CASE REPORT

Mediastinal widening and miliary chest radiograph pattern in a middle aged man: Could it be sarcoidosis?

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SUMMARY

A diagnosis of sarcoidosis is based on suggestive radiographic pattern, presence of non-caseating granulomas and negative fungal and acid-fast bacilli (AFB) cultures. Sarcoidosis usually presents with hilar and/or mediastinal lymphadenopathy and distinct parenchymal radiographic patterns, such as fine nodular, reticulonodular or acinar opacities and rarely focal nodules or masses. A diffuse miliary pattern occurs in less than 1% of cases and can be identical to patterns seen in tuberculosis, fungal infections, histiocytosis and miliary metastases. Here the authors report the case of a 48-year-old man who presented with mediastinal widening and miliary pattern on chest radiograph, initially erroneously treated for tuberculosis. Transbronchial biopsies, bronchoalveolar lavage (BAL) and serological tests were compatible with sarcoidosis, while BAL cultures were negative for fungi and AFB growth. The patient finally demonstrated clinical and radiological remission under corticosteroids. Clinicians should consider sarcoidosis in the differential diagnosis when bilateral miliary-type lesions are revealed on chest X-ray.

BACKGROUND

Sarcoidosis is a generalised inflammatory disease of unknown aetiology that is characterised by the presence of non-caseating granulomas in the involved tissue or organ.¹ Any organ may be affected (including the liver, spleen, skin, eyes, bones, salivary glands, cardiac and nervous system), but mediastinal lymph nodes and lung parenchyma involvement is the most common, and frequently the sole, manifestation of the disease.² Thoracic involvement is described in up to 90% of patients with sarcoidosis. The most common radiological finding of pulmonary sarcoidosis is bilateral hilar lymphadenopathy with or without mediastinal lymph node enlargement, followed by interstitial lung disease with predominant reticulonodular shadowing pattern with perilymphatic distribution.³ Atypical patterns, such as alveolar or mass-like opacities, honeycomb-like cysts and pleural disease, may also be seen, while diffuse miliary pattern presents in less than 1% of cases and can be identical to patterns seen in tuberculosis (TB), fungal infections, histiocytosis and miliary metastases.⁴⁻⁸ Here we report the case of an adult, immunocompetent patient with sarcoidosis who presented with mediastinal widening and miliary pattern on chest radiograph and showed clinical and radiological remission under corticosteroids.

CASE PRESENTATION

A 48-year-old ex-smoker (60 packs/year) male patient working as a gardener with a known history of thalassaemia heterozygosity was admitted to our hospital due to low-grade fever, non-productive cough and stage II mMRC dyspnoea that initiated a month prior to admission. The patient had been hospitalised a year ago with similar symptomatology and a 'tree-in-bud' appearance on chest CT. Although TB infection was not proven at the time (negative tuberculin skin test, negative sputum and bronchoalveolar lavage (BAL) culture), the patient was empirically treated with anti-TB therapy (INH-RIF-EMB-PRZ). He gradually demonstrated clinical and radiological improvement; however, treatment was stopped after 4 months due to drug-induced liver injury.

The patient had remained asymptomatic for a year before being admitted to our hospital and his symptoms had begun a month earlier. On admission, the patient was apparently in a good state of health. Blood pressure was 110/50 mm Hg, heart rate was 74 bpm, body temperature was 36.7°C, respiratory rate was 16 breaths/min, oxygen saturation while breathing room air was 98% and arterial blood analysis was normal. Auscultation was unremarkable and further physical examination revealed no abnormalities.

INVESTIGATIONS

Haematological examination revealed mild anaemia (haematocrite 39%, haemoglobin 12.8 g/dL) with normal total leucocyte and platelet counts (white cell count 10 000/ μ L, 58% neutrophils, 18% lymphocytes, 5% monocytes, 3% eosinophils and platelets 349 000/ μ L). Erythrocyte sedimentation rate was normal (5 mm/h) and C reactive protein was slightly elevated (0.46 mg/dL, normal <0.3 mg/dL). Serum glucose, urea, creatinine, electrolytes and liver enzymes were within normal limits. Several other serological tests, including rheumatoid factor, antinuclear antibody, antinative DNA antibodies were all negative. Protein electrophoresis and urinary protein excretion were within normal limits. Serum IgE was slightly elevated (247.5 U/mL). Serum and urine calcium measurements were normal (9.6 mg/dL and 240 mg/24 h, respectively). Serum ACE (SACE) was elevated (116 U/L, normal <57 U/L). Blood, urine and sputum cultures were also negative for mycobacteria, common bacteria and fungi. Tuberculin skin test and interferon- γ release assay (Quantiferon TB-Gold) were negative. Lung function testing was indicative of restrictive

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disease (forced expiratory volume in 1 s (FEV₁): 2.9 L, 79% predicted; forced vital capacity (FVC): 3.75 L, 82% predicted; FEV₁/FVC: 77%; carbon monoxide transfer capacity: 7.6 mmol/min/kpa, 75% predicted; total lung capacity: 4.49 L, 66% predicted; residual volume: 1.37 L, 66% predicted)

Chest X-ray on admission showed a miliary pattern and enlarged hilar lymph nodes (figure 1A). The patient subsequently was subjected to a high-resolution CT (HRCT) scan which demonstrated bilateral hilar and mediastinal lymphadenopathy, more prominent in the right paratracheal lymph nodes (LN4R), accompanied by numerous small (1–4 mm) pulmonary nodules scattered in all lung fields (figure 1B–D). The patient underwent fiberoptic bronchoscopy. Direct examination of the bronchi revealed only hyperaemia of bronchial mucosa. BAF fluid (BALF), transbronchial needle aspirates and biopsies, as well as transbronchial (TBB) and endobronchial biopsies (EBB) were also obtained. Cultures for bacteria, fungi and *Mycobacterium tuberculosis* were negative. Cytological examination of the BAL was negative for malignancy but revealed a lymphocytic predominance (22%) and an elevated (8.3) CD4/CD8 T-cell ratio. EBB and TBB specimens were negative for malignancy but revealed non-caseating granulomas (figure 2A,B). Patient underwent an ophthalmological and cardiological examination, which revealed no abnormalities.

DIFFERENTIAL DIAGNOSIS

In the case of miliary opacities on chest radiography, the differential diagnosis includes, apart from sarcoidosis, infectious diseases (mainly miliary TB but also nocardiosis, fungal and viral pneumonitis), haematogenous metastases (from thyroid, renal cell, breast and pancreatic carcinomas, malignant melanoma and osteosarcoma), pneumoconioses and hypersensitivity pneumonitis.^{9 10} In particular, entities such as histoplasmosis, chickenpox and Langerhans cell histiocytosis can also present with miliary opacities, however even more rarely than sarcoidosis.¹¹ Therefore, differential diagnosis may often be very challenging for clinicians.

TREATMENT, OUTCOME AND FOLLOW-UP

The patient was diagnosed with sarcoidosis and was treated with corticosteroids (prednisolone) at 0.5 mg/kg (40 mg) for 1 month, gradually tapered to 5 mg/day. Steroids were stopped after 6 months, with clinical and radiological improvement (figure 3A–D). After 1 year follow-up, he was in good health, with normal chest radiograph and lung function tests. The patient, however, presented with a radiological and clinical relapse 18 months after treatment (figure 4A–D). Oral corticosteroids (prednisolone) at 40 mg/day for 1 month were once again prescribed, with gradual tapering to 5 mg/day within the following months, at which point his status (clinical and

Figure 1 Radiological examinations on admission of the patient. (A) Chest X-ray showing small nodular opacities corresponding to miliary pattern. (B) High resolution CT showing right paratracheal lymphadenitis as well as bilateral diffuse parenchymal micronodular pattern in the upper (C) and lower lobes (D), where some poorly defined macronodules are also present.

Figure 2 (A) Representative microphotographs of transbronchial lung biopsies stained with H&E ($\times 100$) showing lesions of granulomatous chronic inflammation (B) and in higher magnification ($\times 200$) small epithelioid granulomas in the presence of Langhans giant cells with no signs of caseous necrosis.

radiological) improved (figure 5A). Steroids were stopped again after 6 months of treatment and 1 year after his relapse, the patient is still in good health with normal chest X-ray (figure 5B).

DISCUSSION

A diagnosis of sarcoidosis is established when compatible clinical and radiological findings are supported by histological evidence of non-caseating epithelioid granulomas, provided that other diseases with similar findings are ruled out.³ Chest X-ray remains an essential examination not only because it can raise suspicion for the disease in otherwise asymptomatic patients, but also because of the staging system (table 1) that has been

based on chest radiographic findings and has great prognostic value.⁸

While chest X-ray remains a useful diagnostic tool, HRCT can reveal lesions that cannot otherwise be detected on chest X-ray. Chest radiographs only detect 50–60% of lymph nodes and 30–40% of parenchymal abnormalities found with HRCT.¹³ Bilateral hilar lymph node enlargement, alone or in combination with mediastinal lymph node enlargement, occurs in an estimated 95% of patients affected with sarcoidosis.⁸ When interstitial parenchymal changes are present, they usually follow a reticulonodular pattern,³ most commonly consisting of bilateral, symmetric and well-defined micronodular lesions of a perilymphatic distribution predominantly in

Figure 3 Radiological evaluation of the patient after treatment with oral corticosteroids. (A) Chest X-ray showing marked improvement. (B) High resolution CT demonstrating reduction in the size of the right paratracheal lymph nodes and almost complete absence of micronodules in the upper (C) and lower lobes (D).

Figure 4 Radiological evaluation of the patient on readmission 18 months later. (A) Chest X-ray showing deterioration. (B) High resolution CT demonstrating a small increase in the size of the right paratracheal lymph nodes compared with the previous scan as well as reappearance of the miliary pattern in upper (C) and lower lobes (D).

Figure 5 Chest X-rays of the patient after repeating treatment with oral corticosteroids (A) as well as 1 year after the relapse (B) showing no signs of miliary disease.

Table 1 Staging of pulmonary sarcoidosis based on chest radiography (Siltzbach staging¹²)

Stage 0	Absence of chest X-ray abnormalities	5–10%
Stage 1	Lymphadenopathy only	50%
Stage 2	Lymphadenopathy and parenchymal lung disease	25–30%
Stage 3	Parenchymal disease only	10%
Stage 4	Pulmonary fibrosis (honeycombing pattern)	5%

Percentages indicate the proportion of the population with a diagnosis of sarcoidosis who had the stage of disease at presentation.

the upper and middle zones. Linear opacities, traction bronchiectasis and architectural distortion are suggestive of fibrotic changes usually occurring in most advanced stages of the disease.¹⁴

Atypical HRCT findings of sarcoidosis may include uncommon patterns of lymphadenopathy, such as unilateral hilar lymph node enlargement (usually on the right side, seen in less than 5% of cases) or enlargement of mediastinal but not hilar lymph nodes.^{8 15 16} Atypical parenchymal manifestations include pulmonary nodules and masses, which are more often

Box 1 Differential diagnosis of diffuse micronodular (miliary) pattern in the lung

- ▶ Haematogenous metastatic diseases
 - Thyroid carcinoma (common)
 - Renal cell carcinoma
 - Pancreatic carcinoma
 - Breast cancer
 - Melanoma
 - Osteosarcoma
- ▶ Infectious diseases
 - Nocardiosis
 - Histoplasmosis (rare), coccidioidomycosis
 - Cytomegalovirus (common), varicella-zoster (rare)
- ▶ Hypersensitivity pneumonia
- ▶ Granulomatous diseases
 - Tuberculosis (most common)
 - Sarcoidosis (rare)
- ▶ Occupational lung diseases
 - Silicosis
 - Pneumoconiosis
- ▶ Smoking-related interstitial lung diseases
 - Respiratory bronchiolitis-associated
 - Langerhans cell histiocytosis (rare)

seen bilaterally in perihilar or peripheral lesions and along with smaller satellite nodules at their periphery, can produce an appearance that has been termed the 'galaxy sign'.¹⁷ Alveolar or airspace opacification and linear reticular opacities as the predominant radiological feature of the disease are also not common.³ Pleural disease is also sporadic in sarcoidosis, occurring in only 1–4% of patients.

Miliary opacities are quite rare in sarcoidosis, seen in less than 1% of cases and diagnosis can be particularly challenging for clinicians (box 1). History of exposure to beryllium and silica may be suggestive of pneumoconiosis. Elevated SACE levels are helpful as a marker but have low specificity.¹⁸ Cytological examination of BALF may detect possible malignancies and cultures can lead to a tuberculosis infection diagnosis. The study of the cellular composition of BAL can also be useful

as lymphocytic predominance and elevated CD4/CD8 ratio are highly predictive of sarcoidosis.¹⁹ Since histological confirmation is crucial in establishing a diagnosis of sarcoidosis, biopsies from enlarged lymph nodes as well as TBB should be obtained.³ In our case, negative microbiological and cytological tests, compatible BAL findings, combined with typical pathological findings of hilar lymph nodes and TBB established the diagnosis of sarcoidosis.

Knowledge of typical and atypical radiological manifestations of sarcoidosis, combined with consistent medical history, symptomatology and laboratory findings as well as high index of clinical awareness, is essential for a prompt diagnosis and treatment.

Contributors Authors were not only involved with the patient's care but have actively contributed to this article. CB researched and drafted the initial manuscript. KS and EZ wrote the article and edited the graphical content. CG evaluated all tissue samples, prepared the graphical content and implemented final revisions and MG was involved in the writing and critical reviewing of the manuscript. All authors approved the final version of the manuscript.

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Learning points

- ▶ Sarcoidosis is a generalised inflammatory disease of unknown aetiology that is characterised by the presence of non-caseating granulomas.
- ▶ The most common radiological finding of pulmonary sarcoidosis is bilateral hilar lymphadenopathy with or without mediastinal lymph node enlargement, followed by interstitial lung disease with a predominant reticulonodular shadowing pattern with perilymphatic distribution.
- ▶ Diffuse miliary opacities in sarcoidosis are seen in less than 1% of cases and can be identical to patterns seen in tuberculosis, fungal infections, histiocytosis and miliary metastases.
- ▶ Knowledge of typical and atypical radiological manifestations of sarcoidosis is essential for a timely diagnosis and treatment.

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