Airway involvement in interstitial lung disease

Carlos Robalo Cordeiro

Purpose of review

After briefly discussing several ways to approach airway involvement in interstitial lung diseases – by diagnostic methodologies used to assess it, considering different topographical involvement, related to its presence in the diffuse lung diseases with higher prevalence, or from a causal point of view – the author describes in more detail, taking into account recent literature, new proposed entities combining airways (at different levels) and interstitial damage, like airway-centered interstitial fibrosis and acute fibrinous organizing pneumonia.

Recent findings

These proposed patterns are being discussed, as possible autonomic interstitial lung disease disorders, and also from the perspective of its relationship with the main differential diagnosis, within known interstitial pictures.

Summary

Thus, airway-centered interstitial fibrosis and acute fibrinous organizing pneumonia may widen the spectrum of the yet described long list of interstitial lung diseases, and its diagnosis may be considered, under specific circumstances, when there is airway involvement associated with interstitial damage.

Keywords

acute fibrinous organizing pneumonia, airway-centered interstitial fibrosis, interstitial lung diseases, peribronchiolar metaplasia, sarcoidosis

Curr Opin Pulm Med 12:337–341. © 2006 Lippincott Williams & Wilkins.

Department of Pneumology and Allergology, University Hospital of Coimbra, Coimbra, Portugal

Correspondence to Carlos Robalo Cordeiro, Department of Pneumology and Allergology, University Hospital of Coimbra, 3000 Coimbra, Portugal
Tel: +351 239836262; fax: +351 239836262; e-mail: crobalo@mail.telepac.pt

Current Opinion in Pulmonary Medicine 2006, 12:337–341

Abbreviations

ACIF	airway-centered interstitial fibrosis
AFOP	acute fibrinous organizing pneumonia
BAL	bronchoalveolar lavage
COP	cryptogenic organizing pneumonia
CT	computed tomography
DAD	diffuse alveolar damage
ILD	interstitial lung diseases
PBM	peribronchiolar metaplasia
SARS	severe acute respiratory syndrome

1070-5287

Introduction

The methodology for reviewing airway involvement in interstitial lung diseases (ILD) may be understood through the different options that it offers.

Thus, besides the recognition of obstructive functional syndromes (although sometimes misleading or confusing), the important role of high-resolution computed tomography (HRCT) and specific histological findings, assessment of airways damage may also include several clinical and laboratory features, such as endoscopic observations.

In this latter context, bronchostenosis has been described in association with sarcoidosis (perhaps the most frequent interstitial clinical pattern with airway involvement, exhaustively studied from a bronchoscopic point of view) as being related either to the granulomatous lesions of this disease, due to compression caused by mediastinal lymphadenopathy, or even to distortion damage caused, in bronchi, by severe pulmonary fibrosis in sarcoidosis stage 4 [1••].

Chambellan *et al.* [2•] pointed out that, in stages 1–3, besides the granulomatous infiltration and the compression from enlarged hilar nodes, the bronchial narrowing may also be related to the presence of an endobronchial mass lesion.

In this context, Fridlender *et al.* [3•] described a unique clinical case of Langerhans cell histiocytosis – actually considered as a bronchiolitis rather than an interstitial lung disorder – [4], in a nonsmoker, manifesting itself as an obstructing tracheal lesion, with complete resolution after endoluminal resection. This study may be included in a differently described form of nonsmoking-related Langerhans cell histiocytosis that may be seen as a neoplastic disorder, involving, on rare occasions, the large airways.

In the study previously published in *Chest* [2•], the authors presented a retrospective study of 2500 patients with sarcoidosis, in which endoluminal stenosis of proximal bronchi, defined as lumen narrowing in at least 50%, was found in only 18 cases (0.72%), occuring as single stenosis (three cases), multiple stenosis (12 cases) or diffuse narrowing of bronchial tree (three cases).

On the other hand, some years ago, Olsson *et al.* [5] reviewed the bronchoscope findings in a group of 99

patients, of whom eight (8%) showed severe bronchi stenosis, implying that sarcoidosis must be included in the differential diagnosis of obstructive diseases – either chronic obstructive pulmonary disease or bronchial carcinoma presenting itself with atelectasis.

More recently, Udwadia *et al.* [6] reported bronchographic findings in 12 patients with this granulomatous disease and airways obstruction, showing several areas of segmental bronchial stenosis in 10 patients (about 83%).

In any case, granulomatous infiltrative lesions are usually present, mainly in bronchial submucosa, allowing an accurate diagnosis of sarcoidosis by bronchial biopsies (this has been related to ethnicity, higher in Afro-Caribbean and lower in Caucasian patients). By some, this accuracy is set at 41–57% [7], and in other studies considered a consistent finding [2•], as, in all cases, at least one bronchial biopsy showed noncaseating granulomata (48 biopsies from a total of 62 specimens).

These excellent data have been reported and fluorescent bronchoscopy seems to be a promising tool to improve the diagnostic accuracy of bronchial biopsies in the assessment of sarcoidosis, thus extending the indications of this endoscopic tool.

Besides these introductory points, in the following sections of the review, we will lay emphasis upon two newly described patterns of ILD which are associated with airway involvement. The first relates to proximal distribution – the airway centered interstitial fibrosis (ACIF) – the other to alveolar involvement – the acute fibrinous organizing pneumonia (AFOP). These may be approached in an updated discussion, focusing on their autonomous existence and, on the other hand, as disorders that widen the spectrum of differential diagnosis within ILD.

Airway-centered interstitial fibrosis

In 2002, Yousem *et al.* [8] reported on 10 patients from their unclassified files of interstitial pneumonias, with a common main finding of centrilobular and bronchiolocentric inflammatory infiltrate, allowing this entity to be classified as 'idiopathic bronchiolocentric interstitial pneumonia'. This pattern was defined based on certain distinctive characteristics in relation to the main differential diagnosis (hypersensitivity pneumonitis and nonspecific interstitial pneumonia): the propensity for women (eight in 10), occurrence in middle age (40–50 years), absence of granulomas, major bronchiocentric injury with peribronchiolar fibrosis and the worst prognosis (33% of deaths and 56% of persistent or progressive disease, in a mean follow-up of 4 years).

More recently, Churg *et al.* [9] described a group of 12 patients with similar histologic findings, in which there was peribronchiolar distribution of interstitial inflammation and fibrosis with bronchiolar metaplasia.

Besides the bronchiolocentric interstitial damage, these patients showed fibrosis around small airways (histological-based evidence) and large airways (CT scan-based evidence), which led the authors to propose the term 'airway-centered interstitial fibrosis' (ACIF).

In fact, the discussion was centered on whether airway fibrosis was the earliest manifestation and at what level – whether mostly peripheric (alveolar or bronchiolar) or more central (which seems to be the case according to various imaging and morphologic findings suggesting that damage was mainly of central distribution, not wholly assessed by lung biopsy).

As in the Yousem study [8], Churg *et al.* [9] discuss the main differential diagnosis, namely with hypersensitivity pneumonitis, which may also present with both interstitial and airways lesions.

Nevertheless, these ACIF patients had a number of particular characteristics (clinical, radiographic, laboratory and histologic) which were distinctive from the hypersensitivity pneumonitis pattern.

Interestingly, there was no consistent antigenic exposure and even two patients with pigeon exposure had negative specific antibodies. Also, the mean percentage of lymphocytosis in bronchoalveolar lavage (BAL) – approximately 20% and not always higher than normal – is much lower than the expected values in hypersensitivity pneumonitis. As to radiological differences, the authors did not find any granulomatous lesions in the ACIF patients, in whom the presence of the previous underlined bronchiolar metaplasia was a common feature. This lesion, consisting of peribronchiolar metaplasia (PBM) of bronchiolar-like epithelium, is a common finding in several ILD. Nevertheless, its presence as the only major finding in lung biopsy in patients with ILD was recently described by Fukuoka *et al.* [10•].

These authors present a group of 15 patients in whom PBM is the sole histological finding in clinical cases with ILD (PBM–ILD). These patients also share some characteristics, not only with the patients reported by Yousem [8] (idiopathic bronchiolocentric interstitial pneumonia) and by Churg [9] (ACIF), namely the predominance of females (13 females and two males) and the mean age, around 57 years, but also with a group of so-called centrilobular fibrosis patients, discussed before by de Carvalho *et al.* [11].

Nevertheless, the PBM–ILD patterns published by Fukuoka [10•] had a much better prognosis (even with

a short mean follow-up of 2.4 years) and different computed tomography (CT) findings, without demonstrating the worst features of extensive peribronchiolar interstitial lesions found in the previous studies.

Again, the main differential diagnosis – hypersensitivity pneumonitis – must be excluded, although there were only two patients with known inhalatory exposures (one with pigeons, the other asbestos-related) and granulomatous lesions were only seen in three lung biopsy specimens.

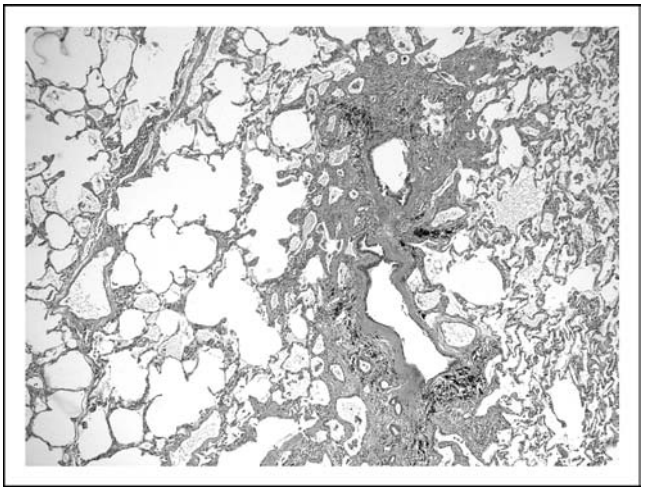
More recently, Colombat *et al.* [12] had the chance to examine the entire lungs of a patient submitted to lung transplantation for end-stage respiratory failure.

In this observation, the authors found interstitial fibrosis centered on large airways (not accessible by open lung biopsy, as performed in previous studies) and on small airways, bronchi and bronchiolar distortions in close proximity with fibrosis and bronchiolar metaplasia. This study supports the hypothesis that the fibrotic lesions could have begun in the periairway tissue, being predominant in the upper lobes, and that the main differential diagnosis may be excluded, as there were no morphologic characteristics of hypersensitivity pneumonitis in the entire lung studied. This patient, however, had a history of exposure to pigeons (without the presence of antibodies), in resemblance to previously described ACIF cases.

In the abstract of the last published study about ACIF pattern (written in Chinese), Xu *et al.* [13] described a patient from Peking Union Medical College Hospital, with the same characteristic fibrosis centered on membranous and respiratory bronchioles. It also underlines the ongoing discussion about this entity, difficult to include into any known category of ILD, and which may, eventually, in this context, be classified as an autonomous disease.

In Fig. 1, we can see the morphologic pattern of ACIF in a 42-year-old woman presenting with a nonproductive cough admitted to our Department of Pneumology and Allergology at Coimbra University Hospital. She was a nonsmoker who had birds (budgies), though negative related antibodies and normal immunological analysis, namely without autoantibodies and immunocomplexes. Diffusing capacity was 31.7%, CT scan showed diffuse micronodular pattern, more evident in the upper lobes, and BAL had approximately 220×10^3/ml cells, 22% lymphocytes, 78% macrophages and CD4/CD8 ratio of 0.7. This patient improved after therapy with prednisone.

Figure 1 Morphologic pattern of ACIF in a 42-year-old woman presenting with a nonproductive cough



Acute fibrinous organizing pneumonia

The AFOP was initially described by Beasley *et al.* [14], as a new pattern of lung injury associated with an acute or subacute clinical presentation.

These authors published a review of open lung biopsy and autopsy specimens, from the files of the Armed Forces Institute of Pathology, showing histological findings of intra-alveolar fibrin and organizing pneumonia, excluding cases of classic diffuse alveolar damage (DAD), bronchiolitis obliterans organizing pneumonia, or, as a recently [15] proposed preferred term, cryptogenic organizing pneumonia (COP) or eosinophilic pneumonia.

From the 17 patients reviewed, nine had fulminating illness and eight a more subacute disease, with recovery. All biopsy specimens showed the dominant finding of intra-alveolar fibrin resembling 'fibrin balls' in the alveoli.

Within acute lung injury, the main differential diagnosis with the clinical patterns of DAD, COP and eosinophilic pneumonia could be made, in these specimens, based on several particular characteristics, namely patchy distribution of lesions mainly in the lower lobes (as opposed to the diffuse pattern in DAD); absence of hyaline membranes (usually present in DAD); lack of noticeable eosinophils (observed in eosinophilic pneumonia); and common finding of organizing intra-alveolar fibrin, with mild to moderate interstitial inflammation (distinction from the classic DAD and COP) [16].

Although there is a similar outcome in these patients, with over 50% mortality, allowing AFOP to be classified as a fibrinous variant of DAD, there were eight cases in which progression was less disastrous than usually seen in typical DAD.

Recently, Hwang *et al.* [17•] reported autopsy examination data from the lungs of 20 patients who died between March and July 2003, in Toronto, with severe acute respiratory syndrome (SARS). The histological findings

of this acute lung injury were either a predominant DAD pattern, in eight patients, or predominantly an AFOP pattern in six cases, or both patterns in the remaining patients. This study, again, suggests that AFOP could represent a histological variant of DAD, although there was a clear distinction between the two patterns in 70% of patients (14 of 17). This description of AFOP in patients with the newly discovered SARS-associated coronavirus seems to confirm the array of possible underlying associations clinically related to that acute lung injury initially reported by Beasley, such as the existence of infectious causes (*Haemophilus influenza* and *Acinetobacter* sp.), collagen vascular diseases, occupational and drug exposures, in the majority of the 17 cases from this latter study [14].

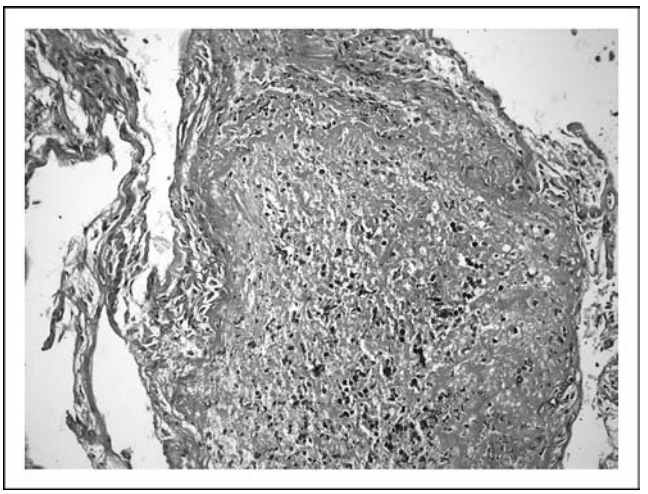
The same is also the case in a more recent study [18] describing AFOP in the context of an inflammatory myopathy. In this publication, Prahalad *et al.* [18] present a clinical case of a 14-year-old girl with juvenile dermatomyositis who developed extensive pulmonary parenchymal injury with a patchy pattern, prevailing in both lower lobes. The patient was admitted to hospital but died 2 weeks later, despite various therapeutic measures undertaken, including intravenous administration of immunoglobulin, methylprednisolone, azithromycin, cyclosporine, cyclophosphamide and, finally, mechanical ventilation. AFOP diagnosis was obtained through video-assisted thoracic surgery (VATS) lung biopsy showing the previously described balls of organizing fibrin without hyaline membranes in the airspaces.

Nevertheless, the autopsy data revealed that there was also the presence of hyaline membranes, related to progression to end-stage DAD, but also reinforcing the discussion of AFOP and DAD as different forms of acute lung injury.

In a recent issue of the *European Respiratory Journal*, Poletti *et al.* [19] wrote a letter to the Editors with comments on a case of COP previously reported by Chee *et al.* [20] in the same journal, discussing not only the diagnosis, probably AFOP, on the basis of histological findings, namely the existence of 'diffuse intraalveolar exudate of granular, fibrinous material', but also the diagnostic approach for alveolar opacification shadows, which, according to these authors, is less sensitive and specific with fine-needle aspiration compared with transbronchial lung biopsy.

The same methodological issue is also pointed out by Beasley [14], underlining the fact that the diagnosis of AFOP (as well as of COP) is best made on larger specimens, obtained by VATS, open lung biopsies or even from autopsy data, especially when considering the possibility that an AFOP pattern may be a secondary reaction of other processes.

Figure 2 Fibrin and cellular debris

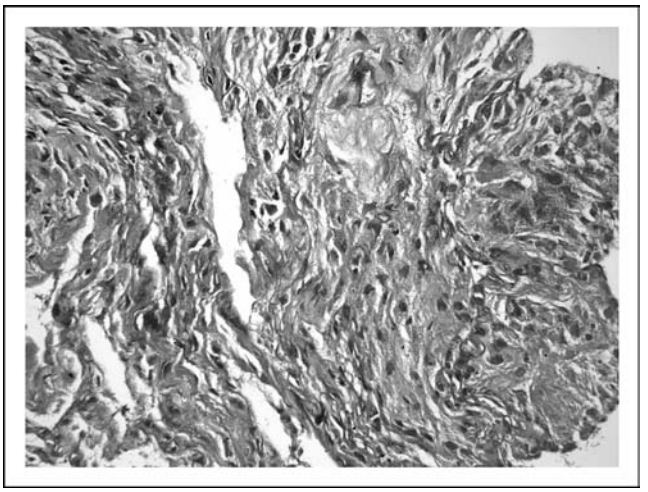


Pattern of AFOP from a surgical lung biopsy of a 35-year-old patient presenting with pharyngitis, medium lobe pneumonia and sepsis, who developed ARDS.

In the last published study on AFOP, Kobayashi *et al.* [21] reported a clinical case of a 55-year-old man presenting initially with a solitary nodule showing air bronchogram, which progressed into multiple lung consolidations, with a patchy distribution and several peribronchial changes. These findings were assessed by CT scanning.

Again, the differential diagnosis with COP is discussed, not only due to the initial imaging findings but also because there was improvement after steroid therapy, setting this case of AFOP into the more subacute presentations discussed originally by Beasley.

Figure 3 Fibroblast polip with macrophages and fibroblastic proliferation



A second pattern of AFOP from a surgical lung biopsy of the same patient as in Fig. 2.

Figures 2 and 3 show the pattern of AFOP from a surgical lung biopsy of a 35-year-old patient presenting with pharyngitis, medium lobe pneumonia and sepsis, who developed ARDS and was admitted to the Intensive Care Unit of our University Hospital in Coimbra. BAL reveals 75% neutrophils in a normal total cellularity. Immunologic assay, namely autoantibodies, was negative, as were serologic, haemocultures and microbiologic studies in bronchial secretions and in bronchoalveolar lavage. Despite all the therapeutic measures undertaken, including, antibiotics, antifungals, steroids and mechanical ventilation, the patient died after 19 days in hospital.

Conclusion

The author reviews two recently proposed patterns of ILD associated with airway involvement, ACIF and AFOP, which, under certain specific circumstances, may need a high diagnostic accuracy.

The ACIF pattern, mostly involving proximal airways and the surrounding interstitium, must specially be differentiated from hypersensitivity pneumonitis, namely in its chronic appearance, that may be related with inhaled contaminants or drugs (cocaine, for example), as its association to several inhalatory exposures is frequent and presentation is insidious.

The AFOP pattern, which has noticeably an alveolar involvement, has as its main differential diagnosis diffuse alveolar damage and organizing pneumonia. It frequently occurs within the context of underlying conditions, such as collagen vascular diseases, and may signal an acute or subacute lung injury.

Acknowledgement

The authors are indebted to: Lina Carvalho, PhD, pathologist at University of Coimbra, for providing the iconography presented; Venerino Poletti, PhD, from Morgagni Hospital, Forlì, for his helpful suggestions; Jessica Cemlyn Jones, MD, resident from the Department of Pneumology and Allergology, for reviewing the text.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 375).

1 Lynch JP, White ES. Pulmonary sarcoidosis. In: Drent M, Costabel U, editors.
•• Sarcoidosis: Monograph 32. Eur Respir Society; 2005. pp. 105–129.
Vast revision of pulmonary manifestations in sarcoidosis, with emphasis on specific local complications, such as bronchostenosis, and included in the most recent European Respiratory Monograph on Sarcoidosis.

2 Chambellan A, Turbie P, Nunes H, *et al.* Endoluminal stenosis of proximal
• bronchi in sarcoidosis: bronchoscopy, function and evolution. Chest 2005; 127:472–481.
Retrospective review of 2500 patients with sarcoidosis, with different bronchial stenosis patterns, that were present in fewer than 1% of cases.

3 Fridlender ZG, Glazer M, Amir G, Berkman N. Obstructing tracheal pulmonary
• Langerhans cell histiocytosis. Chest 2005; 128:1057–1058.
In this study, the authors report the first case of Langerhans cell histiocytosis in which the only finding was an endotracheal obstructing lesion, found unusually in a nonsmoking woman.

4 Kambouchner M. Three-dimensional characterization of pathologic lesions in pulmonary Langerhans cell histiocytosis. Am J Respir Crit Care Med 2002; 166:1483–1490.

5 Olsson T, Bjornstad-Pettersen H, Stjernberg NL. Bronchostenosis due to sarcoidosis: a cause of atelectasis and airway obstruction simulating pulmonary neoplasm and chronic obstructive pulmonary disease. Chest 1979; 75:663–666.

6 Udwadia ZF, Pilling JR, Jenkins PF, Harrison BDW. Bronchoscopic and bronchgraphic findings in 12 patients with sarcoidosis and severe or progressive airways obstruction. Thorax 1990; 45:272–275.

7 Bjermer L, Thunell M, Rosenhall L, Stjernberg N. Endobronchial biopsy positive sarcoidosis: relation to bronchoalveolar lavage and course of disease. Respir Med 1991; 85:229–324.

8 Yousem SA, Dacic S. Idiopathic bronchiolocentric interstitial pneumonia. Mod Pathol 2002; 15:1148–1153.

9 Churg A, Myers J, Suarez T, *et al.* Airway-centered interstitial fibrosis: a distinct form of aggressive diffuse lung disease. Am J Surg Pathol 2004; 28:62–68.

10 Fukuoka J, Franks TJ, Colby TV, *et al.* Peribronchiolar metaplasia: a common
• histologic lesion in diffuse lung disease and a rare cause of interstitial lung disease. Am J Surg Pathol 2005; 29:948–954.
Description of a new proposed entity, centered on histologic findings (peribronchiolar metaplasia) usually seen in association with several ILD, but here described as the sole finding in patients presenting with ILD.

11 de Carvalho ME, Kairalla RA, Capelozzi VL, *et al.* Centrilobular fibrosis: a novel histological pattern of idiopathic interstitial pneumonia. Pathol Res Pract 2002; 198:577–583.

12 Colombat M, Groussard O, Taillé C, *et al.* Lung transplantation in a patient with airway-centered fibrosis. Am J Surg Pathol 2004; 28:1540–1542.

13 Xu L, Cai BQ, Liu HR, Zhu YJ. Diagnosis and differential diagnosis of airway-centered interstitial fibrosis. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2005; 27:99–102.

14 Beasley MB, Franks TJ, Galvin JR, *et al.* Acute fibrinous and organizing pneumonia: a histological pattern of lung injury and possible variant of diffuse alveolar damage. Arch Pathol Lab Med 2002; 126:1064–1070.

15 Travis WD, King TE, Baternan ED, *et al.* American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002; 165:277–304.

16 Katzenstein AL. Acute lung injury patterns: diffuse alveolar damage and bronchiolitis obliterans-organizing pneumonia. In: Katzenstein and Askin's surgical pathology of non-neoplastic lung disease. 3rd ed. Philadelphia, PA: WB Saunders; 1997. pp. 14–47.

17 Hwang DM, Chamberlain DW, Poutanen SM, *et al.* Pulmonary pathology
• of severe acute respiratory syndrome in Toronto. Mod Pathol 2005; 18: 1–10.
From 20 autopsy lung studies of patients who died during the outbreak of SARS in Toronto, six cases showed the newly described pattern of AFOP as the sole histologic finding, reinforcing the autonomic existence of this entity.

18 Prahalad S, Bohnsack JF, Maloney CG, Leslie KO. Fatal acute fibrinous and organizing pneumonia in a child with juvenile dermatomyositis. J Pediatr 2005; 146:289–292.

19 Poletti V, Casoni GL. Cryptogenic organising pneumonia or acute fibrinous and organising pneumonia? Eur Respir J 2005; 25:1128.

20 Chee CBE, Da Costa JL, Sim CS. A female with dry cough, progressive dyspnoea and weight loss. Eur Respir J 2005; 25:206–209.

21 Kobayashi H, Sugimoto C, Kanoh S, *et al.* Acute fibrinous organizing pneumonia: initial presentation as a solitary nodule. J Thorac Imaging 2005; 20:291–293.