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Clinical spectrum of cryptogenic organising pneumonitis

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Abstract

Cryptogenic organising pneumonitis (bronchiolitis obliterans organising pneumonia) is an uncommon condition that often responds to steroids. It is characterised clinically by constitutional symptoms, pathologically by intra-alveolar organising fibrosis, and radiologically by patchy pulmonary infiltrates. Its full clinical spectrum and course are only partially described and understood. Six patients are described, seen over three years, with considerably diverse clinical and radiological presentations (two had diffuse lung infiltrates, two had peripheral lung infiltrates, and two had localised lobar involvement) and with very varying severity of disease (two with a life threatening illness, three with appreciable subacute constitutional symptoms, and one with mild symptoms). It is concluded that cryptogenic organising pneumonitis can present in various ways. A set of diagnostic criteria are proposed which will help in the recognition of this syndrome, which is probably underdiagnosed.

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Although the concept of organising pneumonia is old,[1-3] the term cryptogenic organising pneumonitis was introduced only recently.[4] Since the initial description of cryptogenic organising pneumonitis a very similar condition has been described in America under the name of bronchiolitis obliterans organising pneumonia.[5,6] Both terms have been used for patients who typically have a restrictive lung disorder of unknown aetiology, bilateral peripheral lung infiltrates, a subacute clinical course, intraluminal (alveolar or bronchiolar, or both) filling with buds of young fibrous tissue, and a favourable response to steroids. This clinical profile may be too narrow, however, and may exclude patients with variants and different clinical features.[7,8] We report on six patients with intraluminal buds of organising fibrous tissue affecting the distal airspaces in the context of a cryptogenic disease of the lung. These

Table 1 Clinical features of the patients

Patient No	*Age (y)*	*Sex*	*Symptoms*	*Physical findings*	*History*	*Treatment before diagnosis*	*White cell count on admission*	*Change in white cell count*	*Erythrocyte sedimentation rate (mm in first hour)*
1	71	M	Eight weeks of sweats, malaise, weight loss, cough, dyspnoea	Tachypnoea++, cyanosis++, biliary crackles++, temperature 37·4°C, very ill+++	Smoker, healthy	Erythromycin, doxycycline	3·5 × 10^6/l	Neutropenia	99
2	70	F	Eight weeks of malaise, fever, rapidly increasing dyspnoea	Tachypnoea++, cyanosis++, biliary crackles++, temperature 38·5°C, very ill+++	Smoker, healthy	Erythromycin, penicillin, gentamicin, ampicillin, clavulonic acid	11·2 × 10^6/l	Neutrophilia	80
3	77	M	Three weeks of cough, malaise and mild dyspnoea	Crackles++, not severely ill, not cyanosed, temperature 37·2°C	Ethanol liver disease, atrial fibrillation, former smoker	Erythromycin	10·5 × 10^6/l	Neutrophilia	43
4	68	M	Three months of weight loss, anorexia, cough, dyspnoea	Crackles+++, not severely ill, not cyanosed, not febrile	Carcinoma in situ (stomach), former smoker	Erythromycin, doxycycline	14·3 × 10^6/l	Neutrophilia	30
5	71	M	Four weeks of cough, malaise, increasing dyspnoea	Crackles in right apex, tachypnoea+, not cyanosed, not severely ill, temperature 38·5°C	Former smoker, congestive heart failure, taking amiodarone	Amoxycillin, diuretics	12·2 × 10^6/l	Neutrophilia	55
6	70	M	Four weeks of cough	Crackles in left base, not febrile, not ill	Former smoker, healthy	Erythromycin	8·3 × 10^6/l	Normal	80

patients had a wider clinical spectrum than the classically described one and highlight the need for a broader concept of this disorder.

Methods

After caring for five patients with an organising pneumonia of unknown aetiology over 12 months, we searched the pathology department's files for patients in whom organising pneumonia had been diagnosed on pathological examination in the preceding two years. One such patient was found, in whom the following were excluded: malignancy, a history of taking drugs, infection by known agents, connective tissue disease, and exposure to toxic fumes. In all six patients organising pneumonia was diagnosed on the basis of either open or transbronchial lung biopsy samples independently by pathologists who had limited clinical information and were unaware of the possibility of cryptogenic organising pneumonia. In all patients a chest radiograph was taken and full blood count, erythrocyte sedimentation rate, and renal and liver function determined. The medical records were analysed; tables 1 and 2 summarise the patients' clinical features.

Results

The six patients (five men and one woman) had a mean age of 71 years (range 68–77 years). Two of them (patients 3 and 4) had a radiological and clinical presentation which fitted the typical pattern described for cryptogenic organising pneumonitis, and the other four had atypical clinical and radiological findings. All six patients had several clinical features in common, however, including a subacute course of varying duration; a dry, non-productive cough; and a history of having received treatment for a chest infection. Five patients had been treated for atypical pneumonia before presentation and had had an influenza like illness at the onset of their symptoms. Only one (patient 5) had been taking drugs (frusemide and amiodarone) before the onset of illness. On clinical examination all six patients had inspiratory crackles

Table 2 Pulmonary features of the patients at presentation

					Bronchoalveolar lavage										
		Arterial blood (on air)													
Patient No	*Chest radiograph*	*pH*	*PaO_2 (kPa)*	*$PaCO_2$ (kPa)*	*Macrocytes (%)*	*Lymphocytes (%)*	*Polymorphonuclear neutrophils (%)*	*Eosinophils (%)*	*Type of biopsy*	*FVC (% pred)*	*FEV_1 (% pred)*	*FEV_1/FVC (%)*	*TLCO (% pred)*	*Treatment*	*Outcome*
1	Diffuse patchy consolidation, peripheral confluence	7·45	7·1	5·1	90	7	3	0	Open lung	Not done				Prednisolone 60 mg	Great improvement (over days)
2	Diffuse patchy, mostly peripheral, basal opacification	7·40	6·3	4·7	Not done				Transbronchial	63	70	92	25	Prednisolone 50 mg	Great improvement (over days)
3	Bilaterial peripheral infiltrates	7·42	8·0	5·5	16	70	7	7	Transbronchial	Not done				Prednisolone 25 mg	Complete response over weeks
4	Bilateral, patchy peripheral infiltrates with confluence	7·49	7·9	4·1	Not done				Open lung	91	89	70	44	Prednisolone 50 mg	Resolution over weeks
5	Localised right apical infiltrate	7·43	7·7	4·5	Not done				Transbronchial	61	54	63	56	Observation	Death from cardiac arrest (unrelated)
6	Left lower lobe infiltrate/consolidation which cleared followed by similar changes at right lower lobe	7·43	11·2	5·5	79	4	16	1	Transbronchial	63	67	78	82	Observation	Well despite lung changes, resolution

FVC—forced vital capacity; FEV_1—forced expiratory volume in one second; TLCO—transfer factor for carbon monoxide.

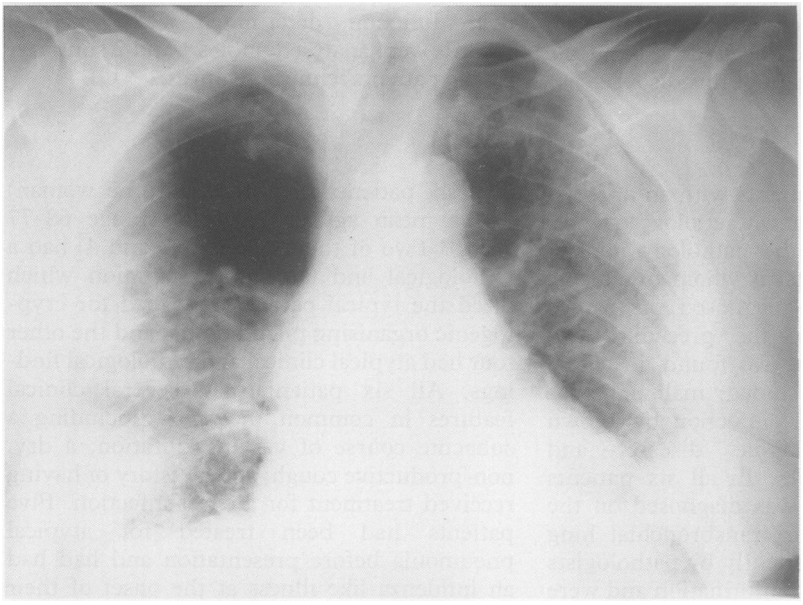

Figure 1 Bilateral, predominantly peripheral confluent opacification of lung fields with patchy perihilar consolidation (patient 1).

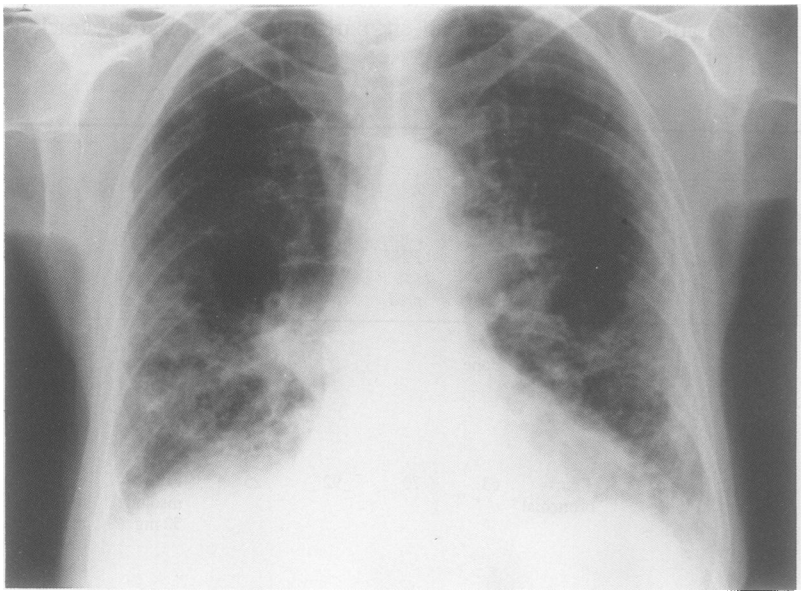

Figure 2 Bilateral diffuse interstitial and alveolar opacification of lung fields with particular basal and peripheral involvement (patient 2).

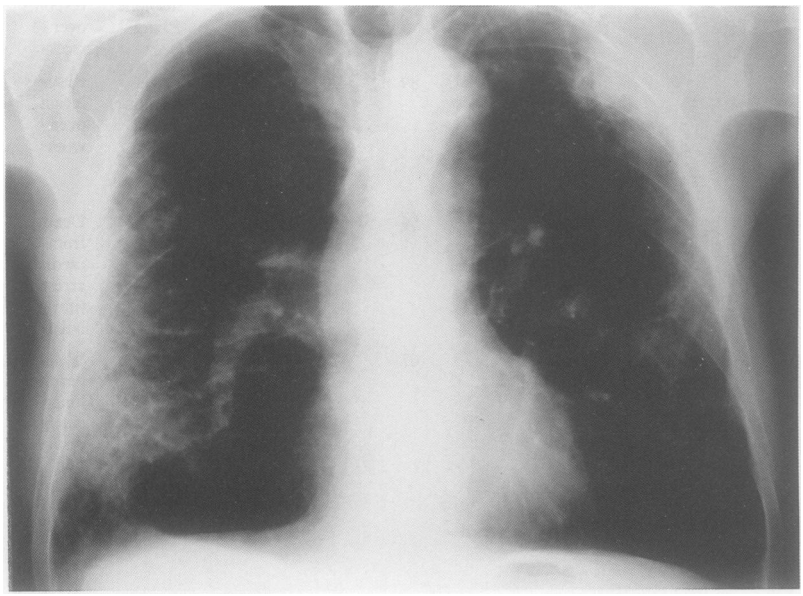

Figure 3 Bilateral patchy opacification of lung fields with particular peripheral involvement and confluence (patient 3).

and four were febrile; three were moderately unwell, one had only minor symptoms, and two (patients 1 and 2) were severely ill with acute respiratory failure that was close to requiring assisted ventilation. These two patients, who were treated initially for pneumonia, deteriorated over about two weeks with spreading lung field opacification on radiography and life threatening hypoxaemia. They were transferred to our hospital for possible assisted ventilation.

INVESTIGATIONS

All patients had negative serology for mycoplasma, chlamydia, legionella, the organism that causes Q fever, and influenza A and B viruses, and no autoantibodies. Three patients had leucocytosis and one leucopenia. The erythrocyte sedimentation rate was raised in all six patients. The chest radiograph showed diffuse bilateral patchy consolidation with peripheral confluence in two patients (figs 1 and 2), typical peripheral changes in two patients (figs 3 and 4), and localised infiltration/consolidation in the remaining two (figs 5 and 6). Five patients had significant resting hypoxaemia (Pa_{O_2} < 8 kPa) and three had a Pa_{CO_2} of < 4·5 kPa.

Bronchoalveolar lavage was performed in three patients and did not show a consistent pattern. One patient had a degree of eosinophilia, one a predominance of neutrophils, and the third a lymphocyte count at the upper limit of normal. Table 3 summarises the distribution of the clinical, biochemical, and spirometric findings.

The histological diagnosis was confirmed in all patients: in two by open lung biopsy and in the remaining four by transbronchial biopsy. All six patients showed the typical histological features of cryptogenic organising pneumonitis with polypoid buds of "young" organising fibrous tissue filling the distal airspaces (alveoli, alveolar ducts, and, when seen in the biopsy sample, respiratory bronchioles) (fig 7). There was some mild to moderate thickening of the alveolar septa, but this was not a major feature. No eosinophilic infiltrate was seen and

Table 3 Clinical, biochemical, and radiological features at presentation in the six patients

Features	*Incidence*
History:	
Cough	All patients
Exertive dyspnoea	Five patients
Subacute illness	All patients
Influenza like onset	Five patients
Examination:	
Crackles	All patients
Biochemical findings:	
Low transfer factor for carbon monoxide (TLCO)	All four patients tested
Leucocytosis	Three patients
High erythrocyte sedimentation rate	All patients
Resting hypoxaemia	Five patients
Chest radiograph pattern:	
Diffuse infiltrates	Two patients
Localised infiltrates	Two patients
Peripheral infiltrates	Two patients

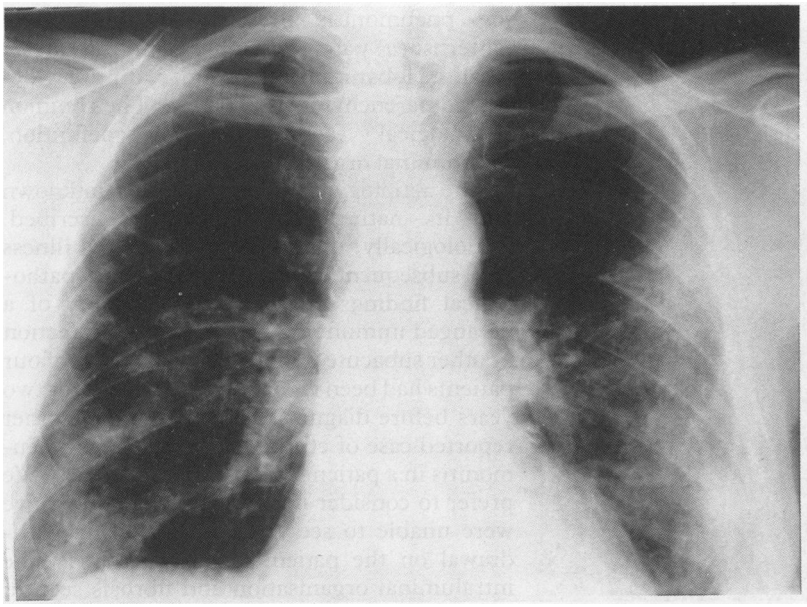

Figure 4 Peripheral lung infiltrates bilaterally with confluent opacification along the lateral aspect of both lungs (patient 4).

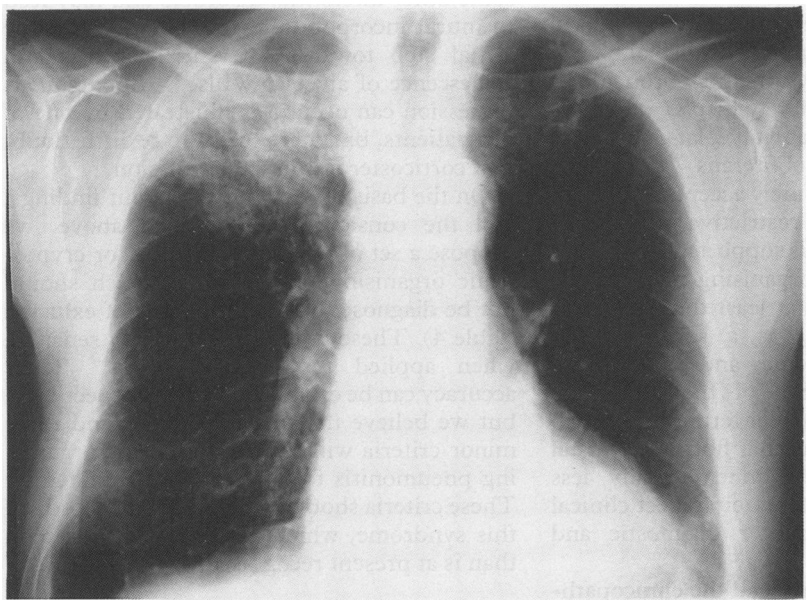

Figure 5 Right apical consolidation with patchy surrounding alveolar and interstitial opacification (patient 5).

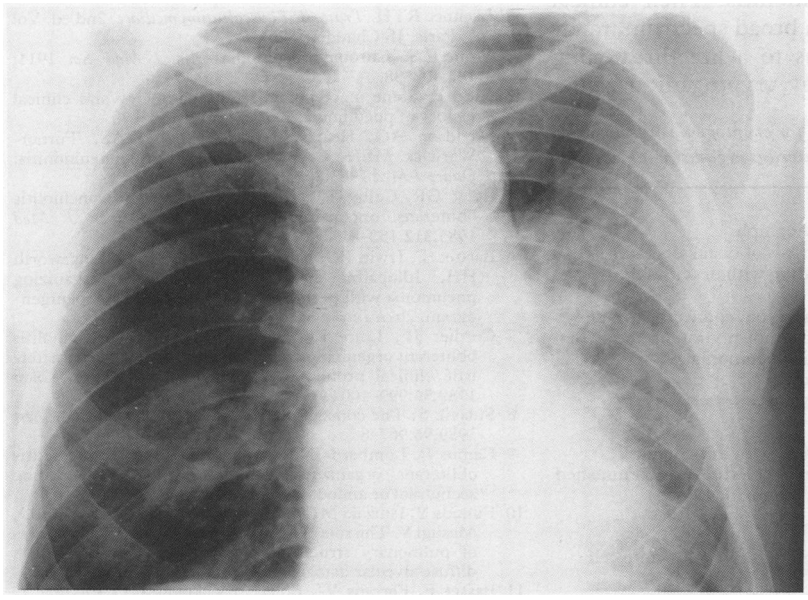

Figure 6 Patchy widespread left lower lobe consolidation (patient 6).

staining for microorganisms gave negative results in all patients.

OUTCOME

Four of the six patients were treated with corticosteroids. Of the two untreated patients, one died of ventricular fibrillation while steroids were being considered (patient 5). He had been taking amiodarone for ventricular tachycardia for 24 months. The other untreated patient (patient 6) continued to be almost free of symptoms, despite pronounced evolving radiological changes consisting of left lower lobe lateral and basal consolidation, complete left lower lobe consolidation three weeks later, right lower lobe consolidation at five weeks with resolution of left sided changes, and full resolution at eight weeks after initial diagnosis. Two of the patients who received steroids were extremely ill and severely hypoxaemic at the time of initiation of treatment (patients 1 and 2). Their responses to 1 mg/kg of prednisolone were impressive: by day 10 both were well enough to be discharged. The other two patients had a clinical course, symptoms, and a radiological picture similar to the typical picture of bronchiolitis obliterans organising pneumonia as described by Epler.[5] One (patient 4) initially received prednisolone 50 mg a day, which was reduced to 10 mg a day over six months and stopped at nine months without recurrence. He had an excellent symptomatic response over several weeks. His chest radiograph returned to normal. The other (patient 3), who had alcoholic liver disease, was treated with prednisolone 25 mg a day. His symptoms disappeared and his chest radiograph cleared over four weeks. His dose of steroid was decreased slowly and the drug stopped at six months. There was no evidence of recurrence three months later.

Discussion

Since its initial description[4] cryptogenic organising pneumonitis has been reported only rarely, the largest group of cases being described by Epler, who used the term bronchiolitis obliterans organising pneumonia.[5] In both of these retrospective studies patients had fever, malaise, dyspnoea, a non-productive cough, peripheral lung infiltrates on radiography, and a lung biopsy sample that showed an intraluminal organising pneumonitis. The patients in the two reports clearly had a very similar disorder or group of disorders. Epler used the term bronchiolitis obliterans organising pneumonia because his computerised retrospective clinical study was originally aimed at finding patients with bronchiolitis obliterans recorded in their final pathological report. Since then case reports have used the terms cryptogenic organising pneumonitis and bronchiolitis obliterans organising pneumonia interchangeably. Emphasis on the presence of bronchiolitis obliterans on histological examination as an implied criterion for diagnosing this disorder has, however, appreciably and, in our opinion, detrimentally narrowed

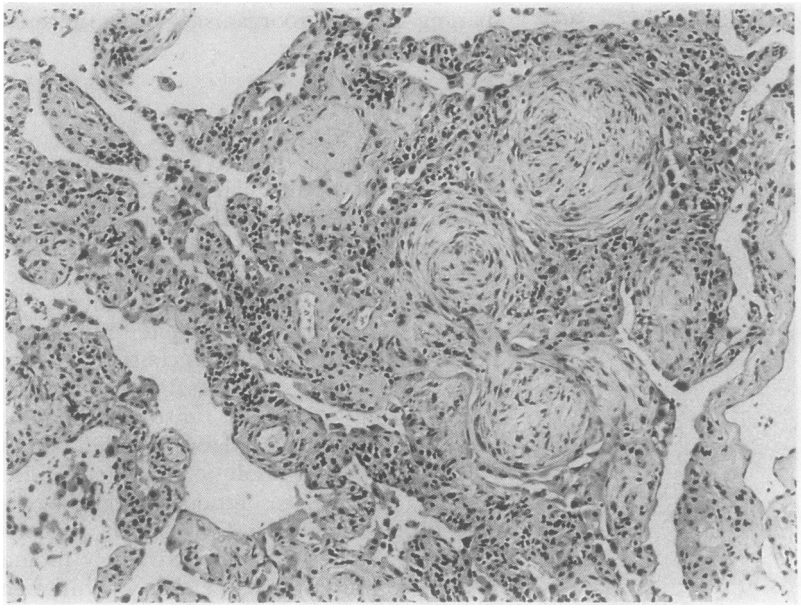

Figure 7 Polypoid buds of loose connective tissue filling air spaces and small airways (top right).

the clinical spectrum reported. Given the focal nature of the disorder, a transbronchial biopsy sample may not always include bronchioles that are obliterated and may display organisation only in the alveoli and alveolar ducts. The term bronchiolitis obliterans organising pneumonia, although widely accepted in North America, may be too restrictive, and hence undesirable. This view is supported by a recent report of cryptogenic organising pneumonitis presenting clinically in at least three ways: as the typical syndrome, as a solitary lobar pneumonia like syndrome, and as a diffuse pulmonary manifestation of the interstitial lung disease. Thus a broader terminology such as "cryptogenic intraluminal fibrosis of distal airspaces," while being mnemonically less appealing, may more accurately reflect clinical features and be of greater diagnostic and therapeutic use.

Our six patients clearly had the clinicopathological disorder, or group of disorders, which can, for simplicity's sake, be named cryptogenic organising pneumonitis. Their clinical presentations covered a broad spectrum, ranging from a mild illness to a life threatening condition. Radiologically, cryptogenic organising pneumonitis presents in three main patterns: (*a*) patchy peripheral infiltration; (*b*) localised lobar infiltration, and (*c*) diffuse widespread parenchymal infiltration. The common pathological feature is, by definition, intraluminal organising pneumonitis.

Table 4 Diagnostic criteria for cryptogenic organising pneumonitis/bronchiolitis obliterans organising pneumonia

Major criteria
1 Pulmonary infiltrates in radiograph
2 Intraluminal organising fibrosis of distal airspaces as dominant histological finding with or without bronchiolitis obliterans
3 Exclusion of toxic fume inhalation; connective tissue disease; recent infection by known viral, bacterial, or fungal agents; eosinophilic pneumonia; or hypersensitivity pneumonitis
4 Clinical and radiological response to steroids
Minor criteria
1 Subacute constitutional illness with dry cough
2 Restrictive pattern of spirometric values and diminished transfer factor for carbon monoxide (TLCO)
3 Hypoxaemia
4 Inspiratory crackles
5 Raised erythrocyte sedimentation rate and white cell count
6 Absence of finger clubbing
7 Cough (non-productive)

The aetiology of this syndrome is unknown and its natural course poorly described. Aetiologically, the influenza like initial illness and subsequent subacute course and pathological findings suggest the possibility of a deranged immunological response to infection or other subacute pulmonary insult. One of our patients had been receiving amiodarone for two years before diagnosis, and there is one other reported case of cryptogenic organising pneumonitis in a patient receiving amiodarone.[9] We prefer to consider our case as idiopathic as we were unable to see the effects of drug withdrawal on the patient's clinical course. The intraluminal organisation and fibrosis seen in cryptogenic organising pneumonitis is poorly understood. It can be seen, less severely, in some other interstitial disorders and may lead to mural incorporation, this being a possible initial step towards interstitial fibrosis and coalescence of alveolar walls.[10 11] Spontaneous regression can occur,[5] as illustrated by one of our patients, but there seems to be little doubt that corticosteroids hasten remission.

On the basis of previous work, our findings, and the considerations outlined above, we propose a set of diagnostic criteria for cryptogenic organising pneumonitis, which should not be diagnosed just on the basis of exlusion (table 4). These criteria seem highly sensitive when applied to reported cases.[4-7] Their accuracy can be established only prospectively, but we believe that the four major and three minor criteria will allow cryptogenic organising pneumonitis to be diagnosed confidently. These criteria should facilitate further study of this syndrome, which may be more common than is at present recognised.

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