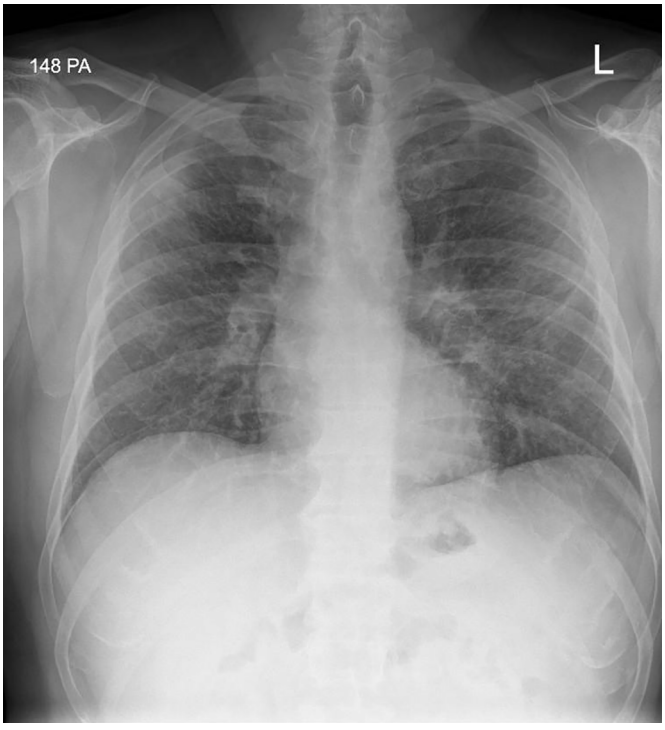

FIGURE 1 Posteroanterior chest radiograph on initial presentation.

Investigations

A chest radiograph was organised in the first instance (figure 1).

Task 1

Describe the findings on the chest radiograph.

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Subsequently the patient underwent chest high-resolution computed tomography (HRCT), which showed enlarged mediastinal and hilar lymph nodes, upper zone dense bilateral subpleural opacities and reticulation extending towards the periphery (figure 2).

Task 2

What further investigations would you arrange at this stage?

a) Endobronchial ultrasound (EBUS) and lymph node biopsies
b) Interstitial lung disease (ILD) screening bloods including antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), extractable nuclear antigen (ENA) antibodies, anti-double-stranded DNA (anti-dsDNA) antibodies, complement C3 and C4, rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP) antibody, anti-glomerular basement membrane (anti-GBM) antibody, immunoglobulins, myositis panel, avian precipitins, *Aspergillus* precipitins, creatine kinase (CK) and serum angiotensin-converting enzyme
c) Pulmonary function tests: spirometry and diffusing capacity of the lung for carbon monoxide (D_{LCO}) test
d) All of the above

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The patient underwent all of the above investigations.

The EBUS histology showed necrotising granulomatous inflammation. The EBUS bacterial, mycobacterial and fungal cultures were negative, as was the tuberculosis (TB) PCR test. Bronchial washings cytology showed no malignant cells.

Screening blood tests, including full blood count, renal profile, liver function tests, bone profile and autoimmune screen, revealed only a raised angiotensin-converting enzyme at 117 $U \cdot L^{-1}$.

Mantoux was negative at 11 mm, but not completely anergic, *i.e.* there was a degree of skin reactivity to the injected antigens as opposed to a completely absent reaction as would be seen in an anergic test. Given the patient had no risk factors for immunosuppression, a cut-off value of 15 mm would denote a positive test.

Baseline pulmonary function tests showed forced expiratory volume in 1 s (FEV_1) 3.03 L (81% predicted), forced vital capacity (FVC) 3.52 L (74% predicted), FEV_1/FVC 0.86, D_{LCO} 54% predicted, and transfer coefficient of the lung for carbon monoxide (K_{CO}) 90% predicted. These results would fit with a restrictive

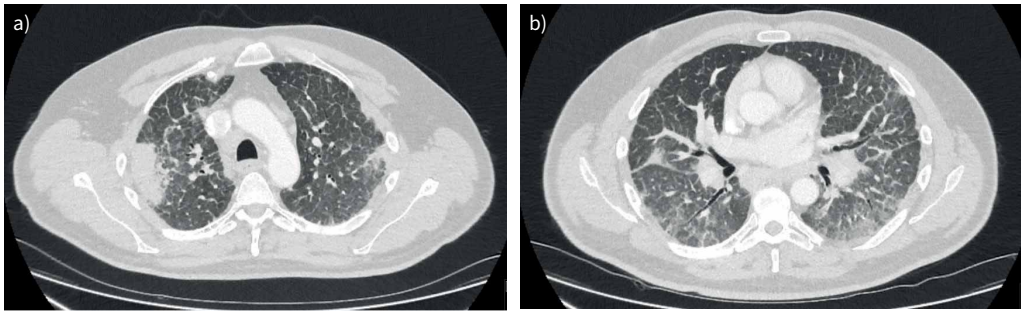

FIGURE 2 High-resolution computed tomography showing mediastinal and hilar lymphadenopathy, upper zone dense bilateral subpleural opacities and reticulation extending towards the periphery. a, b) Different cross sections.

pattern given the reduced FVC, but preserved FEV_1/FVC ratio. There is also a moderate reduction in the diffusing capacity.

The case was discussed at a dedicated ILD multidisciplinary team (MDT) meeting and a diagnosis was reached.

Task 3

What is your provisional diagnosis at this stage?

a) TB
b) Hypersensitivity pneumonitis
c) Granulomatosis with polyangiitis (GPA)
d) Lung cancer
e) Sarcoidosis

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Clinical course

The patient received an MDT working diagnosis of sarcoidosis. He was treated with intravenous methylprednisolone and subsequently with 10 mg of oral prednisolone.

On clinical review 2 months after the initial presentation, the patient reported progressive dyspnoea, cough and a new central chest discomfort.

Repeat lung function testing 8 weeks after he had been pulsed with methylprednisolone showed a deterioration, with FEV_1 2.4 L (65% predicted), FVC 2.84 L (60% predicted), FEV_1/FVC 0.84, D_{LCO} 45% predicted and K_{CO} 78% predicted.

Repeat HRCT 6 months after the initial HRCT showed progression with dense bilateral subpleural opacities (progressive massive fibrosis) and persistence of the interlobular septal thickening.

The case was discussed again at a dedicated ILD MDT meeting.

Task 4

What further investigations should be suggested by the MDT at this stage?

a) Repeat EBUS
b) Positron emission tomography computed tomography (PET CT)
c) Lung biopsy
d) Thoracic ultrasound
e) a and b
f) b and c

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PET CT was arranged to identify a suitable site for a surgical lung biopsy and showed moderately avid dense peripheral opacities and right hilar/subcarinal lymphadenopathy (maximum standardised uptake value (SUV_{max}) 5.3; figure 3).

A video-assisted thoracoscopic surgery biopsy from the right middle/lower lobe showed non-necrotising granulomas, many of which were completely hyalinised (figure 4). Numerous giant cells with cholesterol clefts and aggregates of chronic inflammatory cells were present.

The histological findings of hyalinised non-necrotising granulomas and cholesterol clefts raised the suspicion of an occupation-related disease. A more detailed occupational history was taken and revealed that the patient worked as a stonemason for 10 years. In addition, the patient's brother-in-law had worked with him as a stonemason and had unfortunately passed away a few months ago. The patient's brother-in-law was still working as a stonemason and had presented with the same symptoms. The patient's brother-in-law had been told he had pulmonary infiltrates, but no further details were known about his respiratory diagnosis.

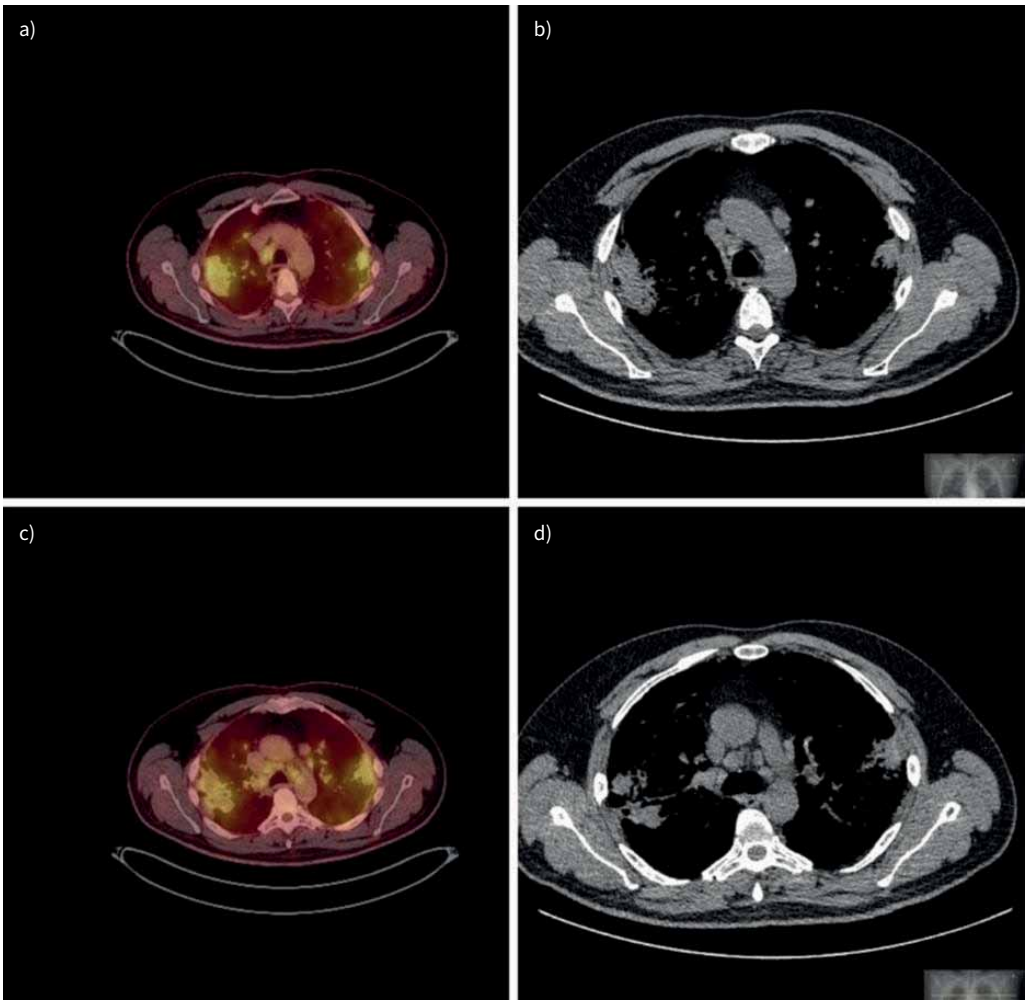

FIGURE 3 Positron emission tomography computed tomography scan showing avid mediastinal lymphadenopathy and upper lobe consolidations. a–d) Different cross sections.

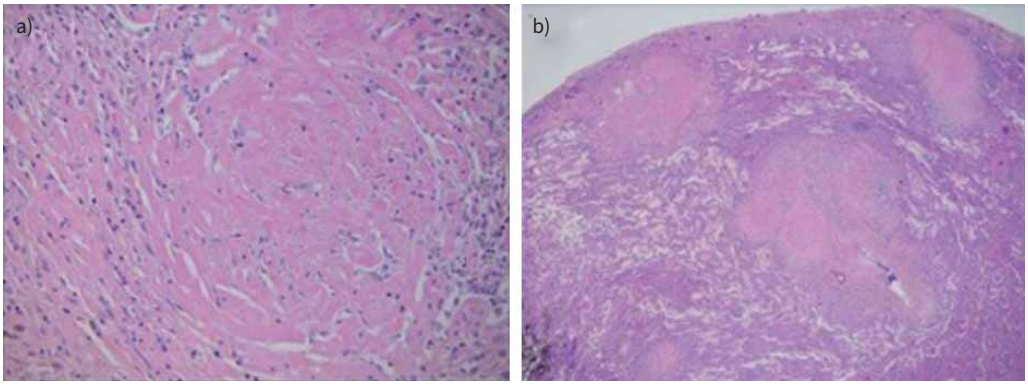

FIGURE 4 Pulmonary biopsy samples showing non-necrotising granulomas, many of which were completely hyalinised. a) High magnification (haematoxylin and eosin 10× magnification) and b) lower magnification (haematoxylin and eosin 4× magnification).

Diagnosis

Task 5

What is the diagnosis?

a) Asbestosis
b) Silicosis
c) Coal-worker's pneumoconiosis
d) Berylliosis
e) Sarcoidosis

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The imaging, histology and silica exposure history were taken into consideration. Following discussion in a specialist ILD MDT meeting, the diagnosis was one of silicosis. Unfortunately, the patient's occupational exposure had already taken place in the past, but normally removing the exposure should be the first step in the management of occupational lung disease. The patient is maintained on 10 mg of prednisolone and is currently clinically stable. He was referred to a lung transplantation centre and has been accepted and added to the lung transplant list.

Discussion

This case highlights the importance of taking a thorough occupational exposure history, which on some occasions may be the only clue towards the underlying diagnosis.

Taking a detailed and comprehensive occupational exposure history is crucial as there can be a very long latency period of up to 50 years between certain occupational exposures and the development of a condition [4]. While there usually is a dose–response relationship with occupational exposures and the corresponding diseases, short-lived exposures can also have a significant impact and should not be neglected. Moreover, while there are working regulations for the maximum permitted concentrations of a range of substances in the workplace, certain respiratory allergic conditions may develop even at levels below the mandated maximum permitted concentration as sensitisation towards these substances can still occur [4].

For these reasons, an adequate occupational exposure history should include each job that the patient has held since they started working, the specific tasks that were performed, any visible dust or mist in the atmosphere in the workplace, any visible dust on work surfaces, any correlation of symptoms with being at work, any visible dust in sputum produced, and any unwell colleagues. It is also critical to clarify what personal protective equipment (PPE) the patient had used and whether they were appropriately fit tested and trained how to use the PPE [4]. In this case both the patient and close members of his family had the same occupation, and in the case of his brother-in-law also had a confirmed respiratory condition. Conversely, identifying an occupational condition in an index patient may have implications for their colleagues who may also be affected; it would be important for the working conditions in that workplace to be scrutinised.

Silicosis, which develops after exposure to silicon dioxide (SiO_2), also known as silica, is the most common occupational respiratory condition worldwide. There are multiple forms of silica, which can be split into crystalline forms (the most common of which is quartz) and amorphous forms. Traditionally, silicosis has been considered to develop after inhalation of freshly fractured crystalline free silica known as respirable free silica (RFS). RFS is composed of particles smaller than 5 μm, which are small enough to reach the terminal airways where they are ingested by macrophages and lymphocytes and are either transported to lymph nodes or lead to further accumulation of macrophages and eventual formation of fibrosing nodules known as "silicotic nodules" [5].

It is crucial for respiratory professionals to be aware of the occupations that are associated with significant exposure to silica. One of the reasons that silicosis incidence remains high is that while there are existing workplace regulations for occupations that are well-known to be associated with significant exposure to silica, such as all types of mining, foundry work, stone masonry, quarry work and brick making, there are emerging sources of silica exposure that have only become apparent in recent decades and for which appropriate workplace regulations may not be applied. An important novel source of silica exposure is the manufacture of artificial stone, which is a mixture of finely crushed rock and polymeric resin. Artificial stone has a very high content of silica, resulting in very high concentrations of RFS when it is cut with a hand-held circular saw. Other emerging sources of silica exposure are the sandblasting of denim jeans, hydraulic fracking and jewellery cleaning [5].

Depending on the pattern of occupational exposure, different clinical forms of silicosis develop, which can be split into chronic, accelerated and acute. Chronic silicosis is associated with exposure to a low

concentration of RFS over a prolonged period of time and is characterised by silicotic nodules which over time increase in size and coalesce to form masses of 1 cm or more, termed progressive massive fibrosis [6].

The diagnosis of silicosis can be challenging and requires referral to specialised centres where a dedicated ILD MDT can provide a working/definite diagnosis and where the patient can be reviewed by experts in occupational health medicine. Further evidence to support the diagnosis can be provided by identifying birefringent crystals intracellularly in macrophages from bronchoalveolar lavage or on lung tissue biopsy [7].

This case highlights the diagnostic challenge of differentiating between sarcoidosis and silicosis. The two conditions have similar radiological appearances, so a computed tomography scan is not enough to differentiate between them [8]. Furthermore, epidemiological studies have demonstrated that exposure to silica increases the risk of developing sarcoidosis making the diagnosis even more challenging [9]. Exposure to silica increases the prevalence of multiple other respiratory conditions also associated with bilateral hilar lymphadenopathy, including TB, nontuberculous mycobacterial infections and fungal infections. The risk of developing lung cancer and rheumatoid arthritis also is increased by exposure to RFS [5].

There is no current effective treatment for silicosis. Once silicosis has been diagnosed, cessation of exposure to silica is vital; but unfortunately, the fibrotic process may continue to progress even after the patient is no longer exposed to RFS. Given the increased risk of developing lung cancer in patients with silicosis, advocating for smoking cessation is paramount. Pulmonary rehabilitation and supplementary oxygen may be indicated. If the patient has developed an obstructive spirometry, they could benefit from bronchodilators [7]. Occupational fibrotic ILDs that present with a progressive phenotype can now be treated with an antifibrotic agent, namely nintedanib [10]. Patients with advanced silicosis who are eligible should be referred for a lung transplant [7].

Key points

- Taking a thorough occupational history is a key part of assessing patients with chronic dyspnoea and cough and may on occasion be the only clue to the diagnosis.
- Silicosis and sarcoidosis have very similar radiological appearances and further tests such as a lung biopsy may be required to clarify the diagnosis.

Self-evaluation questions

1. Regarding occupational exposure to silica, which of the following statements are true?
    a) Foundry workers are at risk of developing silicosis
    b) Working with artificial stone leads to exposure to high levels of RFS
    c) Cristobalite is an amorphous form of silica
    d) Occupational exposure to silica is very common in low- and middle-income countries
    e) Short-term exposure to high concentrations of RFS is not associated with a significant risk of developing silicosis
    f) The fibrotic process of silicosis stops once exposure to silica is removed
2. Which of the following conditions is <u>not</u> a recognised cause of bilateral hilar lymphadenopathy?
    a) Sarcoidosis
    b) Silicosis
    c) Eosinophilic granulomatosis with polyangiitis
    d) Berylliosis
    e) Histoplasmosis
3. Which of these conditions is more commonly associated with necrotising rather than non-necrotising granulomas?
    a) Granulomas with polyangiitis
    b) Sarcoidosis
    c) Silicosis
    d) Hypersensitivity pneumonitis
    e) Berylliosis
4. Which is a recognised radiological feature of chronic silicosis?
    a) Tree-in-bud opacification
    b) Nodules with upper zone distribution
    c) Emphysema
    d) Mosaic attenuation
    e) Cystic airspaces

Answer 1

The initial chest radiograph demonstrated bilateral hilar lymphadenopathy and background fibrotic reticular changes.

<< Go to Task 1

Answer 2

d. The patient's HRCT has demonstrated mediastinal and bilateral hilar lymphadenopathy, as well as features of ILD. EBUS would increase the diagnostic confidence regarding the causes of hilar and mediastinal lymphadenopathy, such as malignancy (lung cancer, lymphoproliferative disorder), infections (tuberculosis (TB)) or ILD (sarcoidosis). Blood tests can screen for connective tissue diseases and certain exposures associated with ILD. Pulmonary function tests can show the pattern of abnormality (obstructive, restrictive or mixed).

<< Go to Task 2

Answer 3

e. The combination of mediastinal and bilateral hilar lymphadenopathy with histology showing granulomatous inflammation and features of ILD on HRCT is suggestive of sarcoidosis [1]. It is possible for tissue samples in sarcoidosis to feature necrotising granulomatous inflammation, even though this is less typical than non-necrotising granulomas [2]. Steroids were initiated as the patient was symptomatic. A negative TB PCR and negative acid-fast bacilli culture make a diagnosis of TB unlikely [3]. There is no evidence to support a diagnosis of hypersensitivity pneumonitis from the clinical history regarding relevant exposures or medications and the precipitins to organic antigens are negative. The negative vasculitic screen and the lack of any epistaxis, haemoptysis or renal involvement make a diagnosis of GPA less likely. There is no evidence from the histology or cytology to support a diagnosis of lung malignancy.

<< Go to Task 3

Answer 4

f (b and c). As the diagnosis of sarcoidosis is becoming less plausible, a surgical lung biopsy was felt to be indicated given the diagnostic uncertainty in this case. A PET CT scan can facilitate targeting metabolically active lesions, increasing the diagnostic yield of the biopsy.

<< Go to Task 4

Answer 5

b. The radiological and pathological findings along with the occupational exposure fit with a diagnosis of silicosis. The diagnosis is challenging to make without a thorough occupational history due to some radiological/pathological similarities to sarcoidosis. Another feature that is unusual for sarcoidosis is the Mantoux test not being anergic (as in this case; it was 11 mm despite being negative). There is no exposure history that would fit with asbestosis, coal-worker's pneumoconiosis or berylliosis.

<< Go to Task 5

Conflicts of interest: All authors declare no conflicts of interest.

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Suggested answers

1. a. true; b. true; c. false; d. true; e. false; f. false.
2. c.
3. a.
4. b.