CASE REPORT

Acute alveolar sarcoidosis presenting with hypoxaemic respiratory failure

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SUMMARY

Alveolar sarcoidosis is a less commonly seen pulmonary manifestation of the disease. An acute presentation of this radiological pattern with hypoxaemic respiratory failure has been documented only once, four decades ago. A 30-year-old man presented with acute onset of progressive and persistent dyspnoea over 20 days ago with hypoxaemic respiratory failure. Imaging demonstrated mediastinal lymphadenopathy and coalescent parenchymal alveolar opacities having ill-defined margins along with air bronchograms in the mid and lower zones bilaterally, suggestive of alveolar sarcoidosis. A restrictive pattern with a diffusion defect was seen on pulmonary function testing. Bronchoscopic evaluation revealed non-caseating granulomas on histopathology confirming pulmonary sarcoidosis. This was further supported by an elevated serum ACE level and negative Mantoux test. Oral prednisolone elicited a rapid clinical and radiological response. Alveolar sarcoidosis can rarely present acutely with hypoxaemic respiratory failure, which can respond remarkably and expeditiously to appropriate therapy.

BACKGROUND

Sarcoidosis, which was often confused for tuberculosis, is now increasingly being recognised in India.^{1,2} A review of the literature from India suggests that Indians have pulmonary disease, which is very similar to the chronic fibrosing relapsing pattern usually seen in African-Americans that is less responsive to treatment. However, in contrast, the disease in Indians is not as common, is far less severe and is still regarded as offbeat.³

Although sarcoidosis is predominantly an interstitial disease, an alveolar filling or acinar pattern is also recognised infrequently. Sometimes, a confluence of acinar shadows can produce large areas of segmental consolidation or scattered, hazy areas of consolidation with irregular borders. This may be seen as peripheral non-segmental airspace consolidation. The consolidation may also show an air-bronchogram.⁴ In a recent retrospective review of 164 patients with sarcoidosis over a period of 6 years from India, acute presentation of sarcoidosis in the form of Lofgren's syndrome and Heerfordt's syndrome was reported in 10 (6.1%) patients.⁵ The authors observed an alveolar pattern in 3 (1.8%) patients, but none of these 3 patients had an acute presentation.⁵ It appears that alveolar sarcoidosis is a distinct form of pulmonary sarcoidosis, which is not commonly seen and does not manifest acutely. A review of the literature revealed only one report of an acute presentation of alveolar

sarcoidosis with acute hypoxaemic respiratory failure that was documented four decades ago.⁶ However, acute respiratory failure has been documented in six other patients with pulmonary sarcoidosis.^{7–12} Paucity of the literature on the subject prompted this report of a young man with acute alveolar sarcoidosis who presented with sudden onset of dyspnoea and hypoxaemic respiratory failure.

CASE PRESENTATION

A 30-year-old HIV-negative businessman, a non-smoker, was referred to our Institute for evaluation of breathlessness which had developed acutely over a period of 2 days. This occurred while the patient was descending from a pilgrimage site situated at a height of 6500 ft. He presented to us twenty days after the onset of the symptoms. During this period, he had exertional dyspnoea which was progressive along with cough and scanty mucoid sputum. He also developed a low grade intermittent fever without chills and rigours which was associated with a general feeling of fatigue. He had no wheeze, chest pain, palpitations, haemoptysis or any other symptoms. Symptomatic treatment prior to presentation did not resolve his symptoms.

General physical examination revealed a young man in respiratory distress. There was no pallor, clubbing or cyanosis. He was tachypnoeic with a respiratory count of 32/min and was febrile also. The oxygen saturation at room air was 89% with pH 7.37, pCO₂ 54 mm Hg and pO₂ 53 mm Hg. Diaphragmatic excursion was comparable on both sides. On auscultation, vesicular breath sounds of equal intensity were audible bilaterally along with fine end-inspiratory 'Velcro-like' crackles in bibasilar areas.

INVESTIGATIONS

Complete blood counts, ECG, urine analyses and renal as well as hepatic functions were within normal limits. A review of the chest X-ray (figure 1), performed a fortnight after the onset of symptoms, showed mediastinal widening along with coalescent parenchymal alveolar opacities having ill-defined margins and air-bronchograms in the mid and lower zones bilaterally. The contrast-enhanced high-resolution CT of the thorax performed after presentation, demonstrated right para-tracheal, subcarinal and bilateral hilar lymphadenopathy (figures 2 and 3), confluence of alveolar opacities showing hazy areas of consolidation with irregular borders and air bronchograms (figure 4). Non-homogeneous peribronchiolar opacities with peribronchiolar thickening, which was beaded in appearance, were also

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Figure 1 Chest X-ray on presentation, showing mediastinal widening along with coalescent parenchymal alveolar opacities.

Figure 3 Contrast-enhanced CT (mediastinal window) on presentation, showing subcarinal and bilateral hilar lymphadenopathy.

visible. Ultrasonography of the abdomen was within normal limits. Pulmonary function testing was suggestive of a restrictive pattern with moderately severe impairment of the diffusion capacity (table 1).

Sputum stains and cultures for *Mycobacterium tuberculosis*, other aerobic organisms and fungi were negative. The serum ACE level was 92 (8–52) IU/L while the serum calcium, rheumatoid factor, and 24 h urinary calcium were within normal limits, and antinuclear antibodies were not detected. The cytoplasmic antineutrophil cytoplasmic antibody (CANCA) and perinuclear antineutrophil cytoplasmic antibody (PANCA) too were negative. Mantoux test with 5 TU was recorded as negative after 48 h.

Fibreoptic bronchoscopy visualised multiple granulomatous lesions in the bronchial mucosa throughout the bronchial tree. Multiple endobronchial and *trans*-bronchial biopsies revealed non-caseating granuloma consisting of epithelioid cells and multinucleated giant cells. A transbronchial needle aspiration taken from the carinal nodes also confirmed the presence of non-caseating granulomas. Bronchial aspirates for acid fast bacilli, fungus and pyogenic organisms were negative.

DIFFERENTIAL DIAGNOSIS

- ▶ Bilateral pneumonia
- ▶ Pulmonary oedema
- ▶ Bronchioloalveolar cell carcinoma

TREATMENT

A diagnosis of acute alveolar sarcoidosis was made on the basis of sudden onset of dyspnoea with type 1 respiratory failure at presentation along with the radiological picture. Imaging

demonstrated right para-tracheal, subcarinal and bilateral hilar lymphadenopathy. This was associated with confluent alveolar opacities coalescing into hazy areas of consolidation having irregular borders and the presence of air bronchograms and peribronchiolar thickening which was beaded in appearance. The association of bilateral hilar lymphadenopathy and an acinar pattern was suggestive of alveolar sarcoidosis. The diagnosis was confirmed by demonstration of non-caseating granulomas on histopathology. Serum ACE levels too were elevated while the Mantoux test was negative.

The patient was initiated on oral prednisolone in the dosage of 40 mg daily, which was reduced to 40 mg on alternate days after 2 weeks and gradually tapered after 3 months at the rate of 5 mg every month over 6 months. With this, he experienced marked symptomatic relief.

OUTCOME AND FOLLOW-UP

A chest X-ray was performed after 2 months of therapy showed resolution of the alveolar opacities and a decrease in size of the mediastinal lymph nodes. After 6 months of therapy, the chest X-ray (figure 5) showed complete resolution and a pulmonary function test also showed marked improvement (table 1).

DISCUSSION

Pulmonary sarcoidosis presenting with acute hypoxaemic respiratory failure is rather unusual as only seven such presentations have been documented in the literature with one from India (table 2).^{6–12} Of these seven patients, only one⁶ had an

Figure 2 Contrast-enhanced CT (mediastinal window) on presentation, showing right para-tracheal lymphadenopathy.

Figure 4 Contrast-enhanced CT (lung window) on presentation, showing confluent alveolar opacities and hazy areas of consolidation along with irregular borders and air bronchograms.

Table 1 Pulmonary function testing at presentation and after 6 months of therapy

Spirometry	Pre-treatment						Post-treatment					
	Predicted value	Observed		Observed		Per cent change	Predicted value	Observed		Observed		Per cent change
		Pre-BD	%pred	Post-BD	%pred			Pre-BD	%pred	Post-BD	%pred	
FVC (L)	4.94	2.82	57	2.96	59	4	5.19	4.67	89	4.66	89	
FEV ₁ (L)	4.12	2.49	60	2.66	64	6	4.32	3.98	92	4.01	92	
FEV ₁ /FVC	83	88	106	90	108	2	83	85	102	86	103	1
Lung volume												
TLC (L)	6.46	4.26	65				6.78	6.43	94			
Diffusion capacity												
DLCO	32.8	19.36	59				33.78	32.03	94			

BD, bronchodilator; DLCO, single breath diffusing capacity. FEV, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity.

uncommon form recognised as an alveolar or acinar pattern, which in India⁵ was reported in 1.8% of patients with sarcoidosis. The duration of dyspnoea in the six cases where information was available ranged from 7 days to 3 weeks. Of the seven patients reported in the literature, six had either reticulonodular opacities and/or hilar lymphadenopathy and only one patient had an alveolar pattern in the radiograph.

Alveolar sarcoidosis is estimated to occur in 1–4.4% of patients,^{5 13 14} with only one study¹⁵ taking a much broader definition, suggesting that this radiological pattern can occur in up to 20% of patients with pulmonary sarcoidosis. This radiological pattern in sarcoidosis was highlighted by Felson¹⁶ to describe opacities of the infiltrative type, non-retractile, with ill-defined margins and sometimes an air bronchograms, or nodules with ill-defined limits and diameters greater than 15 mm.

While reviewing 746 patients with pulmonary sarcoidosis from France,¹³ the authors detected 33 (4.4%) patients with this specific radiological presentation. They observed that alveolar sarcoidosis occurred predominantly in men (23/33, 69.6%) and in the younger age group (mean age=28.4±1.85 years). Of 33 patients, 30 were between 20 and 30 years. The authors remarked that alveolar sarcoidosis appears to be an acute form of the disease in view of the younger age group, presence of mediastinal lymph nodes and the frequent normal chest X-ray

during the previous year. Our patient too was a 30-year-old man, but in contrast he had an acute presentation with hypoxaemia. None of the 33 patients described in the series had an acute presentation with hypoxaemia.

The mechanism proposed by Felson¹⁶ and supported by Reed and Madewell¹⁷ for occurrence of alveolar sarcoidosis was due to alveoli being compressed or filled with coalescent interstitial nodules. Battesti *et al*¹³ performed lung biopsies in 4 of 33 patients and also thought that this occurred due to the collapse of alveolar walls by the confluence of interstitial granulomas. In contrast, Sahn *et al*⁶ who presented the only other patient of alveolar sarcoidosis with acute hypoxaemic respiratory failure observed on biopsy that the alveoli were invaded by mononuclear cells, which was a non-specific reaction to the sarcoid granuloma in the interstitium. Disagreeing with the findings of Sahn *et al*,⁶ Shigematsu *et al*,¹⁵ while describing their 20 patients of alveolar sarcoidosis, found on lung biopsies closely packed epithelioid cells in the alveoli. It appears that the exact mechanism for alveolar sarcoidosis still needs to be elucidated.

The alveolar pattern of sarcoidosis is almost always accompanied by mediastinal lymphadenopathy. Shigematsu *et al*¹⁵ documented the presence of bilateral mediastinal lymphadenopathy in all 20 (100%) patients of alveolar sarcoidosis. This was further supported by Battesti *et al*,¹³ who in their series of 33 patients with alveolar sarcoidosis observed the presence of bilateral mediastinal lymphadenopathy in 27 (81.81%) patients. However, Sahn *et al*,⁶ in their description of the only other patient with alveolar sarcoidosis presenting with acute hypoxaemic respiratory failure, did not observe mediastinal lymphadenopathy. In contrast, our patient, on presentation, had right para-tracheal, subcarinal and bilateral hilar lymphadenopathy accompanying the alveolar pattern of sarcoidosis.

A striking feature of alveolar sarcoidosis has been rapid radiological clearing after initiation of corticosteroid therapy or even spontaneously. The only other patient with alveolar sarcoidosis presenting with acute hypoxaemic respiratory failure had a rapid and marked clinical and radiological improvement with therapy within 21 days of the initial chest X-ray. The authors⁶ reported that they could not detect any abnormality on the chest X-ray. Of the 20 patients with alveolar sarcoidosis from Japan, 15 remained untreated. Ten of these 15 patients experienced spontaneous radiological resolution within nine months.¹⁵ Of the 33 patients from France,¹³ 22 were followed up; 15 of them received therapy with corticosteroids while 7

Figure 5 Chest X-ray performed 6 months after therapy showing complete resolution of the alveolar opacities along with remarkable reduction of the size of the mediastinal lymph nodes.

Table 2 Summary of the seven documented patients with pulmonary sarcoidosis presenting with acute hypoxaemic respiratory failure along with the patient being reported

S. No.	Age, sex, year of publication, country, reference	Occupation	Smoking history	Comorbidity	Pulmonary symptoms	Systemic features	Signs	Duration	Hypoxaemia	Chest X-ray	CT	Mantoux test	PFT pattern	Serum ACE	Serum calcium	24 h Urinary calcium	Confirmation on biopsy	Treatment	Clinical outcome
1	26, female, 1974, USA ⁷	Not stated	Not stated	Not stated	Dyspnoea on exertion, productive cough, substernal pain	Fever No skin rash, arthralgia	Decreased bilateral expansion, dullness to percussion, increase in fremitus and medium rales at the bases	1 month	Yes (PaO ₂ 56 mm Hg at 2 L/m O ₂)	Bilateral, diffuse acinar rosette pattern without hilar adenopathy	Not done	Not stated	Moderate to severe restrictive ventilatory defect	Not stated	9.4 mg%	Normal	Open lung biopsy	Prednisone 60 mg daily	Improvement after 6 days
2	55, male, 1990, Japan ⁸	Stone mason	Not stated	Not stated	Dyspnoea on exertion	Remittent fever	Not stated	10 days	Yes (PaO ₂ 32.2 Torr at room air)	Diffuse small nodular opacities, minimal pleural effusion, bilateral hilaradenopathy	Not done	Not stated	Not stated	49 IU/L (reference range—not mentioned)	Not stated	Not stated	Transbronchial lung biopsy, biopsy from liver and bone marrow	Prednisolone	Improvement in clinical condition, chest X-ray films, ACE
3	50, male, 2002, USA ⁹	Not stated	Not stated	Diabetes Mellitus type 2	Dyspnoea on exertion, productive cough	Poor appetite	Bibasilar inspiratory crepitations	3 weeks	Yes (PaO ₂ 7.1 kPa at room air)	Extensive bilateral 'interstitial' infiltrates	Not done	Not stated	Not stated	83 IU/L (reference range—not mentioned)	Not stated	Not stated	Bronchoscopic biopsy	Prednisone at 60 mg/day	Improvement after 6 days
4	41, female, 2004, Israel ¹⁰	Not stated	20 pack-years	CVID	Dyspnoea		Clubbing, bi-basilar rales with diminished breath sounds on left	1 week	Yes SpO ₂ 70–77% at room air	Bilateral ill-defined reticulonodular densities	Ill-defined reticulonodular densities, mediastinal lymphadenopathy	Negative	Severe restrictive defect with TLC 34% of predicted	Not stated	Normal	Normal	Mediastinal lymph node biopsy	Prednisone—2 mg/kg	Improvement in several days
5	33, male, 2005, USA ¹¹	Part time job—frozen meat department	Minimal smoking	Not stated	Acute respiratory distress on 7th hospital day	On presentation, acute onset severe headache, fever	Not stated	4 days	On 7th day, yes (PaO ₂ 42.9 mm Hg at room air)	On presentation, minimal blunting of both costophrenic angles initially. Later bilateral patchy pulmonary infiltrates developed	On presentation, minimal bilateral pleural effusion, minimal mediastinal lymphadenopathy (mainly subcarinal); no significant parenchymal abnormality	Not stated	Moderate reduction of diffusion capacity	76 U/L (reference range 9–67 U/L)	Not stated	Not stated	Transbronchial lung biopsy	Intravenous methylprednisolone succinate, 40 mg prednisone on discharge	Improvement within 24 h
6	66, male, 2007, Japan ¹²	Not stated	Not stated	Not stated	On follow-up, acute respiratory failure	On presentation, leg cramps, fever	Not stated	Not stated	Not stated	Not stated	Bilateral ground-glass opacity and pleural effusion	Negative	Not stated	Elevated	Not stated	Not stated	Skin biopsy	High-dose steroid therapy	Prompt improvement
7	40, male, 2011, India ¹³	Surgeon	20 pack-years	Not stated	Dyspnoea on exertion, cough	Fever, fatigue, malaise, weight loss	Bilateral basal crackles	3 weeks	Yes PaO ₂ 63 mm Hg (PaO ₂ /FIO ₂ 157 mm Hg)	Bilateral peripheral reticulonodular shadows	Bilateral patchy ground-glass opacity, areas of peribronchovascular thickening, interlobular septal thickening and septal nodules	Negative with 1 TU	Not stated	71 (8–65) U/L	9.6 mmol/L	Not stated	Surgical lung biopsy	Intravenous methylprednisolone 1 g daily for 3 days followed by oral prednisolone 40 mg/day	Improvement within 1 week

Continued

Table 2 Continued

S. No.	Age, sex, year of publication, country, reference	Occupation	Smoking history	Comorbidity	Pulmonary symptoms	Systemic features	Signs	Duration	Hypoxaemia	Chest X-ray	CT	Mantoux test	PFT pattern	Serum ACE	Serum calcium	24 h urinary calcium	Confirmation on biopsy	Treatment	Clinical outcome
8	30, male, India Current patient	Businessman	Never smoker	Nil	Dyspnoea on exertion, productive cough,	Fever, fatigue	Fine end-inspiratory 'Velcro-like' crackles in bibasilar areas	20 days	Yes (PaO ₂ 53 mm Hg at room air)	Mediastinal widening, coalescent parenchymal alveolar opacities having ill-defined margins and air bronchograms in mid and lower zones bilaterally	Right para-tracheal, subcarinal and bilateral hilar lymphadenopathy, confluent of alveolar opacities showing hazy areas of consolidation with irregular borders and air bronchograms. Non-homogeneous peribroncholar opacities with beaded peribroncholar thickening	Negative with 5 TU	Restrictive pattern with moderately severe impairment of diffusion capacity	92 (8–52) IU/L	Normal	Normal	Endobronchial and transbronchial lung biopsies	Prednisolone 40 mg/day	Improvement in 2 months

The table has been adapted and modified from Gupta *et al.*¹²
CVID, Common variable immunodeficiency; PaO₂, partial pressure of oxygen in blood; PFT, pulmonary function tests; SpO₂, saturation of haemoglobin with oxygen; TLC, total lung capacity.

remained untreated. All 15 patients had rapid radiological resolution of the alveolar pattern within a few weeks and of the 7 untreated patients, 6 had spontaneous radiological clearance. Our patient too had a remarkable clinical and radiological improvement after initiation of prednisolone therapy. The chest X-ray at 2 months showed tremendous improvement and at 6 months, when the treatment was stopped, parenchymal lesions were no longer visible. The pulmonary function test too showed marked improvement in lung volumes and diffusion capacity.

Our case highlights the fact that patients with alveolar sarcoidosis can rarely present acutely with hypoxaemic respiratory failure. Since these patients usually have a remarkable and rapid clinical and radiological response to appropriate therapy, it is imperative to establish a rapid diagnosis.

Learning points

- ▶ Hypoxaemic respiratory failure as an initial presentation of pulmonary sarcoidosis is extremely uncommon.
- ▶ Alveolar sarcoidosis, a less commonly seen pulmonary manifestation of the disease, presenting with acute hypoxaemic respiratory failure was documented only once before four decades ago.
- ▶ It is imperative to establish a rapid diagnosis as patients with alveolar sarcoidosis usually have a remarkable and rapid clinical and radiological response to therapy with oral corticosteroids.

Contributors KG, NG, AA and AS collected the clinical data and reviewed the literature. KG, NG, AA and AS drafted the manuscript and were responsible for the clinical workup of the patient. AS is responsible for the genuineness of the data, the concept and is also the guarantor of the paper. All authors have read and approved the final manuscript.

Competing interests None.

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