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Case Report

Cryptogenic organising pneumonia: clinical, pathological, and prognostic analysis of 27 cases

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Abstract: Background: Buds of granulation tissue within the lumen of distal pulmonary airspaces characterises organising pneumonia (OP). This study aimed to analyse the clinical and pathological features and prognosis of patients with cryptogenic OP. Methods: Twenty-seven patients were retrospectively analysed. A multidisciplinary team (a clinician, radiologist, and pathologist) diagnosed all patients. Clinical features, laboratory data, chest radiology, treatment and prognosis, pulmonary function, and haematoxylin-eosin and immunohistochemical staining were assessed. Results: Symptoms (in decreasing prevalence) were cough, dyspnoea, fever, and chest tightness. The erythrocyte sedimentation rate (in most patients) and C-reactive protein level were increased. Radiologic findings (in decreasing prevalence) were consolidation, nodules, and band-like opacities. The lung function results were 'normal' and 'restrictive' in 30.8% and 38.5% of patients, respectively. Most patients responded to corticosteroids. The prognosis of the patients was excellent in 77.8% and poor in 22.2%. Organised polypoid granulation inflammatory tissue was in the distal bronchiole airways, respiratory bronchioles, alveolar ducts, and alveoli. Transforming growth factor (TGF)-β and alpha-smooth muscle actin (α-SMA) expression was not significantly different between the good and poor prognosis groups ($P>0.05$). There was increased expression of fibrin (poor prognosis group, $P<0.05$) and Krebs von den Lungen-6 (KL-6) (good prognosis group, $P<0.05$). Conclusions: Organised polypoid granulation inflammatory tissue in the distal airway spaces is a pathological feature of OP. The good and poor prognosis groups had similar expressions of TGF-β and α-SMA. Fibrin and KL-6 expression was increased in the poor prognosis group and good prognosis group, respectively.

Keywords: Cryptogenic organising pneumonia, diagnosis, prognosis

Introduction

Organising pneumonia (OP) is a nonspecific response to lung injury. Buds of granulation tissue within the lumen of distal pulmonary airspaces is a characteristic pathological pattern [1]. It can be secondary or cryptogenic (i.e., idiopathic). Secondary OP may result from inhaling toxic fumes; immunologic and connective tissue disorders; reaction to viral, bacterial, or fungal infections; inflammatory bowel disease; human immunodeficiency virus infection; common variable immune deficiency; radiation therapy, myelodysplastic syndrome, drug reactions, malignant diseases, and bone marrow or solid organ transplantation [2]. Cryptogenic OP (COP) and secondary OP are not significantly different. Because of buds of granulation tissue within the lumen of distal pulmonary airspaces, COP was initially called 'bronchiolitis obliterans with organising pneumonia'. However, the nomenclature was abandoned for the reason that bronchiolitis is clearly not the major lesion in COP [3]. The radiographic features of COP, pneumonia, lung cancer, and other lung diseases are similar. Correctly diagnosing COP is difficult because it lacks characteristic symptoms and signs. The clinical misdiagnosis rate is therefore high. With glucocorticoid treatment, most COP clinical and radiographic features rapidly improve with no obvious adverse effects. However, the optimal dose and duration of treatment remain undetermined [4]. The aim of

Table 1. Clinical features in 27 patients with COP

Sex	
Male (n, %)	17 (63.0)
Female (n, %)	10 (37.0)
Age, mean ± SD, years	63.2±10.0
Age, range, years	49~85
Somking (n, %)	12 (44.4)
Symptoms	
Cough (n, %)	26 (96.3)
Dyspnea (n, %)	14 (51.9)
Fever (n, %)	14 (51.9)
Chilly (n, %)	8 (29.6)
Sputum (n,%)	16 (59.3)
Pleuritic chest pain (n, %)	6 (22.2)
Chest tightness (n, %)	10 (37.0)
Hemoptysis (n, %)	1 (3.7)
Physical findings	
Crackles (n, %)	14 (51.9)
Wheeze (n, %)	0 (0.0)
Clubbing (n, %)	0 (0.0%)
None (n, %)	13 (48.1)

§Values are expressed as n (%) or mean ± SD.

Table 2. Laboratory data in 27 patients with COP

Variable	Number (%)
CRP>10 mg/L	20 (74.1)
ESR>20 mm/h	22 (81.4)
WBC<4×10^9/L	1 (3.7)
WBC>10×10^9/L	4 (14.8)
PLT>300×10^9/L	10 (37.0)
N%>75%	10 (37.0)
EOS>300×10^6/L	9 (33.3)
IgE>100 Ku/L	10 (37.0)
PaO_2<8 Kpa	3 (11.1)
PaO_2: 8~10.8 Kpa	13 (48.1)
$PaCO_2$<4.7 Kpa	4 (14.8)
$PaCO_2$>6.0 Kpa	4 (14.8)
ANA (+)	5 (18.5)
ANCA (+)	0 (0.0)

§Values are expressed as n (%).

this study was to analyse the clinical and pathological features and prognosis of patients with COP. During a 6-year period, we diagnosed 27 patients with biopsy-proven COP. In this paper, we detail the clinical and radiographic data and therapeutic scheme of this cohort.

Methods

We retrospectively analysed 27 patients with biopsy-proven COP who had been in our hospital from March 1, 2008 to April 1, 2014. A multidisciplinary team (i.e., an experienced clinician, radiologist and pathologist) diagnosed all patients. The Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine (Shanghai, China) approved the study and certified that it was conducted in accordance with the Declaration of Helsinki.

Epidemiological data, personal history, clinical features, laboratory data, radiological data, pulmonary function, bronchoscopy, and microbiological studies and cellular count in bronchoalveolar lavage fluid were recorded. The clinician diagnosed COP or secondary OP, based on the absence or presence, respectively, of established clinical causes. The respiratory medicine clinician collected the COP patients' medical history. Based on computed tomography (CT) images, the chest radiologist assessed the pattern and distribution of pulmonary abnormalities as 'unilateral', 'bilateral', 'upper zone', 'middle zone', 'lower zone', 'migration of opacities', and 'peripheral'. The pulmonary abnormalities comprised parenchymal abnormalities and pleural abnormalities. The parenchymal abnormalities classifications were 'consolidation', 'ground-glass opacity', 'nodules', 'band-like opacities', 'reticulation', 'reverse-halo sign', 'interlobular septal thickening', and 'honeycombing'. The pleural abnormalities classifications were 'pleural thickening' and 'pleural effusion.' The pulmonary function results were interpreted as 'normal', 'restrictive', 'obstructive', or 'mixed pattern'.

Patients were divided into two groups, based on the effect of corticosteroid therapy. We considered the prognosis as 'good' with corticosteroid treatment on seeing most abnormalities on CTs were absorbed, clinical symptoms and pulmonary signs nearly disappeared, and pulmonary function was generally normal in 1 year. We otherwise considered the prognosis 'poor'.

We obtained pulmonary tissue via percutaneous lung biopsy (14 patients), video-assisted thoracoscopy (10 patients), or transbronchial biopsies (4 patients). All pulmonary tissues were fixed in formalin (4%), embedded in paraffin, and serially sectioned into 4-μm slices.

Table 3. CT findings in 27 patients with cryptogenic organizing pneumonia

Findings	Number (%)
Distribution	
Unilateral	7 (25.9)
Bilateral	20 (74.1)
Upper zone	12 (44.4)
Middle zone	15 (55.6)
Lower zone	18 (66.7)
Migration of opacity	2 (7.4)
Peripheral distribution	21 (77.8)
Parenchymal abnormality	
Consolidation	25 (92.6)
Groun-glass opacity	22 (81.5)
Nodules	10 (37.0)
Band-like opacity	9 (33.3)
Reticular opacity	4 (14.8)
Revers-halo sign	2 (7.4)
Interlobular septal thickening	3 (11.1)
Honeycombing	0 (0)
Extrapulmonary abnormality	
Pleural thickening	6 (22.2)
Pleural effusion	4 (14.8)
Mediastinal lymph node	7 (25.9)

§Values are expressed as n (%).

Alveolar structure, fibroplasia, histiocytosis, inflammatory cell infiltration, alveolar septal thickening, and other pathological changes were examined by haematoxylin-eosin staining.

Immunohistochemical analysis was performed to examine the expression of alpha-smooth muscle actin (α-SMA) (Novocastra, England), transforming growth factor-beta (TGF-β) (Novocastra, England), fibrin (FB) (Novocastra, England), and Krebs von den Lungen-6 (KL-6) (Abcam, England). The results were categorised by the degree of positive immunohistochemistry: level 0 (i.e., negative); level 1 (i.e., positivity in small cell clusters); and level 2 (i.e., extensive positivity). The pulmonary tissue of 16 patients underwent immunohistochemical staining. Data are expressed as the mean ± SD. Between-group differences were statistically evaluated by the Mann-Whitney Test. Statistical significance was defined as $P<0.05$.

Results

*Clinical features (**Table 1**)*

We collected 17 males and 10 females with COP. Their overall mean age was 63.2±10.0 years, and 44.4% of the patients had a smoking history. The mean duration of symptoms before diagnosis was 4.3±1.5 weeks. Cough was the most common symptom (96.3% of patients), followed by dyspnea (51.9%), fever (51.9%), and chest tightness (37.0%). Cough was accompanied by sputum or haemoptysis in 69.3% or 3.7% of patients, respectively. Crackles were the most common sign (51.9%), but 48.1% of the patients had no signs.

*Laboratory data (**Table 2**)*

Most (81.4%) patients had an increased erythrocyte sedimentation rate (>20 mm/h); 74.1% of patients had a C-reactive protein level >10 mg/L; 37.0% of patients had a platelet level $>300\times10^9$/L; 37.0% of patients had a neutrophilic granulocyte percent >75%; and 37.0% of patients had an immunoglobulin E (IgE) level >100 kU/L. Approximately 48.1% of patients had mild hypoxia (PaO_2, 8-10.8 kPa). Most patients had negative immunological tests. Antinuclear antibody was mildly positive in 5 patients.

*Chest radiology (**Table 3** and **Figure 1**)*

On chest high-resolution CT, the most common radiologic findings were consolidation (92.6%), nodules (37%), and band-like opacities (33.3%). Nodules always accompanied consolidation. Pleural thickening and diaphragm enlargement affected 25.9% of patients. No patient had honeycombing.

*Pulmonary function (**Table 4**)*

Pulmonary function test results were available for 26 patients. The lung function results among the patients were normal in 30.8%, restrictive in 38.5%, obstructive in 11.5%, and mixed in 19.2%. Fifty percent of patients had impaired diffusion.

Bronchoscopy and bronchoalveolar lavage fluid

Most patients received bronchoscopy without obvious anomaly, except hyperaemia and oedema of the bronchial mucosa and airway secretions and longitudinal changes but no stenosis or occlusion. Bronchoalveolar lavage fluid was obtained from 17 patients; 13 (76.5%) patients had an increased percentage of lymphocytes and 11 (64.7%) patients had an increased percentage of neutrophils.

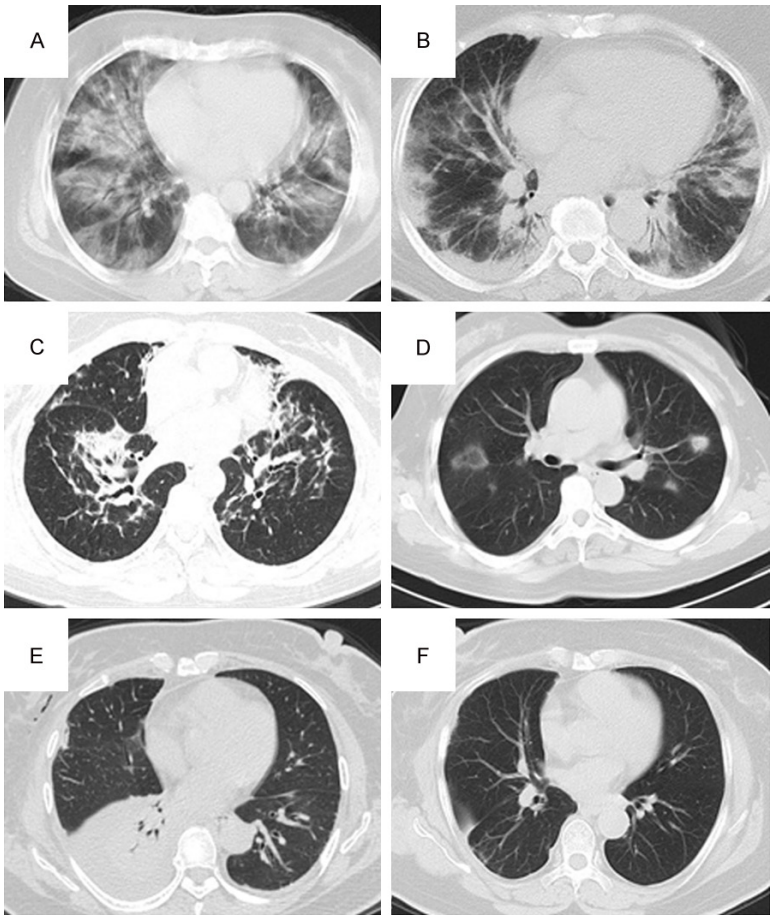

Figure 1. A, B: High-resolution CT scan of the lower lobes shows bilateral consolidation, with ground-glass attenuation and Nodules; C: High-resolution CT scan of the lower lobes shows bilateral demonstrates reticular opacity, with extensional bronchiectasis, pulmonary structure deformation; D: High-resolution CT scan of the lower lobes shows bilateral halo sign; E, F: For the same patient, before and after corticosteroid treatment respectively.

Table 4. Pulmonary function of 21 patients with COP

Findings	Values
FVC, % predicted	70.3±21.0
FEV1, % predicted	68.6±20.4
FEV1/FVC, %	77.1±10.9
DLCO/SB, % predicted	54.1±16.5
DLCO/VA, % predicted	73.4±15.9

§Values are expressed as mean ± SD.

Treatment and prognosis

Most patients responded to corticosteroid treatment. Twenty-one (77.8%) patients had a good prognosis; 6 (22.2%) patients had a poor prognosis; 9 (11.1%) patients relapsed; and 1 (3.7%) patient died in 6 months.

*Histopathological examination (**Figure 2**)*

The partially reconstructed alveolar structure and alveolar septal thickening mixed with fibroplasia and histiocytosis were present on histopathological examination. Inflammatory cells (especially lymphocytes and macrophages) infiltrated the small pulmonary vasculature and alveoli. Our patients had localised small airway epithelial hyperplasia without obvious lung tissue structure damage, alveolar wall collapse, and honeycombing. Furthermore, some patients had organised polypoid granulation inflammatory tissue in the distal bronchiole airways, respiratory bronchioles, alveolar ducts, and alveoli.

*Immunohistochemical analysis (**Table 5** and (**Figure 3**)*

The expression of α-SMA was level 1 or greater in 13 patients, TGF-β was level 1 or greater in 11 patients, FB was level 1 or greater in 15 patients, and KL-6 was level 1 or greater in 3 patients. The expression of TGF-β and α-SMA was not significantly different between the good and poor prognosis groups ($P>0.05$). However, the poor prognosis group had increased FB expression ($P<0.05$), and the good prognosis group had increased KL-6 expression ($P<0.05$).

Discussion

Cryptogenic organising pneumonia is a clinical, radiological, and pathological diagnosis and the internationally recognised term for 'bronchiolitis obliterans organising pneumonia'. The duration of onset is 3 months or less, with a subacute onset lasting a few weeks. The diagnosis is often delayed by 6-12 weeks, and after patients have received antibiotics [1]. Infectious pneumonia is the most common differential diagnosis.

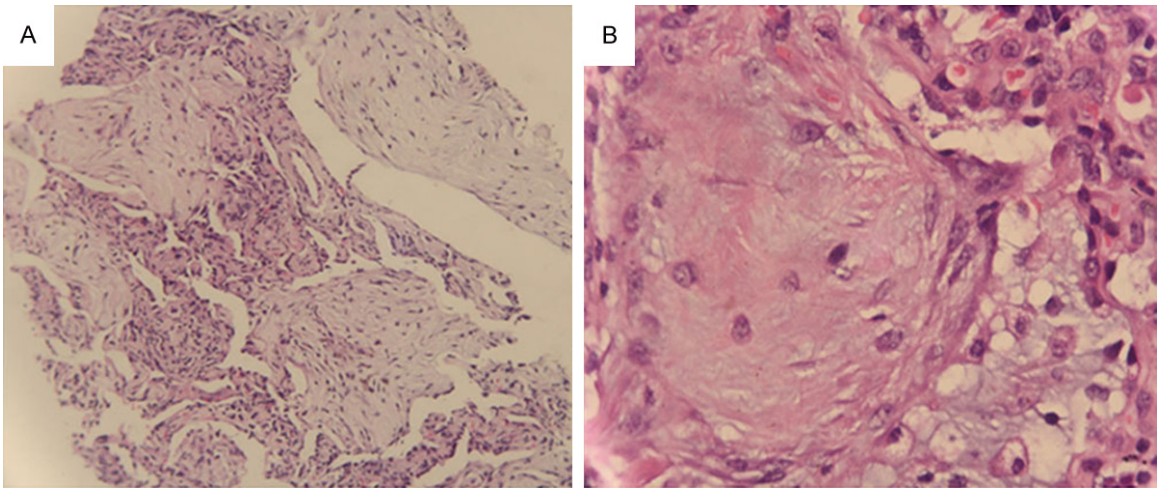

Figure 2. A, B: Photomicrograph (magnification, 100 and 400 respectively; hematoxylin-eosin stain) shows alveolar interval fibrous tissue hyperplasia, partly prensented organized polypoid granulation into alveolar cavity, with local alveolar epithelial hyperplasia and inflammatory cells (especially lymphocytes and macrophages) infiltration.

Table 5. Immunohistochemical analysis of 16 patients with COP

Findings	Grade	Poor prognosis	Good prognosis
α-SMA	0	2	1
	1	5	5
	2	0	3
TGF-β	0	2	3
	1	5	6
	2	0	0
FB*	0	0	1
	1	6	5
	2	1	3
KL-6*	0	6	7
	1	1	2
	2	0	0

§Values are expressed as n. α-SMA, Alpha-smooth muscle actin; TGF-β, Transforming growth factor-beta; FB, Fibrin; KL-6, Krebs von den Lungen-6. The expression of FB increased in poor prognosis group (*P<0.05), while the expression of KL-6 increased in good prognosis group (*P<0.05).

Cryptogenic organising pneumonia mostly occurs in the fifth or sixth decade of life [1, 5]. It has no sex differences. Cases are rare in children [6-8]. Whether COP is associated with current or previous smoking is controversial [5]. However, most scholars believe COP has no correlation with tobacco use and it is generally more common in nonsmokers or exsmokers [1, 9, 10]. Our study's findings are in line with published data, but the sex differences that males (17) were more than females (10) in our patients. The clinical manifestations are non-specific: a flu-like illness with a progressive onset of mild fever, cough, malaise, anorexia, weight loss, and progressive but usually mild dyspnoea [1, 5, 11]. Most patients had cough with sputum. However, one study found patients had a mostly dry cough [11]. Haemoptysis and chest pain described in other reports [1, 5, 11] were uncommon in our study. Our patients had focal and sparse crackles, which are frequently detected on auscultation [1, 5]. Our patients lacked finger clubbing described in previous reports [1].

The erythrocyte sedimentation rate and C-reactive protein levels are increased in COP [2, 12, 13], which occurred in 81.4% and 71.4% of patients, respectively, in our study. Our patients (48.1%) had mild hypoxia. Thirty-seven percent of patients had elevated levels of platelets, neutrophilic granulocytes, and IgE. None of these laboratory data helped in diagnosing COP [2].

The main radiologic finding is reportedly peripheral or multifocal consolidation with or without ground-glass opacity [2, 11, 14]. In our study, consolidation was the most common radiologic manifestation in 25 (92.6%) patients. Ground-glass opacity presented in 81.5% of patients, followed by nodules and band-like opacity. Consolidation with ground-glass opacity presented in 55.6% of 27 patients, followed by consolidation with ground-glass opacity and nodules (25.9% of patients). However, most

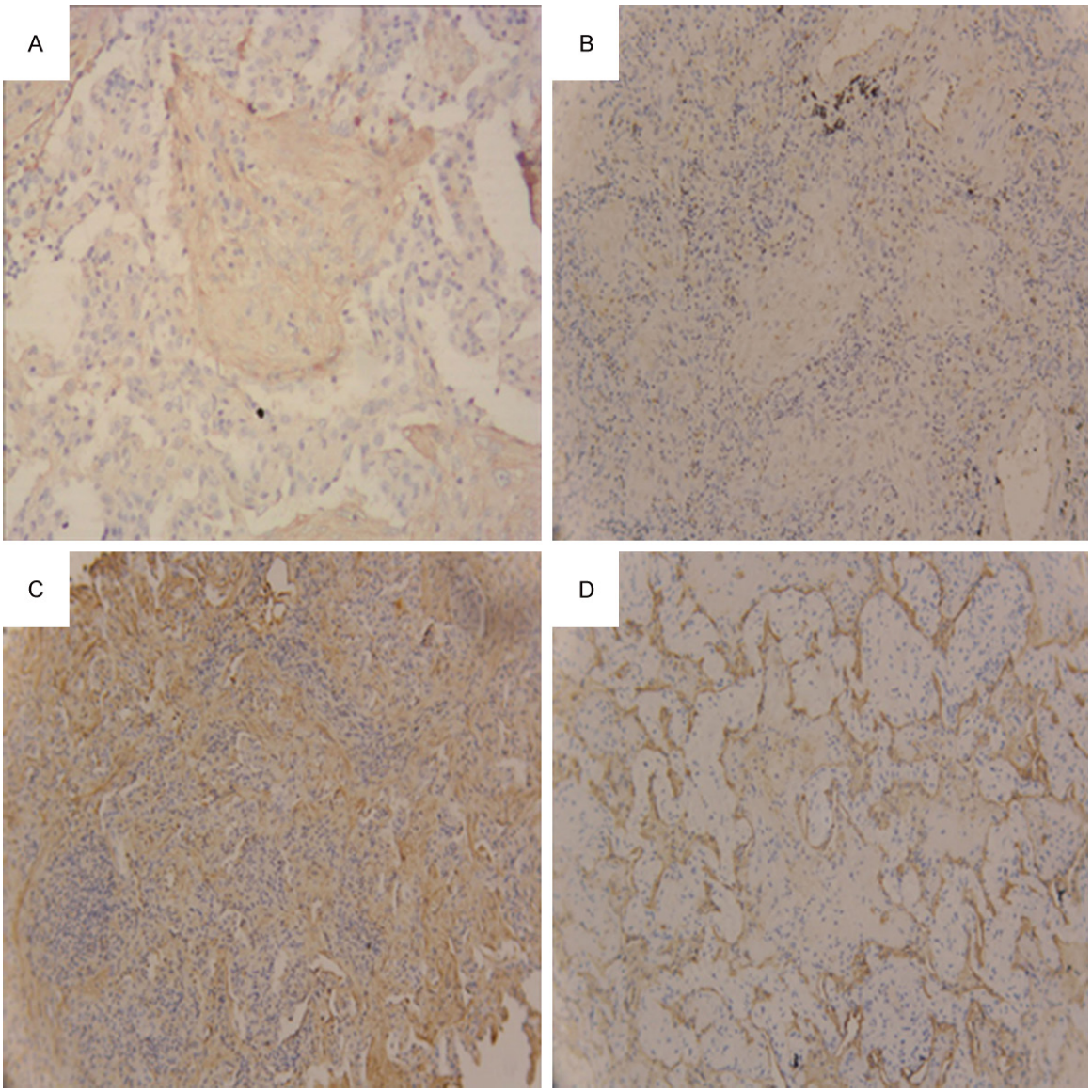

Figure 3. A: α-SMA+; B: TGF-β+; C: FB+; D: KL-6+.

patients had ground-glass opacity in one study of COP [14]. Reticular opacity on the initial CT scan constituted a poor prognosis-determining factor on univariate or multivariate analysis [15]; however, we cannot conclude this because only two (50%) patients with reticular opacity had a poor prognosis. The reverse-halo sign highly suggests a COP diagnosis [1, 16-18]. However, the reverse-halo sign has been rarely been reported and was present in only two of our patients. Some authors have described a migratory sign in which pulmonary opacities become clear but return in a different location [11, 12, 19]. Migration narrows the differential diagnosis and assists doctors in diagnosing COP. Interlobular septal thickening is not usually a prominent feature, but was previously described [10, 14]. Other uncommon features are pleural effusion [11, 20, 21], pleural thickening [14, 21], and mediastinal lymph nodes [20, 21].

Lung function tests in patients with COP have shown a predominantly restrictive abnormality [1, 2, 14]. In one study [11], an obstructive abnormality was common, possibly because most patients had a smoking history. The most common finding in our patients was a restrictive ventilatory defect, followed by normal, mixed, and obstructive ventilatory defects. By

percentage of the predicted value, the mean percent of forced vital capacity (FVC) and single-breath carbon monoxide diffusing capacity of the lung (DLCO/SB) were 70.3%±21.0% and 54.1%±16.5%, respectively. Patients with significantly higher values for initial FVC and initial DLCO/SB more easily recovered from COP [21].

Bronchoalveolar lavage (BAL) could be useful for patients whose clinical and radiological presentation suggests COP with nondiagnostic transbronchial biopsy or who cannot undergo a confirmatory biopsy [10, 22]. The BAL differential cell count typically demonstrates a mixed pattern consisting of increased percentage of lymphocytes (20%-40%), neutrophils (approximately 10%), and possibly eosinophils (approximately 5%) [1, 10]. In our study, the mean percent of lymphocytes and neutrophils were 30.0%±17.6% and 14.7%±14.7%, respectively. However, we did not examine the CD4+: CD8+ ratio of lymphocytes, which is usually decreased in BAL.

Cryptogenic organising pneumonia usually responds spectacularly well to corticosteroid treatment, which is the standard therapy, and typically runs a benign course [1, 2, 10, 13, 21]. Typical COP symptoms improve dramatically within days after initial corticosteroid therapy. Imaging results improve rapidly in which consolidation evolves to ground-glass opacity and eventually regresses completely within a month without significant sequelae [21]. However, the doses and duration of corticosteroid treatment have not been established, and should aim at having the optimal balance between disease control and adverse effects [1, 5, 23]. The initial daily doses of prednisone vary 0.75-1.5 mg/kg [2, 10, 21, 23]. Further megadoses of methylprednisolone are administered for the first few days, and then progressively decreased for the following weeks of treatment, usually 1 year. Because of the risk of iatrogenic complications with corticosteroid treatment, we began with prednisone at 0.75 mg/kg daily for 4 weeks, and then progressively decreased this dose for 1 year. Most patients were administered corticosteroids by intravenous–oral sequential therapy. For 3 patients with rapidly progressive COP, high-dose intravenous methylprednisolone was used in the initial therapy. Abnormalities on CT imaging were absorbed in 21 patients, and clinical symptoms and signs nearly disappeared, and pulmonary function was generally normal in 1 year with good prognosis. However, COP in one report spontaneously improved in 3-6 months [2]. Clinical monitoring without therapy is recommended for patients with no symptoms or mild radiographic findings [4]. Relapses can occur in 13%-58% of patients after tapering or stopping steroids, and approximately 20% of patients experience more than one relapse [1, 20, 23]. Nine patients relapsed in our study. Because relapses do not increase morbidity or mortality [23], we believe suppressing them may not be a crucial therapeutic objective. The aim should be to minimise the adverse effects of corticosteroids and avoid overtreatment.

Histopathological examination of the lung biopsy demonstrates fibrosis with inflammation in the distal airway. Space buds of granulation tissue comprising fibroblasts and myofibroblasts embedded in connective tissue are the hallmark of COP [1, 9]. Another pathological feature of COP is granulation tissue extending from alveolus to alveolus through interalveolar pores, which presents in a typical butterfly pattern. Small airway-centric lesions stretch to the distal airway. The patchy lesions are uniform under the microscope. However, the lung tissue structure appears undamaged and shows mild interstitial chronic inflammation, type II pneumocyte metaplasia, and increased alveolar macrophages (with some foam cells).

The marker most used for myofibroblasts is α-SMA. The spindle-shaped cells of fibroblast foci in idiopathic pulmonary fibrosis and those of newly formed connective tissue in COP and asbestosis all express α-SMA [24]. In our study, α-SMA expression was at level 1 or greater in 11 (81.3%) patients. However, α-SMA expression was not significantly different between the good and poor prognosis groups. The TGF-β protein, especially TGF-β1, and its downstream SMA and Mad-related protein cascade are pivotal in regulating extracellular matrix (ECM) production, which topples the balance of collagen turnover in fibrous remodelling of the lung [25, 26]. The TGF-β expression was level 1 or greater in 11 patients, but there was no significant difference between our two groups.

The FBs are multifunctional glycoproteins in the ECM of several tissues and plasma. Fibrin is correlated with tenascin-C gene expression and abnormally deposited in lung tissue, plas-

ma, and serum in different interstitial lung diseases, usual interstitial pneumonia, COP, sarcoidosis, hypersensitivity pneumonitis, and nonspecific interstitial pneumonia [26]. The FB expression was level 1 or greater in 15 patients, and significantly increased in the poor prognosis group, which helped us estimate the prognosis of COP.

Serum levels of KL-6 are elevated in various respiratory and nonrespiratory conditions [27-29]. Okada [20] retrospectively compared pulmonary CT findings of COP patients with and without an elevated KL-6 level, and concluded the two groups had no significant differences with regard to steroid treatment response. Three of our COP patients had a immunohistochemical level of KL-6 at level 1 or greater. Furthermore, KL-6 expression was significantly increased in the good prognosis group, compared with the poor prognosis group. The expression of α-SMA, TGF-β, and FB was increased in most COP patients, whereas KL-6 was increased in a few patients; this distinction could help in diagnosing COP. The poor prognosis group had increased FB expression and the good prognosis group had increased KL-6 expression, which assisted us in estimating the prognosis of COP.

The limitations to our study were that the number of patients in the study was small and histological specimens were not obtained on the same days. Further study should be undertaken.

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Disclosure of conflict of interest

None.

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References

[1] Cottin V, Cordier JF. Cryptogenic organizing pneumonia. Semin Respir Crit Care Med 2012; 33: 462-75.

[2] Oymak FS, Demirbaş HM, Mavili E, Akgun H, Gulmez I, Demir R, Ozesmi M. Bronchiolitis obliterans organizing pneumonia. Clinical and roentgenological features in 26 cases. Respiration 2005; 72: 254-62.

[3] American Thoracic Society; European Respiratory Society. American Thoracic Society (ATS)/European Respiratory Society (ERS) International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERSExecutive Committee, June 2001. Am J Respir Crit Care Med 2002; 165: 277-304.

[4] Epler GR. Bronchiolitis obliterans organizing pneumonia, 25 years: a variety of causes, but what are the treatment options? Expert Rev Respir Med 2011; 5: 353-61.

[5] Drakopanagiotakis F, Paschalaki K, Abu-Hijleh M, Aswad B, Karagianidis N, Kastanakis E, Braman SS, Polychronopoulos V. Cryptogenic and secondary organizing pneumonia: clinical presentation, radiographic findings, treatment response, and prognosis. Chest 2011; 139: 893-900.

[6] Inoue T, Toyoshima K, Kikui M. Idiopathic bronchiolitis obliterans organizing pneumonia (idiopathic BOOP) in childhood. Pediatr Pulmonol 1996; 22: 67-72.

[7] Liu JR, Peng Y, Zhou CJ, Zhong LL, Jiang ZF, Zhao SY. Idiopathic interstitial pneumonias in 7 children. Zhonghua Er Ke Za Zhi 2010; 48: 297-300.

[8] Bitzan M, Ouahed JD, Carpineta L, Bernard C, Bell LE. Cryptogenic organizing pneumonia after rituximab therapy for presumed post-kidney transplant lymphoproliferative disease. Pediatr Nephrol 2010; 25: 1163-7.

[9] Cordier JF. Cryptogenic organising pneumonia. Eur Respir J 2006; 28: 422-46.

[10] Jara-Palomares L, Gomez-Izquierdo L, Gonzalez-Vergara D, Rodriguez-Becerra E, Marquez-Martin E, Barrot-Cortés E, Martin-Juan J. Utility of high-resolutioncomputed tomography and BAL in cryptogenic organizing pneumonia. Respir Med 2010; 104: 1706-11.

[11] Vasu TS, Cavallazzi R, Hirani A, Sharma D, Weibel SB, Kane GC. Clinical and radiologic distinctions between secondary bronchiolitis obliterans organizing pneumonia and cryptogenic organizing pneumonia. Respir Care 2009; 54: 1028-32.

[12] Nogi S, Nakayama H, Tajima Y, Okubo M, Mikami R, Sugahara S, Akata S, Tokuuye K. Cryptogenic organizing pneumonia associated with radiation: A report of two cases. Oncol Lett 2014; 7: 321-4.

[13] Cordier JF. Organizing pneumonia. Thorax 2000; 55: 318-28.
[14] Roberton BJ, Hansell DM. Organizing pneumonia: a kaleidoscope of concepts and morphologies. Eur Radiol 2011; 21: 2244-54.
[15] Cordier JF, Loire R, Brune J. Idiopathic bronchiolitis obliterans organizing pneumonia. Definition of characteristic clinical profiles in a series of 16 patients. Chest 1989; 96: 999-1004.
[16] Kim SJ, Lee KS, Ryu YH, Yoon YC, Choe KO, Kim TS, Sung KJ. Reversed halo sign on high-resolution CT of cryptogenic organizing pneumonia: diagnostic implications. Am J Roentgenol 2003; 180: 1251-4.
[17] Maimon N. A 47-year-old female with shortness of breath and "reversed halo sign". Eur Respir Rev 2010; 19: 83-5.
[18] Gudavalli R, Diaz-Guzman E, Arrossi AV, Chapman JT, Mehta AC. Fleeting alveolar infiltrates and reversed halo sign in patients with breast cancer treated with tangential beam irradiation. Chest 2011; 139: 454-9.
[19] Olivares AF, Fica CA, Charpentier VP, Hernández MA, Manríquez A ME, Castro SM. [Cryptogenic organizing non-resolving pneumonia. Report of one case]. Rev Med Chil 2014; 142: 261-6.
[20] Okada F, Ando Y, Honda K, Tanoue S, Matsumoto S, Mori H. Comparison of pulmonary CT findings and serum KL-6 levels in patients with cryptogenic organizing pneumonia. Br J Radiol 2009; 82: 212-8.
[21] Lee JW, Lee KS, Lee HY, Chung MP, Yi CA, Kim TS, Chung MJ. Cryptogenic organizing pneumonia: serial high-resolution CT findings in 22 patients. AJR Am J Roentgenol 2010; 195: 916-22.
[22] Morell F, Reyes L, Doménech G, De Gracia J, Majó J, Ferrer J. Diagnoses and diagnostic procedures in 500 consecutive patients with clinical suspicion of interstitial lung disease. Arch Bronconeumol 2008; 44: 185-91.
[23] Lazor R, Vandevenne A, Pelletier A, Leclerc P, Court-Fortune I, Cordier JF. Cryptogenic organizing pneumonia. Characteristics of relapses in a series of 48 patients. The Groupe d'Etudes et de Recherche sur les Maladles "Orphelines" Pulmonaires (GERM"O"P). Am J Respir Crit Care Med 2000; 162: 571-7.
[24] Lappi-Blanco E, Lehtonen ST, Sormunen R, Merikallio HM, Soini Y, Kaarteenaho RL. Divergence of tight and adherens junction factors in alveolar epithelium in pulmonary fibrosis. Hum Pathol 2013; 44: 895-907.
[25] Jonigk D, Theophile K, Hussein K, Bock O, Lehmann U, Bockmeyer CL, Gottlieb J, Fischer S, Simon A, Welte T, Maegel L, Kreipe H, Laenger F. Obliterative airway remodelling in transplanted and non-transplanted lungs. Virchows Arch 2010; 457: 369-80.
[26] Estany S, Vicens-Zygmunt V, Llatjós R, Montes A, Penín R, Escobar I, Xaubet A, Santos S, Manresa F, Dorca J, Molina-Molina M. Lung fibrotic tenascin-C upregulation is associated with other extracellular matrix proteins and induced by TGFβ1. BMC Pulm Med 2014; 14: 120.
[27] Ishikawa N, Hattori N, Yokoyama A, Kohno N. Utility of KL-6/MUC1 in the clinical management of interstitial lung diseases. Respir Investig 2012; 50: 3-13.
[28] Fathi M, Barbasso Helmers S, Lundberg IE. KL-6: a serological biomarker for interstitial lung disease in patients with polymyositis and dermatomyositis. J Intern Med 2012; 271: 589-97.
[29] Xu H, Inagaki Y, Seyama Y, Du G, Wang F, Kokudo N, Tang W. Expression of KL-6/MUC1 in pancreatic cancer tissues and its potential involvement in tumor metastasis. Oncol Rep 2011; 26: 371-6.