

Case report

A disease with many faces

A 31-year-old black man, previously resident in Angola, was referred to our hospital complaining of 6 months of progressively worsening shortness of breath with exertion and mucous productive cough. During this period, he had a significant weight loss (about 10 kg) and fatigue. His past medical history included suspected pulmonary tuberculosis (TB), for which he had completed 6 months of anti-bacillary treatment in the year before. He is a construction worker and a nonsmoker, with no other environmental exposure or medication. The physical examination was remarkable for slight tachycardia (heart rate 105 beats·min⁻¹), tachypnoea (respiratory rate 20 cycles·min⁻¹), oxygen saturation of 94% and bilateral inspiratory crackles on both lungs. Figure 1 shows the chest radiograph.



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Figure 1 Posteroanterior chest radiograph.

Task 1

What pattern is observed in the chest radiograph?

- a) Bilateral cysts
- b) Bilateral consolidation
- c) Micronodular diffuse opacities
- d) Bilateral hilar node enlargement
- e) Bilateral hilar node enlargement and micronodular diffuse opacities

Task 2

Considering the previous information, which diagnosis is less probable?

- a) Miliary TB
- b) Pulmonary metastasis of malignancy
- c) Sarcoidosis
- d) Langerhans cell histiocytosis
- e) Silicosis

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Can you diagnose this man with progressively worsening shortness of breath, mucous productive cough, weight loss, fatigue and a history of suspected pulmonary tuberculosis? <http://bit.ly/2VUdnTr>



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Answer 1

c) Micronodular diffuse opacities

Answer 2

d) Langerhans cell histiocytosis

The patient underwent further investigation. First, laboratory testing showed mild leukopenia (4.2×10^9 cells·L⁻¹; normal range (NR) 4.5 – 11.0×10^9 cells·L⁻¹), with normal differential white cell count, haemoglobin and platelets. He had a slightly abnormal liver profile: alkaline phosphatase 162 U·L⁻¹ (NR 40 – 150 U·L⁻¹), gamma glutamyltranspeptidase 109 U·L⁻¹ (NR 12 – 64 U·L⁻¹), aspartate aminotransferase 56 U·L⁻¹

(NR 5 – 34 U·L⁻¹) and alanine aminotransferase 71 U·L⁻¹ (NR 0 – 55 U·L⁻¹). No renal dysfunction or electrolyte imbalance was found. Sedimentation rate was elevated (66 mm·h⁻¹; NR <11 mm·h⁻¹), as was C-reactive protein (10.7 mg·L⁻¹; NR <5 mg·L⁻¹). Serological tests for infectious disease were negative (HIV, hepatitis B virus, hepatitis C virus, cytomegalovirus and Epstein–Barr virus). The level of serum angiotensin-converting enzyme (ACE) was raised (307 U·L⁻¹; NR 16 – 85 U·L⁻¹) with normal serum and 24-h urine calcium.

Secondly, three sputum specimens submitted for microscopic detection of acid-fast bacilli and PCR for *Mycobacterium tuberculosis* DNA were negative. Culture results for mycobacteria in sputum and blood were not yet available.

Thirdly, computed tomography (CT) of the chest was performed, which is presented in figure 2.

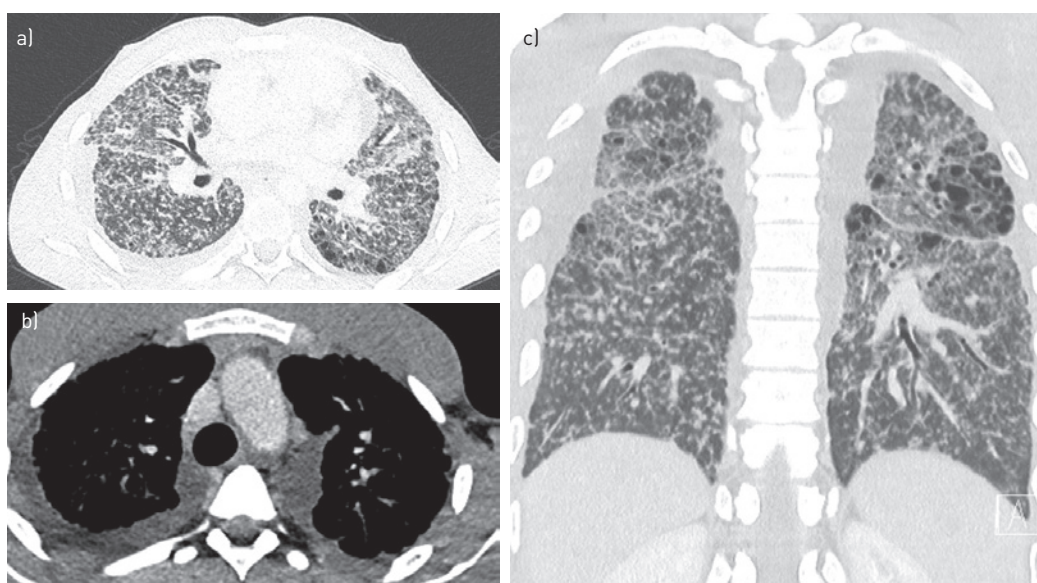


Figure 2 Chest CT shows a) multiple and bilateral micronodules with random distribution, traction bronchiectasis especially in upper lobes; and b) pleural thickening. c) View of coronal section.

Task 3

What would be your next approach?

- No further investigation is needed: the high level of ACE is specific for sarcoidosis and CT findings are typical
- Start empirical anti-bacillary treatment, since the most likely hypothesis is TB reactivation
- Screening for blood tumour markers
- Endobronchial ultrasound (EBUS)
- Bronchofibroscopy with bronchoalveolar lavage (BAL) and biopsies

Answer 3**e) Bronchofibroscopy with BAL and biopsies**

The serum ACE is not specific for sarcoidosis and could be high in a wide variety of conditions, including TB and silicosis. In CT scans, the most common parenchymal pattern in pulmonary sarcoidosis is micronodular lesions with perilymphatic distribution. A miliary micronodular distribution may warrant the inclusion of TB, pneumoconiosis and metastatic lesions in the differential diagnosis. Blood tumour markers are not indicated to diagnose malignancy, since they have low sensitivity and specificity. Our investigation for an occult cancer included abdominal CT scanning, which showed hepatosplenomegaly with millimetric hypodense nodules. There was no lymphadenopathy. No masses or nodules were reported in the gastrointestinal tract. Neck ultrasonography was normal. Additionally, serum electrophoresis had an increased gamma peak, the level of immunoglobulin G was high ($25.9 \text{ g}\cdot\text{L}^{-1}$; NR $7\text{--}16 \text{ g}\cdot\text{L}^{-1}$), but there was no monoclonal peak in serum immunofixation. In this specific case, EBUS is not a useful diagnostic exam due to absence of mediastinal lymphadenopathy.

We then performed a bronchofibroscopy, which is presented in figure 3. Microbiological tests were negative. Bronchial and transbronchial lung biopsies had no granulomas or neoplastic tissue. BAL showed lymphocytosis (25%) with slightly high $\text{CD4}^+/\text{CD8}^+$ and $\text{CD4}^+\text{CD103}^+/\text{CD4}^+$ ratios (2.54 and 0.25, respectively).

At this point, the results of cultures for mycobacteria of sputum, blood and BAL were negative. Lung function tests revealed a severe restrictive pattern: forced vital capacity (FVC) 1.28 L (24% predicted), forced expiratory volume in 1 s (FEV_1) 1.09 L (25% pred), total lung capacity 2.28 L (39% pred) and decreased diffusing capacity of the lung for carbon monoxide (D_{LCO}) at 19% pred, which rose to 70% pred when corrected for alveolar



Figure 3 Bronchofibroscopy, showing no endobronchial abnormalities.

volume (transfer coefficient of the lung for carbon monoxide (K_{CO})).

After discussion in our multidisciplinary team, we proceeded to a CT-guided transthoracic biopsy of the right pleural thickening, which was insufficient for diagnosis. The procedure was complicated by symptomatic pneumothorax of moderate volume, prompting chest drainage and hospital admission. After 1 week without resolution, he was submitted to video-assisted thoracoscopic surgery (VATS). The lung presented with increased thickness, little elasticity and scattered micronodules. The parietal pleura also has dispersed micronodules. Wedge resection of the middle lobe and parietal pleura biopsy was performed, followed by chemical pleurodesis, without complications. Figure 4 shows the histopathological findings.

The patient was diagnosed with systemic sarcoidosis with involvement of lung, pleura, liver and spleen. During the diagnostic process, he became more breathless and developed moderate hypoxaemic respiratory failure with arterial oxygen tension 64 mmHg in room air (NR 80–100 mmHg). Additionally, a transthoracic echocardiogram revealed mild dyssynergy of the interventricular septum without other abnormalities. Cardiac magnetic resonance imaging excluded cardiac sarcoidosis.

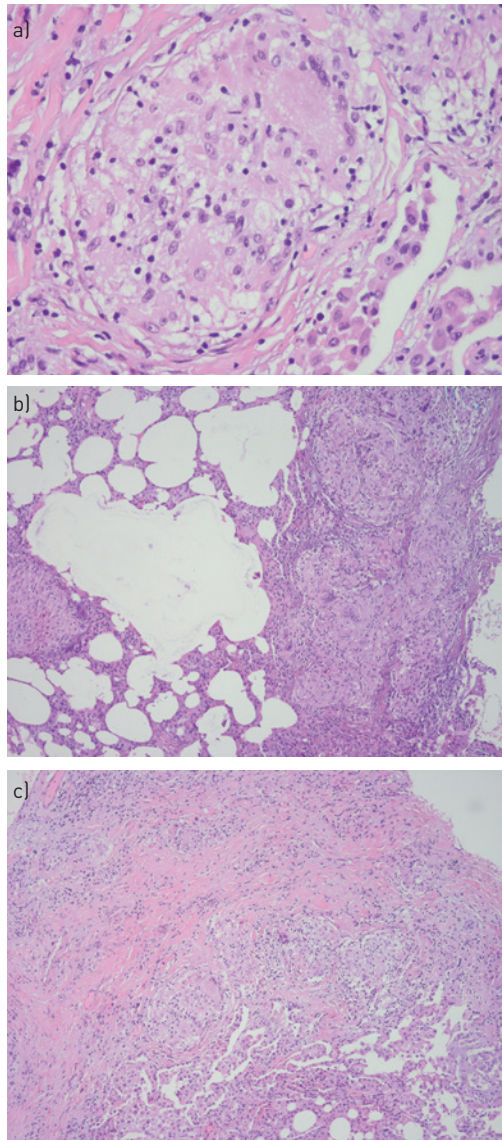


Figure 4 Microscopic examination of lung and pleural biopsies with haematoxylin and eosin stain. a) Non-necrotising epithelioid granulomas with multinucleated giant cells (40× magnification) in b) interstitial and sub-pleural location (10× magnification). c) Fibrotic areas and diffuse inflammatory lymphoplasmacytic infiltrate with granulomas in parietal pleura (10× magnification). No neoplastic tissue. Special stains for fungus and mycobacteria were negative (not shown).

Task 4

How would you proceed?

- a) Observation alone and repeat lung function test and chest CT scan in about 3 months
- b) Start corticosteroids as they are the mainstay of treatment
- c) Immunosuppression with methotrexate is the first choice of treatment
- d) Urgent referral to lung transplant
- e) As the patient has no eye symptoms, no ophthalmological evaluation is recommended

Answer 4

b) Start corticosteroids as they are the mainstay of treatment

The patient started prednisolone 60 mg ($1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) for 10 days, gradually tapered to a maintenance dose of 20 mg. After 6 months of treatment, he experienced a progressive improvement of shortness of breath and fatigue. No other new symptoms were referred and ocular involvement was excluded. Lung function tests showed an increase of lung volumes (FVC 1.98 L (41% pred), FEV1 1.67 L (42% pred)) and of gas transfer (DLCO 33% pred, KCO 89% pred). The arterial oxygen tension was normal and the chest radiograph (figure 5) also showed an improvement of nodular opacities.

Currently, prednisolone has been reduced to 10 mg and the patient will repeat chest CT scanning and lung function tests during the ninth month of treatment.

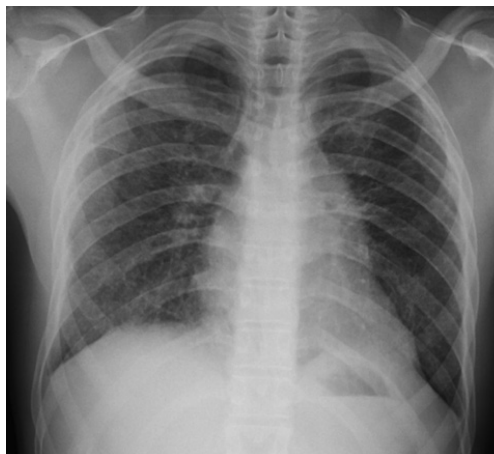


Figure 5 Posteroanterior chest radiograph, showing mild bilateral nodular opacities.

Task 5

For the management of this patient, which of the following is not true?

- It is useful to give supplementation with vitamin D and calcium to prevent osteopenia and osteoporosis
- He was responsive to monotherapy with oral corticosteroids in moderate to high doses
- If disease progresses with the current dose of prednisolone, addition of a second-line agent should be considered
- Methotrexate is one immunosuppressant that can be used as a corticosteroid-sparing agent
- The goal of treatment involves regression of disease to give stabilisation and prevention of progression

Answer 5

a) It is useful to give supplementation with vitamin D and calcium to prevent osteopenia and osteoporosis

For primary prevention of glucocorticoid-induced osteoporosis, bisphosphonate should be used as the first treatment strategy in those patients who are expected to use glucocorticoid for an extended period of time. In the presence of osteopenia or osteoporosis, the supplementation with vitamin D and calcium can be considered with caution due to the risk of hypercalcaemia and hypercalciuria in patients with sarcoidosis.

Discussion

Sarcoidosis is a multisystemic disorder characterised by the presence of noncaseating granulomas in tissues. It most frequently affects the lungs but any organ may be involved.

Multiple environmental and microbial agents have been suggested to cause sarcoidosis and mycobacterial infection has always been one of the most important suspects. However, there is no consensus on microbial pathogenesis of sarcoidosis [1]. This disease occurs worldwide, affecting individuals of all ages and races, but northern Europeans and African Americans are the two ethnic groups consistently reported to be most affected [2]. Notably, in TB-endemic countries, sarcoidosis is frequently undiagnosed [3]. The incidence peaks in men aged 30–50 years and in women aged 50–60 years [4].

A combination of clinical, radiological and histological criteria is used to diagnose sarcoidosis. In the appropriate clinical context, observation of typical imaging features (bilateral hilar lymphadenopathy, perilymphatic nodules, interlobular septal thickening and bilateral perihilar opacities, predominant in the upper and middle lung fields) suggests the diagnosis of pulmonary sarcoidosis with high confidence. In contrast, miliary opacities are atypical and rare, present in <1% of cases of sarcoidosis [5]. Pleural disease is also sporadic in sarcoidosis, occurring in only 1–4% of patients, comprising pleural effusion, pleural thickening, pneumothorax and (rarely) pleural calcification [6].

Some clinical considerations could be useful in the presence of a miliary opacities pattern. History of exposure to beryllium and silica may be suggestive of pneumoconiosis. Cytological examination of BAL may detect possible malignancies and cultural examination can lead to a TB or fungal infection diagnosis. Nevertheless, diagnosis of sarcoidosis can be challenging, as in our case, due to remarkable clinical and imaging similarities of these illness. The diagnostic confirmation includes the presence of noncaseating granulomas in a biopsy specimen, if other causes for granulomatous inflammation are ruled out. The yield of diagnosis is higher if we combine endobronchial and transbronchial biopsies and EBUS-guided transbronchial needle aspiration. The BAL can also be an adjuvant measure, with lymphocytic predominance and elevated CD4⁺/CD8⁺ ratio predictive of sarcoidosis. A positron emission tomography scan can also be used to assess the extent of disease and to uncover a suitable location for biopsy. In our case, because the patient had a pneumothorax with air leak, a more invasive approach was performed. The VATS was performed with both therapeutic and diagnostic purposes.

The management of sarcoidosis is variable and should take into account several factors, such as symptoms, organ involved and severity of the disease. For those who require treatment, the aim is to suppress and limit the burden of granulomatous inflammation. Accordingly, corticosteroids are the mainstay of therapy [7], while immunomodulatory and cytotoxic drugs are generally used in patients who fail to respond to or cannot tolerate corticosteroids, or who require unacceptably high doses of corticosteroids in the long term [8]. The optimal tools and timing to assess response to treatment in patients with pulmonary sarcoidosis have not yet been defined. According to expert opinion, a favourable response to treatment is generally defined by a symptomatic improvement, a reduction or clearing of radiographic abnormalities, and physiological improvement (increase in FVC $\geq 10\%$ or in DLCO $\geq 15\%$ from baseline values) [9]. Lung transplantation might represent a treatment option for selected patients with end-stage disease, although the optimal timing for referral remains uncertain. For primary prevention of glucocorticoid-induced osteoporosis, bisphosphonate should be used as the first treatment strategy [10].

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Conflict of interest

None declared.

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