Sarcoidosis: an under-recognised cause for bullous lung disease?

To the Editors:

A 35-yr-old Caucasian female was admitted with a 2-week history of rapidly progressive dyspnoea on minimal exertion. She denied any associated cough, chest pain or systemic symptoms. She gave a background of a 5-yr history of dyspnoea on moderate exertion, with intermittent cough, but no diurnal variation. This had been previously attributed to asthma and she had been maintained on inhaled corticosteroids and short-acting β-agonists. She had no symptoms suggestive of any connective tissue disease. She had no family history of respiratory disease. She was a heavy smoker, having accrued a 10-pack-yr history of smoking, but denied any illicit drug use. She was unemployed. There was no history of exposure to hazardous dusts.

Physical examination revealed reduced air entry throughout all lung fields but worse on the right, with ipsilateral hyperresonance. A chest radiograph (fig. 1a) showed a right pneumothorax with bilateral diffuse reticular infiltrates predominantly affecting the mid-zones. There were no previous radiographs for comparison. An intercostal drain was inserted and the lung re-expanded. She underwent a high-resolution computed tomography scan of the thorax (fig. 1b and c), which revealed the presence of large bilateral bullae in the upper zones, with infiltrates in a bronchovascular distribution. She subsequently underwent a video-assisted thoracoscopic biopsy of her middle lobe as well surgical pleurodesis. The histology confirmed the presence of noncaseating granulomas (fig. 2). Fungal and mycobacterial stains were negative. A diagnosis of bullous sarcoidosis was made.

Serum angiotensin-converting enzyme was elevated at 160 $U \cdot mL^{-1}$ and α_1-antitrypsin level was within normal limits.

Her lung function tests at baseline showed a forced expiratory volume in 1 s (FEV_1) of 1.18 L (3.26 L predicted) and forced vital capacity (FVC) of 2.24 L (3.75 L pred), with a FEV_1/FVC ratio of 52%. Diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) and carbon monoxide transfer factor were 33% and 58% pred, respectively. Her 6-min walk distance was 389 m with exertional desaturation from 98% to 86% and a pre-test Borg score of 3 and post-test Borg score of 6. She was commenced on oral prednisolone, initially at 30 $mg \cdot day^{-1}$ with gradual dose tapering over subsequent months to 10 $mg \cdot day^{-1}$. The patient noted symptomatic improvement after introduction of steroids, although no changes in her physiological parameters occurred over the subsequent 2 yrs of follow-up.

Sarcoidosis, a granulomatous disorder of unknown aetiology, characteristically involves multiple organs, with lung involvement being predominant. The diagnosis of sarcoidosis is based upon the association of compatible clinicoradiological findings, histological demonstration of noncaseating granulomas, and exclusion of other granulomatous disorders. The pulmonary manifestations of sarcoidosis are diverse, involving the intrathoracic lymph glands and pulmonary parenchyma, as well as the airways. Occasionally, sarcoidosis has been reported to have atypical thoracic manifestations. One such example is the bullous form of the disorder. The condition was first reported in 1949 by ZIMMERMAN and MANN [1]. A Medline search has further revealed a total of 17 more case reports of bullous sarcoidosis since then [1–10].

The age at diagnosis of bullous sarcoidosis varied from 21 to 64 yrs with a mean age of 37 yrs. Males were more frequently affected than females in a ratio of 2:1. In only half of the cases was the race specified [1, 3, 5, 7, 9, 10] and no ethnic differences in incidence was noted. Most patients had been noted to have bullous changes within 3–4 yrs of symptom development [2–4, 7]. In four patients, the symptoms had been attributed to asthma or chronic obstructive pulmonary disease (COPD) [7, 9, 10]. Smoking history was not specified in six of the 18 case reports. Of the remaining 12 patients, three were never-smokers [2, 4, 7], while two had smoking history of <10 pack-yrs [7]. Seven patients had presented with single or recurrent pneumothoraces, affecting the right more frequently than the left [2, 4–6, 10].

Lung function showed an obstructive picture in 11 cases [1–3, 4, 7], restrictive in three cases [2, 5, 6] and preserved spirometry in one case [10]. In all cases in which $D_{L,CO}$ was measured, significant impairment in the values were noted [4, 7, 10]. Few of the reports specifically mentioned the site of predominance of the bullae, but were noted to involve the lower as well as the upper zones equally.

Systemic steroids were given to 10 patients, with variable outcomes [2, 4–7]. Duration of follow-up was highly variable amongst the case reports. Five reported improvement or stability in symptoms, lung function and/or radiographic appearance [4, 6, 7]. However, response to corticosteroid therapy was only transient in three further cases, with further deterioration in symptoms and lung function. Five patients underwent bullectomy, two of which were bilateral [2, 3, 5, 7, 10]. Of these, four had improved while one patient [3] had enlarging contralateral bullae and respiratory failure. One patient underwent single lung transplant [7], owing to worsening lung function and was noted to remain stable on follow-up. Five of the cases were reported to die with respiratory failure and cor pulmonale, two of whom were aged <35 yrs [1–3, 8].

The precise mechanism underlying the formation of bullae remains unclear, and various mechanisms have been proposed [7], as follows. 1) Ball-valve obstruction, whereby endobronchial involvement by sarcoid lesions causes peripheral air trapping and alveolar distension and rupture. However, it is noteworthy that endobronchial involvement with sarcoidosis has not been universally found in cases where the bronchi were biopsied [10]. 2) Formation of bullae by retraction and collapse of surrounding disease lung. 3) Presence of an inflammatory alveolitis, with release of many inflammatory mediators, resulting in tissue destruction.

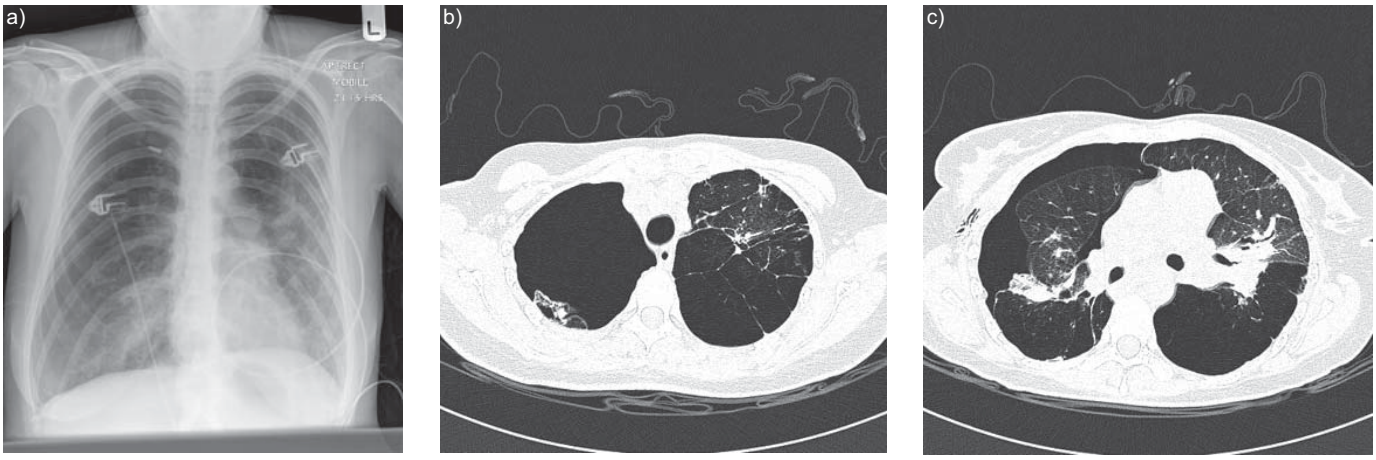

FIGURE 1. a) Anteroposterior chest radiograph on admission demonstrating a pneumothorax on the right, hyperinflated lung fields and faint infiltrates throughout the mid- and lower zones. b) Bullae in the upper zones on high-resolution computed tomography (HRCT). c) HRCT showing parenchymal infiltrates in a bronchovascular distribution.

Although considered to be rare, it is not inconceivable that bullous sarcoidosis may in fact be under-recognised for a variety of reasons. Patients frequently present with nonspecific symptoms, including intermittent wheeze and cough, and these are often attributed to other conditions, such as asthma and smoking-related COPD, especially when there is concurrent heavy smoking history. Bullous lung changes, especially in the upper zones in smokers, may often be attributed to smoking and alternative diagnosis may not be sought. Also, paucity of granulomatous changes [10] have been noted along the walls of bullae, which were resected and examined, hence highlighting the need for biopsy of relatively spared lung tissue as well when attempting histological diagnosis.

There is an increasing number of case reports of bullous sarcoidosis, suggesting that the condition may not be a rare entity as previously considered. It is interesting to note that a recent histopathological review of lung volume reduction surgery specimens revealed noncaseating granulomatous changes in nine out of 80 cases [11]. Most of the patients retrospectively, however, did not have clinical characteristics attributable to sarcoidosis, although mediastinal adenopathy was noted in the vast majority of the patients. A prospective study of cases referred for bullectomy or lung volume reduction surgery would be useful.

From a clinical perspective, one should maintain a high index of suspicion in a young patient with or without significant smoking history, especially when other radiographic abnormalities or clinical features to suggest extrapulmonary sarcoidosis coexist. It is important to recognise that the vast majority of patients may present early in the course of their illness with bullous disease, with a probable poor response to corticosteroid therapy, and among them a subset who rapidly progress to respiratory failure and cor pulmonale. The need for consideration of bullectomy or lung transplantation should be actively sought, although the criteria for patient selection are unclear.

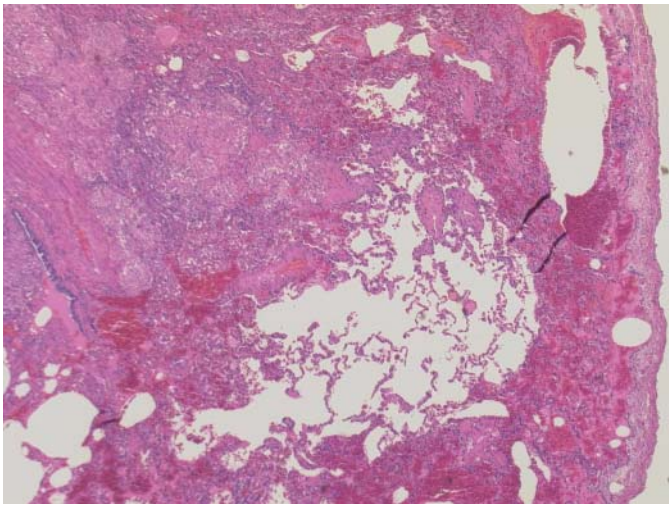

FIGURE 2. Histology specimen of middle lobe demonstrating noncaseating granulomas.

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REFERENCES

1 Zimmerman I, Mann N. Boeck's sarcoid: a case of sarcoidosis complicated by pulmonary emphysema and cor pulmonale. *Ann Intern Med* 1949; 31: 153–162.
2 Harden KA, Barthakur A. Cavitary lesions in sarcoidosis. *Dis Chest* 1959; 35: 607–614.
3 Miller A. The vanishing lung syndrome associated with pulmonary sarcoidosis. *Br J Dis Chest* 1981; 75: 209–214.

4 Packe GE, Ayres JG, Citron KM, *et al.* Large lung bullae in sarcoidosis. *Thorax* 1986; 41: 792–797.
5 Pena CM, Cosgrove DM, Eng P, *et al.* Bullectomies for bullous sarcoidosis. *Cleve Clin J Med* 1993; 60: 157–160.
6 Froudarakis ME, Bouros D, Voloudaki A, *et al.* Pneumothorax as a first manifestation of sarcoidosis. *Chest* 1997; 112: 278–280.
7 Judson MA, Strange C. Bullous sarcoidosis: a report of three cases. *Chest* 1998; 114: 1474–1478.
8 Kumar PD, Epstein DL. Eleven-year survival of a patient with bullous sarcoidosis after bilateral pleurodesis. *Am J Med* 2001; 111: 165.
9 Judson MA, Vincent B, Huggins T, *et al.* Unusual presentations of pulmonary sarcoidosis: cases from the medical university of South Carolina. *Semin Respir Crit Care Med* 2007; 28: 75–82.
10 Mireles-Cabodevilla E, Sahi H, Farver C, *et al.* A young patient with a minimal smoking history presents with bullous emphysema and recurrent pneumothorax. *Chest* 2007; 132: 338–343.
11 Keller CA, Naunheim KS, Osterloh J, *et al.* Histopathologic diagnosis made in lung tissue resected from patients with severe emphysema undergoing lung volume reduction surgery. *Chest* 1997; 111: 941–947.

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Reproducibility and reliability of pleural fluid cytokine measurements

To the Editors:

Cytokine levels in pleural fluid (PF) have been the subject of many reports focusing on their aetiological, diagnostic and prognostic roles; furthermore, cytokine levels are of importance in translational research of pleural diseases [1]. However, data of these studies were based on a single one-off measurement of cytokines in stored PF samples assayed after thawing. Cytokine concentration is a delicate balance of systemic and lung filtration of cytokines, and release from local (mesothelial and inflammatory and/or cancer) cells [2]. Reproducibility of PF cytokine measurements in humans has not previously been established. Our study aimed to: 1) determine short- and long-term changes of PF cytokine concentrations in patients with recurrent/persistent pleural effusions; and 2) examine the influence of freeze–thaw cycles on cytokine levels.

In total, 137 serial PF samples were obtained from 30 patients who required an indwelling pleural catheter (n=19) or repeated pleural aspirations (n=11) for management of malignant (n=24) or benign (n=6) recurrent effusions. 26 of these patients had PF collected as part of a separate study on the use of PF mesothelin [3]. Additional samples were collected from seven patients (malignant, n=5; benign, n=2) to assess the effects of storage and freeze–thaw cycles. Short-term reproducibility was assessed between paired PF samples taken from patients within any 10-day period. Multiple paired samples were included from patients who had repeated sampling. PF samples were collected and centrifuged as previously published. Supernatants were stored at -80°C until assayed. Vascular endothelial growth factor (VEGF), interleukin (IL)-8, tumour necrosis factor (TNF)-α, macrophage chemoattractant protein (MCP)-1, and transforming growth factor (TGF)-β1 and TGF-β2 concentrations were measured using commercially available ELISA kits (PeproTech EC Ltd, London, UK). Total TGF-β levels were measured by activating the PF samples with HCl, followed by neutralisation with hydroxyethyl piperazine ethane sulfonic acid-NaOH before ELISA assaying, as recommended by the manufacturer. Analyses were repeated on all paired serial samples showing a more than two-fold change for confirmation.

The short-term reproducibility of cytokine measurements in paired samples (n=46) taken within 10 days was excellent (table 1). No significant changes were observed in the cytokines tested (all $p \geqslant 0.05$). Likewise, PF cytokine concentrations remained stable during each patient's disease course. There was no significant change over time in all cytokines

TABLE 1 Cytokine measurements in 46 paired samples taken within 10 days

	Baseline sample ng·mL^{-1}	Paired sample ng·mL^{-1}	Variation of paired samples ng·mL^{-1}	p-value#
VEGF	0.53 (0.16–2.10)	0.40 (0.16–2.16)	0.00±0.90	0.831
TNF-α	0.05 (0.02–0.08)	0.05 (0.02–0.08)	0.00±0.04	0.763
MCP-1/CCL2	0.80 (0.45–2.01)	0.85 (0.55–2.69)	-0.66±3.12	0.076
TGF-β1	7.72 (5.57–17.14)	6.82 (5.15–15.01)	0.90±8.26	0.965
TGF-β2	0.08 (0.03–0.23)	0.07 (0.03–0.20)	0.07±0.23	0.050
IL-8/CXCL8	0.30 (0.10–1.06)	0.36 (0.14–0.91)	0.02±2.97	0.391

Data are presented as median (25th–75th percentile) or mean±SD, unless otherwise stated. VEGF: vascular endothelial growth factor; TNF: tumour necrosis factor; MCP: macrophage chemoattractant protein; CCL2: chemokine (C-C motif) ligand 2; TGF: transforming growth factor; IL: interleukin; CXCL8: CXC chemokine ligand 8. #: Wilcoxon signed rank test.