Case report

Pleuroparenchymal sarcoidosis - A recognised but rare manifestation of disease

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A B S T R A C T

Pleural involvement is rare in sarcoidosis. The presence of a large symptomatic effusion in a patient with sarcoidosis should therefore prompt further investigation for an alternate aetiology. Here we present a case of confirmed pleuro-parenchymal sarcoidosis. We discuss the important differential diagnoses and review the current literature.

1. Case report

A 67-year-old Caucasian non-smoker female with a past medical history of hypertension and hypothyroidism presented to our clinic with a 12-month history of exertional dyspnoea and dry cough. She was otherwise well with no systemic, nasal or gastro-oesophageal symptoms. Her prescribed medications were levothyroxine, aspirin and losartan and these had not changed in recent years. She denied atopy, exposure to previous TB or recent travel and systems enquiry did not reveal any eye, genitourinary or gastrointestinal symptoms. She had worked throughout her career in administration.

Vital signs were recorded as pulse 80 bpm, blood pressure 130/50 mmHg, respiratory rate 17 and oxygen saturations of 97% air. Cardiorespiratory examination was normal. Lung function revealed: FEV1 1.14 (57% predicted), FVC 1.60 (67% predicted), FEV1/FVC ratio 71%, TLCO 3.30 (71% predicted), TLCO 5.48 (79% predicted) and KCO 1.95 (131% predicted). ECG showed sinus rhythm with no evidence of heart block. Chest X-ray showed blunting of the costophrenic angles and bilateral pleural effusion (Fig. 1a). High resolution computed tomography (HRCT) demonstrated bilateral hilar and central mediastinal nodal calcification, in the absence of significant lymphadenopathy, with perilymphatic nodularity in the upper and mid zones of the lungs and bilateral pleural effusions, left larger than right (Fig. 1a). Echocardiogram was normal.

Laboratory investigations revealed a mildly elevated ACE level (summarised in Fig. 2). Left sided chest ultrasound demonstrated an anechoic effusion, with an exudative lymphocytic yellow aspirate (lymphocytes 70%), with a normal adenosine deaminase (ADA) level that was negative to TB culture (summarised in Fig. 2).

Given the suspicion of pulmonary sarcoidosis, flexible bronchoscopy was undertaken to obtain a tissue diagnosis. Bronchoalveolar lavage samples demonstrated 90% macrophages and 10% lymphocytes. Cultures were negative for TB and fungi. Endobronchial biopsies (Fig. 1ci) demonstrated discrete non-necrotising epithelioid granulomas consistent with sarcoidosis. Transbronchial biopsies were non-diagnostic.

Sarcoidosis was considered the most likely overarching diagnosis and thus the patient was commenced on a tapering course of oral prednisolone therapy over the following 9 months. Initial clinical improvement was followed by progressive breathlessness. HRCT demonstrated stable parenchymal appearances but worsening right effusion (Fig. 1a and bii). MRI excluded cardiac sarcoidosis, demonstrating mild diastolic dysfunction only. Attempted diuresis, a repeat trial of tapering doses of prednisolone then introduction of methotrexate (12.5mg weekly) in conjunction with prednisolone 10mg had no significant benefit, with gradual worsening of bilateral effusions and symptoms over the subsequent 12 months (Fig. 1a). In light of this deterioration a definitive diagnosis was sought. Medical thoracoscopy was not technically feasible and thus she proceeded to right-sided video-assisted thoracoscopic (VATS) wedge lung biopsy and pleural biopsy with planned therapeutic drainage and talc pleurodesis.

Pleural biopsies showed features of chronic pleuritis with associated granulomata (Fig. 1c ii-iii). The lung VATS biopsy sections (Fig. 1c iv) showed pleural and subpleural granulomatous inflammation. A small interstitial granuloma was also noted. Ziehl-Neelsen stain was negative. Overall, these features are most suggestive of pleuro-parenchymal sarcoidosis.

A further trial of combination therapy (hydroxychloroquine (200mg bd), azathioprine (150mg daily) and prednisolone (10mg)) was attempted, stabilising the parenchymal disease over a 6-month period,

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but was associated with continued pleural fluid accumulation on the left, in the absence of re-accumulation on the right. The patient was subsequently referred for left-sided talc pleurodesis with a proposed plan to seek funding for anti-Tumour Necrosis Factor-α biological therapy if this failed.

2. Discussion

Sarcoidosis is a multisystem disease characterised by non-caseating granulomas. Whilst it most frequently affects the lungs and lymph nodes, extrapolummary presentations of the skin and eyes are also common. The differential diagnosis for nodal calcification and
parenchymal nodularity in this patient includes sarcoidosis, tuberculosis (TB) and occupational lung disease. The perilymphatic distribution of nodules would be suggestive of sarcoidosis and could account for the lymph node calcification. There has been no exposure to TB or silica making the latter diagnoses less likely.

Pleural involvement is a rare manifestation with variable reported incidence of effusion on chest radiograph as low as 0.16% in the largest retrospective cohort analysed to date [1]. Studies using thoracic ultrasound, with its superior sensitivity in detecting effusions indicate a higher incidence of 2.8% [2]. The limited data available from small case series of sarcoidosis-related pleural effusions (PEs) suggests they are often exudative and lymphocytic [2], typically with a CD4+/CD8+ ratio between 2.61 and 8.6 [3]. They are also more commonly right-sided (45%) and less frequently bilateral (22%) [4]. The largest case series has demonstrated that 60% of PEs in such cases were not related to sarcoidosis itself [2], and were attributable other processes such as ischaemic cardiomyopathies or infection. Serum amyloid A, soluble interleukin-2 receptor (sIL-2R), lysozyme and the glycoprotein KL-6 have all been proposed as potential serum biomarkers for sarcoidosis but each lacks specificity and sensitivity for clinical usage and to the authors knowledge have not been validated in pleural fluid [5]. The identification of pleural effusions (PEs) in this patient therefore prompted thorough investigation of the aetiology of both the interstitial lung disease and PEs.

The differential diagnosis of a lymphocytic PE includes; carcinoma, TB, lymphoma, chronic heart failure, autoimmune diseases and sarcoidosis. As the effusion was cytologically negative and CT showed no evidence of nodular or mediastinal thickening, malignancy was less likely. It is important to exclude tuberculosis and this was effectively achieved with normal pleural ADA levels in a Caucasian female. Lymphoma should also be considered and assessment of fluid lymphocyte subsets is useful to exclude this possibility. Finally, as the effusions were bilateral and lymphocytic, the chances of this being due to an autoimmune process or heart failure were increased. The patient was investigated accordingly with autoimmune profile, ECHO and cardiac MRI.

The significant, bilateral pleural involvement at initial presentation in this case is atypical for pleural sarcoidosis, as is the worsening of pleural disease control despite immunomodulatory therapy (Fig. 3 [6–15]). The vast majority of sarcoidosis-related PEs reported in the literature have been small and spontaneously resolve [16], whilst patients with larger symptomatic effusions have received corticosteroid therapy alone or in combination with hydroxychloroquine, with a good response (see Fig. 3 [6–15]).

Current paradigms suggest PEs may develop in the context of sarcoidosis due to inflammation of the visceral and parietal pleura secondary to peripheral lung granulomas [2]. The histology presented in this case certainly supports this hypothesis. Whilst PEs can occur in any of the Scadding radiological stages of sarcoidosis [4], there is a tendency to form during acute exacerbations [2]. Suppressing the immune response should therefore decrease net pleural fluid formation. The failure to do so in this case either suggests suboptimal control or an alternative mechanism behind fluid formation.

3. Conclusion

In summary, the presence of a large symptomatic PE in a patient with sarcoidosis is uncommon and should prompt further investigation for an alternate aetiology. In refractory cases, such as the one illustrated, invasive pleural intervention and immunomodulatory therapies may be required.

Declarations

None declared.
| Author          | Demographics | CT findings                                                                 | Pleural fluid characteristics | Treatment                                                                 |
|-----------------|--------------|------------------------------------------------------------------------------|-------------------------------|--------------------------------------------------------------------------|
| Fontecha Ortega et al. 2017. | 38 yr male African | Bilateral, predominantly right PE with mediastinal and hilar lymphadenopathy and patchy alveolar infiltrates. | Lymphocytic, exudative. ADA 72U/L, CD4+/CD8+ ratio >3.5. | Good response to oral corticosteroids                                   |
| Jha et al. 2016. | 65 yr male   | Multiple discrete and conglomering heterogeneous mediastinal and bilateral hilar lymphadenopathy. Right lower lobe ground glass opacities with minimal pleural right PE. | Haemorrhagic : Haematocrit 1.4%. Lymphocytic, exudative. ADA 53.2U/L. | Drainage of effusion via medical thoracoscopy. Good response to oral corticosteroids |
| Jenkins et al. 2016. | 46 yr male African American | Moderate right PE with moderate to large pericardial effusion | PE not sampled. | Good response to oral corticosteroids                                     |
| Joshi et al. 2015. | 42 yr male   | Diffuse micronodules with predilection for fissures and bronchovascular bundles and associated mediastinal lymphadenopathy. Multiple subcentimetric focal lesions diffusely scattered in liver, spleen and renal parenchyma. Subsequently developed large left PE. | Lymphocytic, exudative. ADA 5.93 U/L. | PE developed whilst on oral corticosteroids (prednisolone 30mg). PE drained by pleuroscopy. No reaccumulation on prednisolone and hydroxychloroquine. |
| Seashore et al. 2015. | 63 yr female African American | Large pericardial effusion with numerous right parapneumonic lung nodules, intrathoracic lymph node calcification and large left PE. | Lymphocytic exudative. ADA 18.6U/L, CD4+/CD8+ ratio >5. | Good response to 12 months of oral corticosteroids. |
| Kumagai et al. 2015. | 64 yr female Japanese | Bilateral hilar and multiple mediastinal lymphadenopathy, multiple parapneumonic nodules, multiple skin nodules and bilateral PEs. | Lymphocytic exudative. ADA 50.4U/L, CD4+/CD8+ ratio >5.62. | Thoracentesis initially. Good response to oral corticosteroids.         |
| Enomoto et al. 2015. | 69 yr male   | Bilateral PIs associated with numerous lung parenchymal and pleurally based micronodules. | Lymphocytic exudative. ADA right, 46.7 U/L; left, 42.6 U/L. | Good response to corticosteroids 0.5mg/kg for one month.                |
| Wang et al. 2014. | 1) 39 yr male | Bilateral diffuse parapneumonic nodules and hilar lymph node enlargement, pericardial effusion and bilateral moderate PIs. | Lymphocytic, exudative. ADA 37U/L. | Good response to oral corticosteroids over 3 months.                   |
|                 | 2) 49 yr female | Right middle lobe atelectasis, right hilar lymphadenopathy and right moderate PE. | Lymphocytic, exudative. ADA 14U/L. | Good response to oral corticosteroids over 3 months.                   |
|                 | 3) 51 yr female | Multiple nodules in upper zones, bilateral hilar lymphadenopathy, and bilateral moderate PE. | Lymphocytic, exudative ADA 17U/L. | Good response to oral corticosteroids. Complete resolution at 6 months. |
| Shin et al. 2014. | 52 yr female | Bilateral mediastinal and hilar lymphadenopathy, left-sided PE, diffuse parapneumonic infiltrates. Endobronchial mass at bronchoscopy. | Lymphocytic, transudative. | Good response to oral corticosteroids over 3 months.                   |
| Ferreiro et al. 2014. | 1) 45 yr male | Bilateral hilar lymphadenopathies, right PE, micronodular disease and probable massive fibrosis in the right side. | Lymphocytic, exudative. ADA 36U/L. Milky: Chylomicrons present, Triglycerides 251 mg/dl. | Good response to octreotide and oral corticosteroids. PE reaccumulated when prednisolone tapered to <10mg/day. |
|                 | 2) 83 yr female | Multiple bilateral hilar and paratracheal mediastinal lymphadenopathies, moderate left PE and suspected micronodular disease. | Lymphocytic. ADA 45U/L. | Good response to oral corticosteroids.                                |
|                 | 3) 39 yr male | Bilateral hilar lymphadenopathies, small left PE and bilateral intestitial disease. | PE not sampled. | Good response to oral corticosteroids.                                |

Fig. 3. Literature review of small case series and case reports of pleural effusion attributable to sarcoidosis between 2014 and 2017. Abbreviations: PE Pleural effusion, yr year, ADA adenosine deaminase.
Contributorship

All authors have contributed to the manuscript and management of the patient equally.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmcr.2018.01.007.

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