

Pulmonary sarcoidosis with a diffuse ground glass pattern on the chest radiograph

Abdellatif Tazi, Tsellina Desfemmes-Baleyte, Paul Soler, Dominique Valeyre, Allan J Hance, Jean-Paul Battesti

Abstract

Background—Several chest radiographic abnormalities have been described in pulmonary sarcoidosis, but a diffuse ground glass pattern is extremely rare.

Methods—The chest radiographs of more than 1600 patients with sarcoidosis evaluated in our service between 1976 and 1991 were reviewed to determine the prevalence of this pattern on chest radiography at presentation, and to assess the clinical characteristics of these patients.

Results—Ten patients (0.6%) were identified with diffuse ground glass abnormalities on the chest radiograph (eight men); all had associated hilar or mediastinal adenopathy. All patients were white and nine were smokers or former smokers. Nine patients were symptomatic and six had inspiratory crackles on physical examination. As a group these patients were remarkable for the frequency and severity of physiological abnormalities and the presence of various findings typically associated with "active" disease. Nine patients were followed for more than three years. All were treated with oral corticosteroids because of significant symptoms or physiological abnormalities, or both. Symptoms and radiological abnormalities disappeared or improved in all patients, but recurred in a high proportion when steroids were tapered or discontinued. By December 1992 only three patients had been withdrawn from treatment.

Conclusions—A diffuse ground glass pattern on the chest radiograph is unusual in patients with sarcoidosis and may occur more commonly in white subjects and cigarette smokers. Its presence suggests the existence of active disease of recent onset likely to require long term treatment with corticosteroids.

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Sarcoidosis is a multisystem disorder of unknown aetiology characterised by the presence of non-caseating granulomas at sites of involvement.¹⁻⁴ Although most organs can be affected by the disease, the lung and thoracic lymph nodes are the most common sites and approximately 90% of patients with sarcoidosis have an abnormal chest radiograph.¹⁻⁴

Various radiographic patterns have been described in patients with pulmonary parenchymal involvement. In patients with parenchymal abnormalities a reticulonodular pattern is most

commonly observed,⁵ but other less common patterns have been reported.⁵⁻⁷ A diffuse ground glass pattern – defined as a homogeneous opacification in which normal anatomical details of the lung are still visible but giving a hazy appearance to the lung fields⁸ – is mainly observed in hypersensitivity pneumonitis, particularly in the acute form of farmer's lung,⁹ and has also been described in some patients with early stages of asbestosis and berylliosis.⁸ A diffuse ground glass pattern on the standard chest radiograph is extremely rare in sarcoidosis, although ground glass opacities (usually localised) have been observed with high resolution computed tomographic scanning of the lung.^{10,11}

We have recently encountered a patient with sarcoidosis who presented with a ground glass pattern on chest radiography. To further investigate this association we have reviewed radiographs of more than 1600 patients with sarcoidosis evaluated at our unit to determine the prevalence of a diffuse ground glass pattern at the time of diagnosis and to better define the clinical characteristics and prognosis of these patients.

Methods

STUDY POPULATIONS

All patients with pulmonary sarcoidosis evaluated at Hôpital Avicenne between January 1976 and December 1991 were included. The diagnosis of sarcoidosis was based on previously described criteria, including the presence of non-caseating granulomas in a biopsy specimen of involved tissue or the site of a Kveim-Siltzbach reaction.¹² Patients whose chest radiograph taken at diagnosis demonstrated a diffuse ground glass pattern – defined as a homogeneous opacity affecting both lungs and in which normal anatomical details are still visible – were identified and their medical records reviewed. Epidemiological data (including age, sex, ethnic group, current and past smoking habits) and clinical history were available for all patients. Apart from routine biological tests, blood and urine calcium concentrations were also noted. Serum angiotensin converting enzyme activity was assayed with hippuryl histidine leucine as a substrate.¹³

PULMONARY FUNCTION TESTS

The forced expiratory volume in one second (FEV₁) and vital capacity (VC) were measured with a spirometer (Godart water sealed spirometer) and residual volume (RV) by multiple breath helium dilution. Carbon monoxide transfer factor (TLCO) was measured by the

Service de
Pneumologie,
Hôpital Avicenne,
Bobigny, France

A Tazi
T Desfemmes-Baleyte
D Valeyre
J-P Battesti

INSERM U 82,
Faculté de Médecine
Xavier Bichat,
75018 Paris, France

A Tazi
P Soler
D Valeyre
A J Hance

Reprint requests to:
Dr A J Hance.

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single breath method and scaled for age and height or alveolar volume (VA) as specified. The results were compared with previously published standards.¹³

BRONCHOALVEOLAR LAVAGE

All patients who underwent bronchoalveolar lavage as part of the diagnostic evaluation gave informed consent before the procedure. Lavage was performed as previously described using five aliquots (50 ml each) of sterile saline.¹² The total number of cells recovered/ml lavage fluid was determined by counting cells present in an aliquot of the resuspended original fluid. Differential cell count was obtained on May-Grünwald-Giemsa stained cytocentrifuged preparations of the lavage fluid by counting at least 500 cells.

STATISTICAL METHODS

Results are expressed as mean (SD). Comparisons of sequential data were made using a paired *t* test, a probability of <0.05 being considered significant.

Results

CHARACTERISTICS OF PATIENTS WITH PULMONARY SARCOIDOSIS AND A DIFFUSE GROUND GLASS RADIOGRAPHIC PATTERN AT THE TIME OF DIAGNOSIS

Clinical, biological and radiological findings

Between January 1976 and December 1991 1652 patients with sarcoidosis were evaluated at our unit. Ten patients (0.6%) had a diffuse ground glass pattern in the lung fields on a chest radiograph performed at the time of diagnosis. In these individuals the diagnosis of sarcoidosis was based on the presence of a compatible clinical picture, no evidence of disease due to other agents known to produce granulomatous lung diseases, and the presence of typical non-caseating granulomas on tissue biopsy samples (skin (n = 1), bronchial mucosa (n = 4), lymph

nodes (n = 3)), or at the site of a Kveim-Siltzbach reaction (n = 2). All patients had coexistent bilateral hilar or mediastinal adenopathy, or both. A typical chest radiograph of one of these patients is shown in the figure. Previous chest radiographs were available for four patients and all were normal two, six, nine, and twelve months respectively before presentation. Two patients underwent thoracic high resolution computed tomographic scanning as part of the diagnostic evaluation and the presence of ground glass abnormalities was confirmed in both cases.

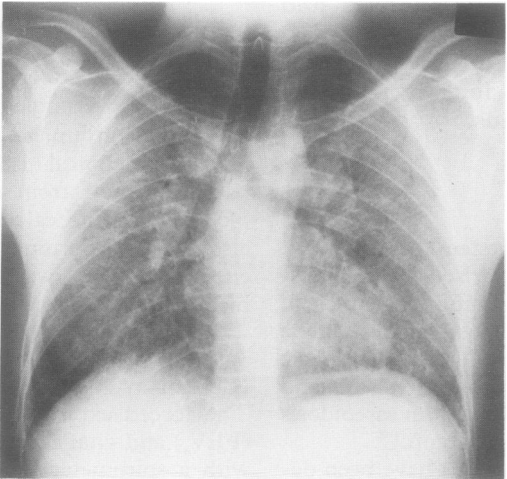
The epidemiological and clinical findings of the 10 patients are summarised in table 1. Nine of the patients were symptomatic at the time of diagnosis. Nine had smoked cigarettes; the six who were current smokers smoked more than 20 cigarettes/day (mean (SD) 25 (8)). Six patients had bilateral inspiratory crackles predominantly at the lung bases. Seven patients had extrathoracic lesions at one or more sites (peripheral lymph nodes (n = 4), ocular (n = 2), skin (n = 1), liver and spleen (n = 1), parotids (n = 1), peripheral nerves (n = 1), and bone (n = 1)). Although no patient had hypercalcaemia, an increase in the daily urinary calcium excretion (>0.1 mmol/kg/day) was noted in five of eight cases studied at the time of initial evaluation. Serum levels of angiotensin converting enzyme were elevated for all patients, ranging from two to five times the maximal normal value.

Pulmonary function

Results of pulmonary function tests were available for eight patients at the time of diagnosis. Seven patients had a restrictive defect, defined by a TLC of <80% predicted (67.8 (12.5)%). The TLC adjusted for age and height was considerably impaired in all cases (48.4 (13)% of predicted) and five of eight patients had a TLC/VA of <80% predicted (71 (17.7)%). Arterial hypoxaemia (PaO₂ <10.6 kPa) was present at rest in five of eight patients.

Bronchoalveolar lavage

Since patients evaluated as early as 1976 were included in this study, lavage results were avail-



Typical chest radiograph from a patient with sarcoidosis with a diffuse ground glass pattern. Note the existence of bilateral hilar and mediastinal adenopathy.

Table 1 Epidemiological and clinical features of patients with sarcoidosis who presented with diffuse ground glass abnormalities on the chest radiograph

Clinical characteristics	No. of patients (n = 10)
Epidemiological features	
Mean (SD) age (years)	38.5 (11.5)
M:F	8:2
Smoking history	
Current	6
Former	3
None	1
Race	
White	10
Clinical signs and symptoms	
Cough	7
Exertional dyspnoea	8
Weight loss	5
Inspiratory rales	6
Extrathoracic localisation	7

Table 2 Results of bronchoalveolar lavage in six patients with sarcoidosis who presented with a diffuse ground glass pattern on the chest radiograph

Smoking history	Total cells/ml ($\times 10^{-3}$)	Percentage of cells				
		Macrophages	Lymphocytes	Neutrophils	Eosinophils	Mast cells
NS	145	48	51	1	0	0
FS	115	24	76	0	0	0
S	395	45.5	53	0	0	1.5
S	791	43	50	6	0	1
S	645	78.5	18	2	1	0.5
FS	150	52	48	0	0	0

NS = non-smoker; FS = former smoker; S = current smoker.

able for only six patients. The number of lymphocytes/ml lavage fluid was increased in all patients (table 2). The CD4/CD8 lymphocyte ratio was evaluated in two smokers and was 4.2 and 2.6 respectively. Increased numbers of inflammatory cells were generally not present although one patient, a current smoker, had a moderate increase in neutrophils in the lavage fluid. Three of the six patients evaluated had an increased percentage of mast cells in the lavage fluid ($\geq 0.5\%$).¹⁴

OUTCOME

Nine patients were followed for more than three years (mean (SD) 99 (38) months, range 36–146 months). Because all these patients initially had significant respiratory symptoms (dyspnoea and/or cough) or severely impaired lung function, or both, all received treatment with oral corticosteroids (0.5 mg/kg/day prednisone). They all improved with treatment and inspiratory crackles disappeared in all cases within three months. Similarly, parenchymal abnormalities on the chest radiographs disappeared within three months of the institution of corticosteroids in seven of the nine patients and were considerably improved in the remaining two. Lung function tests also improved with treatment (table 3). For all patients studied ($n = 7$) TLC returned to within the predicted range during treatment. In parallel, TLC adjusted for age and height increased by $> 10\%$ in five of seven cases, although TLC/VA was not significantly modified (table 3). PaO_2 at rest reached normal values (> 10.6 kPa) in three of the five patients who were initially hypoxaemic and improved in two other cases.

Although all patients showed initial improvement six of the nine patients experienced recur-

rent signs and symptoms of active sarcoidosis while their doses of prednisone were being tapered or after interruption of treatment. Strikingly, during these recurrent episodes of sarcoidosis the chest radiographs always showed a diffuse ground glass pattern. Four patients had multiple episodes of recurrent sarcoidosis. Overall the duration of treatment was 96 (41) months (range 30–143 months), and by the end of December 1992 only three patients had been successfully withdrawn from treatment with corticosteroids after 30, 48, and 128 months, respectively.

Discussion

A review of more than 1600 chest radiographs of patients with sarcoidosis evaluated at our unit has shown that the presence of a diffuse ground glass pattern on the chest radiograph is an uncommon finding at presentation, but is associated with a distinct clinical profile. These patients were all white and tended to be heavy smokers, they had sarcoidosis of recent onset, and were almost always symptomatic. The disease was responsive to treatment with corticosteroids but frequently relapsed when corticosteroids were tapered or stopped, and several required long term treatment.

Several epidemiological features are noteworthy in this form of sarcoidosis. Firstly, nine of the 10 patients had smoked, and six were current heavy smokers. In two studies from our group the overall prevalence of cigarette smoking among patients with pulmonary sarcoidosis was 31%¹² and 39%¹³ and, among smokers, mean tobacco consumption was 10 cigarettes a day.¹³ In contrast, current smokers in the present study smoked more than 20 cigarettes a day. The high proportion of current and past smokers in this series may explain the observed male predominance.

The origin of ground glass abnormalities in our patients and the reason for the association of these abnormalities with cigarette smoking is unclear. Smoking is known to increase alveolar epithelial permeability which might promote alveolar filling. Because some of our patients were non-smokers and others had stopped smoking alterations in pulmonary epithelial permeability induced by smoking, which are rapidly reversible,¹⁵ are not the sole factor responsible for the ground glass abnormalities. Smoking is also known to modify the lung immune responses and such changes might predispose to the development of ground glass

Table 3 Sequential evaluation of mean (SD) results of respiratory function testing for seven patients with sarcoidosis who presented with a diffuse ground glass pattern at the time of diagnosis and after treatment with corticosteroids

Physiological test	Before treatment	After treatment
TLC (% predicted)	66.8 (13.2)	89 (7.2)*
FEV ₁ /VC	78.0 (12.3)	77.4 (9.3)
TLCO (% predicted)	49.1 (13.8)	66.8 (13.6)*
TLCO/VA	72.5 (19.0)	73.5 (9.7)
PaO_2 (kPa)	10.3 (1.7)	11.5 (1.2)*

* $p < 0.05$ comparing results before and after treatment using a paired t test. The best lung function while the patient was receiving corticosteroids was chosen.

abnormalities. Smoking is not thought to modify the prognosis of sarcoidosis in unselected patients,¹³ however, suggesting that smoking in itself cannot explain the unfavourable outcome of these patients.

It is also noteworthy that all patients, without exception, were white. Sarcoidosis is known to occur more frequently among the black population and, in France, among immigrants from the Caribbean.¹¹⁶ In our own series, however, the proportion of white patients with sarcoidosis is approximately 85%. Thus, given the small number of patients identified with ground glass abnormalities, a very large case-control study would be necessary to show that this abnormality is truly more common in the white population.

The presence of hilar or mediastinal adenopathy on the radiograph of all 10 patients, and the observation that chest radiographs taken in the year before diagnosis (when available) were normal, strongly suggest that pulmonary sarcoidosis presenting with a diffuse ground glass radiographic pattern is likely to represent disease of recent onset.

Also striking are the clinical and functional profiles of these patients. Nine presented with severe respiratory symptoms (dyspnoea and cough) and series in which large numbers of unselected patients have been evaluated indicate that respiratory symptoms at presentation are less frequent, particularly in white patients.^{12 16 17} Furthermore, six patients had fine inspiratory crackles mainly in the lower zones. It should be stressed that the presence of inspiratory crackles in our patients was not due to pulmonary fibrosis as they cleared with treatment. In unselected patients crackles are unusual, especially in patients with disease of recent onset who are unlikely to have extensive fibrotic changes. In a study which compares the prevalence of respiratory crackles in various interstitial lung disorders inspiratory crackles were found in only 20% of patients with sarcoidosis.¹⁸ In our series the prevalence of crackles in sarcoidosis of recent onset is less than 10%, and is essentially restricted to non-white patients in whom sarcoidosis is known to be more severe.¹⁹ Because crackles themselves suggest the presence of extensive pulmonary disease, it is difficult to determine whether the presence of ground glass abnormalities adds additional prognostic information or merely indicates the presence of "severe" parenchymal involvement.

Although a moderate restrictive pattern associated with an abnormal diffusing capacity is frequently noted in sarcoidosis,^{20 21} an important decrease in TLC and TLCO, as observed in our patients, is unusual.^{22 23} Furthermore, studies on gas exchange have shown that hypoxaemia at rest, which was present in five of our cases, is unusual.²¹⁻²³ Because of these functional abnormalities and the associated clinical symptoms, all patients needed treatment with oral corticosteroids. Although they responded rapidly, long term oral corticosteroid therapy was required to maintain this improvement. This chronic evolution is also uncommon in sarcoidosis of recent onset in white patients.¹⁹

The activity of the disease at presentation in our patients was supported by the presence of high serum levels of angiotensin converting enzyme in all cases. Although cigarette smoking has been shown to increase serum angiotensin converting enzyme levels in patients with sarcoidosis,¹³ the presence of respiratory symptoms, extrathoracic disease, and hypercalciuria in most of the patients suggests that the elevated levels of serum angiotensin converting enzyme reflect both the clinical activity of their disease and the presence of widespread granulomatous lesions.^{3 4 24 25} The increased recovery of lymphocytes and mast cells by bronchoalveolar lavage also supports the presence of active disease.¹⁴ Although the presence of an elevated number of lymphocytes has been reported to be a good prognostic indicator or to be associated with a good response to treatment, or both,^{26 27} the presence of mast cells is thought to be associated with a poor prognosis.¹⁴

Extensive use of thoracic high resolution computed tomographic scanning has led to the more frequent identification of "ground glass" opacities. Focal ground glass abnormalities have been observed in a broad spectrum of lung disorders including sarcoidosis of recent onset.^{10 11 28 29} In sarcoidosis these localised abnormalities often occur preferentially around bronchovascular bundles and are associated with other lesions.^{10 28} A predominant and diffuse ground glass pattern has also been identified on lung high resolution computed tomography in other conditions,^{28 30} and disseminated, although not diffuse, ground glass abnormalities have been described in sarcoidosis by this technique.^{10 11} A ground glass pattern on lung high resolution computed tomography is thought to reflect either minimal thickening of alveolar septa or partial filling of the alveolar air space with fluid or cells.¹¹ Although the significance of ground glass opacities is incompletely understood, it has been shown to correlate with disease activity in idiopathic pulmonary fibrosis and to be reversible under corticosteroid treatment.^{31 32} In a recent study evaluating the correlation between computed tomographic findings and lung histology in bronchiolitis obliterans organising pneumonia biopsy specimens obtained from areas of ground glass opacities contained "alveolar septal inflammation and alveolar desquamation".³³ Very recently biopsy specimens of localised areas of ground glass pattern have been studied in one patient with sarcoidosis and were found to contain mainly granulomas.³⁴

In summary, a diffuse ground glass radiographic pattern at the time of diagnosis of sarcoidosis was observed exclusively in white patients, many of whom were cigarette smokers. The disease proved to be of recent onset and quite active. Although rare, this mode of presentation of the disease is noteworthy because, in our experience, it tends to have a chronic evolution requiring prolonged treatment with oral corticosteroids.

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