Large lung bullae in sarcoidosis

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ABSTRACT Large lung bullae are a rare manifestation of pulmonary sarcoidosis. Of three patients with this complication, all had pulmonary infiltrates at presentation and two had bilateral hilar adenopathy. Hypercalcaemia developed during the course of the illness in all three patients. In each case the bullae had developed within four years of the diagnosis of sarcoidosis. In one woman a bulla resolved almost completely after it had become infected.

Persistence of pulmonary infiltration in sarcoidosis may lead to irreversible lung fibrosis.¹ This fibrosis becomes evident on the chest radiograph with the appearance of retraction, distortion, and shrinkage of the lung parenchyma. These changes are often accompanied by the presence of small to moderate sized bullae and cavities within strands of fibrosis. Maycock *et al*² reviewed the radiological appearances in 145 patients with pulmonary sarcoidosis and found small and moderate sized bullae in 5.8% of patients. In a series of 300 cases bullae were present in 26.9% of black and 13.5% of white patients.³

More rarely, large lung bullae may develop in sarcoidosis, again usually in association with gross fibrotic change.^{4,5} Miller⁶ has further identified a subgroup of patients with pulmonary sarcoidosis who develop radiological signs of generalised emphysema, usually with large bullae, and with little evidence of fibrosis. He described two such cases of his own and two other cases have been reported.^{7,8}

In this report we describe three patients with sarcoidosis who developed large lung bullae at an early stage after diagnosis.

Case reports

CASE 1

A 40 year old symptomless woman, a lifelong non-smoker, was admitted to hospital in 1971 for investigation because of an abnormal chest radiograph. Physical examination revealed enlarged supra-clavicular nodes bilaterally but no other abnormality.

The chest radiograph showed bilateral hilar lymphadenopathy and fine stippling throughout both lung fields (fig 1a). Cervical node biopsy showed non-caseating giant cell granulomas, and a Kveim test was positive. Treatment was started with prednisolone 25 mg daily, which was subsequently reduced to 5 mg daily.

By mid 1974 the chest radiograph showed clearing of the pulmonary shadowing but there was more pronounced linear shadowing in both mid zones and increasing lucency in the lower zones. She now began to complain of breathlessness on exercise. A maximum expiratory flow-volume loop showed mild airflow obstruction. Specific airways conductance (sGaw) was reduced and carbon monoxide gas transfer (TLCO) impaired (table). Treatment with prednisolone 5 mg daily was continued, but she remained breathless on exertion and after a further three years the chest radiograph showed large bullae in the lower lobes of both lungs (fig 1b). Total lung capacity (TLC) measured by body plethysmography was one litre greater than when measured by helium dilution. Dynamic lung compliance was 0.51 l/kPa (normal > 1.0 l/kPa). Determination of regional lung function by the bronchoscopic single breath argon-freon test showed negligible ventilation and perfusion of the lower lobe bullae, but there did not appear to be compression of adjacent lobes by the bullae at TLC. Arterial blood gas tensions and α_1 antitrypsin concentrations were normal. It was thought that surgical treatment of the bullae would not benefit the patient because there was no compression of adjacent lobes by the bullae.

Nine years after presentation her dose of prednisolone was reduced to 3 mg daily, but she then developed polyuria and polydipsia associated with a raised serum calcium concentration of 3.04 mmol/l (12.2 mg/100 ml). The dose of prednisolone was

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Fig 1 Patient 1: (a) Initial chest radiograph (1971) showing bilateral hilar adenopathy, fine stippling throughout both lung fields, and some horizontal shadowing radiating from both hila; (b) later radiograph (1977) showing extensive bullae in both apices, in the right lower and mid zones, and at the left lung base; (c) chest radiograph (1985) showing a considerable reduction in size of the large right lower lobe bulla.

increased to 30 mg on alternate days and she was also treated with sodium cellulose phosphate, with resolution of the hypercalcaemia and associated symptoms.

In November 1984 she was readmitted to hospital complaining of right pleuritic pain, increasing exertional dyspnoea, and a cough productive of blood stained purulent sputum, unresponsive to several courses of antibiotics. The appearance of the chest radiograph was unchanged. Bronchoscopy showed purulent secretions exuding from the apical segment

Results of pulmonary function tests in three patients with sarcoidosis who developed lung bullae early in the course of the disease

	Case 1*			Case 2†		Case 3†	
	1974	1984	1985	1974	1985	1981	1985
FEV ₁ litres (% pred)	1.20 (47)	0.86 (38)	1.17 (52)	3.25 (76)	2.15 (54)	1.30 (30)	1.38 (33)
FVC litres (% pred)	1.75 (60)	1.36 (51)	1.78 (67)	4.60 (91)	4.60 (97)	3.15 (61)	4.15 (82)
TLC litres (% pred)	4.59 (100)	3.44 (75)	3.75 (82)	5.90 (86)	6.42 (94)	5.75 (81)	7.27 (102)
RV litres (% pred)	3.24 (212)	2.09 (124)	1.90 (111)	1.50 (95)	1.48 (81)	3.05 (177)	2.23 (124)
sGaw s kPa ⁻¹ (normal > 1.04)	0.48	0.44	0.84	—	—	—	—
TLCO mmol min ⁻¹ kPa ⁻¹ (% pred)	5.16 (65)	4.11 (55)	4.27 (57)	7.16 (61)	4.98 (45)	6.50 (55)	7.59 (65)
Kco mmol min ⁻¹ kPa ⁻¹ (% pred)	1.70 (82)	1.86 (92)	1.91 (94)	1.56 (72)	0.94 (46)	1.50 (70)	1.40 (67)

*Lung volumes measured by body plethysmography.

†Lung volumes measured by multi-breath helium dilution.

FVC—forced vital capacity; TLC—total lung capacity; RV—residual volume; sGaw—specific airways conductance; TLCO—transfer factor for carbon monoxide; Kco—transfer coefficient.

of the right lower lobe bronchus; culture of the secretions was negative. She was treated with physiotherapy and chloramphenicol. Her symptoms persisted and after two months an air-fluid level was evident in the right basal bulla. She received several more courses of antibiotics and over the ensuing months there was a progressive reduction in the size of the bulla (fig 1c), with a concomitant improvement in her exercise capacity and lung function (table).

CASE 2

A man aged 24 was admitted to hospital in 1974 with a history of increasing dyspnoea on exertion for the

past year and of three weeks of nausea, vomiting, weight loss, and malaise. He smoked 20 cigarettes a day. In 1969 he had had a right spontaneous pneumothorax, which had been treated by intubation; a follow up radiograph had been normal.

On examination there were palpable cervical nodes on the right; auscultation of the chest showed nothing abnormal. The chest radiograph showed extensive pulmonary shadowing (fig 2a). The serum calcium concentration was raised at 3.8 mmol/l (15.2 mg/100 ml). Lung function tests (table) showed a mild obstructive defect with reduced gas transfer. Histological examination of a supraclavicular node

Fig 2 Patient 2: (a) Initial chest radiograph (1974) showing widespread mottling and several large confluent shadows in the middle and upper zones; (b) subsequent chest radiograph (1977) and (c) a thoracic computed tomography scan showing large bullae occupying both upper lobes.

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showed appearances consistent with sarcoidosis. He was treated with prednisolone 30 mg daily and over the next two weeks the calcium concentration fell to normal and his symptoms receded. Treatment with prednisolone 7.5 mg daily was continued.

His chest radiograph remained unchanged until mid 1976, when clearing of the pulmonary shadowing became evident in the upper and lower zones. Over the next 12 months linear streaks appeared in the mid zones bilaterally with increasing lucency in the upper and lower zones, and large bullae appeared in the upper lobes of both lungs (fig 2b). Dynamic lung volumes showed an increasing obstructive pattern.

(a)

(b)

In 1984 he was reassessed. The chest radiograph was unchanged. Computed tomography confirmed the presence of large bullae in the upper lobes (fig 2c), with smaller bullae at both lung bases; the remainder of both lungs appeared normal. Serum electrolyte concentrations, angiotensin converting enzyme activity, and α_1 antitrypsin concentration were normal. Transbronchial lung biopsy showed normal lung tissue with minor interstitial fibrosis. The most recent lung function tests show airflow obstruction (table), with minor improvement after inhalation of salbutamol. The maximum expiratory flow-volume curve shows a rapid reduction in airflow early in expiration and gas transfer remains impaired. Arterial blood gas tensions are normal.

The patient experiences moderate breathlessness when walking up a gradient but is able to work full time as a sales representative.

CASE 3

A 28 year old man was admitted to hospital in 1981 with a four month history of weight loss, progressive dyspnoea on exertion, wheeze, and cough productive of mucopurulent sputum. He smoked 20 cigarettes a day and gave a history of childhood asthma.

On examination there were fine crackles at both lung bases. A chest radiograph showed widespread shadowing throughout both lung fields, with enlargement of both hila (fig 3a). The serum calcium and electrolyte concentrations were normal. Serum angiotensin converting enzyme activity was 88.0 $\mu\text{mol/l/min}$ (normal < 59 $\mu\text{mol/l/min}$). Serial

(c)

Fig 3 Patient 3: (a) Initial chest radiograph (1981) showing diffuse mottling and large nodular masses scattered irregularly throughout both lung fields, with enlargement of both hila; (b) later chest radiograph (1984) showing left apical bullous change; and (c) thoracic computed tomography scan showing a large bulla sited posteromedially in the left upper lobe and scarring in the right upper lobe.

measurements of peak expiratory flow rate showed diurnal variation of up to 40% of the baseline value, consistent with asthma. Pulmonary function tests showed airflow obstruction and impaired gas transfer (table). Bronchial and transbronchial biopsy specimens showed non-caseating granulomas.

Treatment with prednisolone, 30 mg on alternate days, and a salbutamol inhaler improved his symptoms but there was only marginal improvement in his lung function. After six months there was substantial clearing of his pulmonary shadowing, but lucent areas appeared, especially in the left upper zone.

Over the next two years, apart from transient hypercalcaemia of 2.72 mmol/l (10.9 mg/100 ml), his condition remained unchanged. The serum angiotensin converting enzyme activity fell to normal, and he was weaned off prednisolone. By 1984 his chest radiograph showed left apical bullous change (fig 3*b*). Computed tomography confirmed a large bulla in the left upper lobe (fig 3*c*) and also showed severe scarring throughout the remainder of the lung fields with numerous smaller bullous areas. A maximum expiratory flow-volume loop showed a rapid reduction in airflow early in expiration compatible with emphysema. Forced vital capacity and TLC had increased while residual volume had decreased (table). Serum angiotensin converting enzyme activity and α_1 antitrypsin concentrations were normal.

Although he complains of dyspnoea during moderately heavy exertion, he is able to work full time as a fork lift driver.

Discussion

In all three patients large lung bullae had formed within four years of the diagnosis of sarcoidosis. Each patient initially had pulmonary shadowing and the bullae appeared to develop as the infiltration progressively cleared. The two men were cigarette smokers and could have had underlying emphysema, but in both the bullae had developed by the age of 30, so that emphysema is unlikely to have been a major causative factor. Alpha₁ antitrypsin concentrations were normal in all patients. There are several other possible mechanisms that could have given rise to bullae in these three patients.

Thick walled cavities are a feature of fibrotic pulmonary sarcoidosis, sometimes attaining a large size.¹⁰⁻¹⁴ It has been suggested that such cavities are caused by coalescence and ischaemic necrosis of large conglomerates of granulomas.¹ More rarely, cavitation may occur in the early stages of the disease (so called primary acute cavitation), and these cavities are thought to arise in the same way.¹⁵ In our cases 2 and 3 dense infiltrations were evident on the chest radiograph at presentation, and such a process may

have contributed to the destruction of lung tissue and formation of bullae in these two cases.

In fibrotic pulmonary sarcoidosis evidence of airway disease is common, being due to cicatricial fibrosis and distortion of small and large airways.^{16,17} In prefibrotic pulmonary sarcoidosis bronchial narrowing may also occur, as a result of sarcoid infiltration of the bronchial mucosa.¹⁸ In all three patients airway narrowing was noted. In case 1 airflow obstruction was noted on the maximum expiratory flow-volume loop at an early stage. Patient 2 had no evidence of airways narrowing at the start of his illness but within two years had developed evidence of fixed airflow obstruction. Patient 3 had asthma but also had residual airflow obstruction after treatment with inhaled bronchodilators and corticosteroids. Endobronchial sarcoidosis was also detected histologically during the active phase of his disease. Scadding¹ described a patient with a small pre-existing bulla that rapidly enlarged when she developed pulmonary sarcoidosis. These changes were ascribed initially to a reduction in the calibre of the airway leading to the bulla because of endobronchial disease, possibly producing a ball valve effect. Subsequent deflation of the bulla occurred and could be explained by resolution of the endobronchial sarcoidosis. A similar sequence of events was seen in patient 1, in whom partial closure of basal bullae occurred after pneumonia. Previous reports of spontaneous closure of large emphysematous bullae have been attributed to blockage by inflammatory exudate of any communication between a bulla and the bronchial tree, resulting in absorption of the contents of the bulla.¹⁹

When fibrosis supervenes in pulmonary sarcoidosis it often develops in a characteristic manner.^{1,20} The first sign is the appearance of coarse strands radiating from the hila. Resolution of the pulmonary shadowing in the upper and lower zones may then occur with increasing condensation of fibrous tissue in the middle zones and the development of translucent areas in both upper and lower zones indicative of emphysema. This evolutionary pattern of pulmonary shadowing was seen in cases 1 and 2. This process could lead to tearing of the lung parenchyma and the formation of frank bullae in the lung apices or bases as a consequence of traction on surrounding lung by scar tissue near the hila.²¹

Hypercalcaemia occurred in each of our cases. It was found at presentation in case 2 but did not develop until nine years after presentation in case 1 and two years in case 3. The reported incidence of hypercalcaemia in sarcoidosis varies from 2% to 63%.²² Hypercalcaemia was not mentioned in connection with the previous reports of large bullae in sarcoidosis, so the hypercalcaemia in our three

patients is likely to have indicated merely that they had severe or widespread disease.

These three cases illustrate the sequence of changes leading to the development of large bullae in sarcoidosis. Cases 1 and 2 latterly showed few of the characteristic features of sarcoidosis, when the diagnosis could not have been made without knowledge of the earlier phase of the disease. Many patients remain symptomless throughout the initial stages of sarcoidosis and may present at a later stage when the disease is no longer active.¹ The presentation of a young patient with large bullae not explained by emphysema should therefore suggest the possibility of pulmonary sarcoidosis.

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