Original Article

Analysis of the clinical characteristics of 176 patients with pathologically confirmed cryptogenic organizing pneumonia

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Background: Cryptogenic organizing pneumonia (COP), is a form of idiopathic interstitial pneumonia (IIP) and is diagnosed by clinical-radiologic-pathologic (CRP) diagnosis. To summarize the clinical, imaging, pathological, and prognostic characteristics of 176 patients with confirmed COP.

Methods: Patients who were diagnosed with organizing pneumonia (OP) by lung biopsy between January 1, 2000, and December 31, 2013, in our hospital were retrospectively analyzed and followed up until 12/31/2017. COP was confirmed by CRP diagnosis.

Results: A total of 1,346 OP cases were identified including 1,170 (86.9%) secondary OP cases (31 cases were originally misdiagnosed as COP but later confirmed as secondary OP during follow-up) and 176 (13.1%) cases of COP. The 176 patients with COP presented with no specific clinical symptoms and chest CT revealed diverse imaging features, such as patchy ground-glass opacity (112/176, 63.6%), consolidation (100/176, 56.8%), nodules (70/176, 39.8%), and fibrous stripes (69/176, 39.2%). The majority of patients (65.3%, 115/176) presented mixed patterns, and 12 (6.8%) showed a reversed halo sign. Of the 176 patients, 83 patients had unilateral lesions (ULs) and did not undergo glucocorticoid therapy. Of the 93 patients with bilateral lesions (BLs), 3 underwent complete resection and were radically cured. The other 90 patients underwent partial resection; of these patients, 37 cases achieved spontaneous remission, and 53 were treated with glucocorticoid therapy. After steroid therapy was reduced or stopped, 35 (66%) patients experienced recurrence. Overall, the 5-year survival rate for the COP patients in our study was 98.3%.

Conclusions: Our study showed that the majority of the patients pathologically diagnosed as OP had secondary OP (86.9%), with COP accounting for only 13.9% of cases. CRP diagnosis and continuous follow-up may be the key for the accurate diagnosis of COP.

Keywords: Clinical-radiologic-pathologic diagnosis (CRP diagnosis); cryptogenic organizing pneumonia (COP); organizing pneumonia (OP)

Submitted May 19, 2020. Accepted for publication Jun 19, 2020.

doi: 10.21037/atm-20-4490

View this article at: http://dx.doi.org/10.21037/atm-20-4490

Introduction

Cryptogenic organizing pneumonia (COP), which was formerly termed idiopathic bronchiolitis obliterans with organizing pneumonia (iBOOP), is typically diagnosed based on based on the presence of pathological organizing pneumonia (OP) and the absence of the etiological clinical and medical characteristics of OP (1). COP is an idiopathic interstitial pneumonia (IIP) and is diagnosed by clinical-

radiologic-pathologic (CRP) diagnosis (1). In the 2002 IIP Consensus of the American Thoracic Society (ATS) and European Respiratory Society (ERS), it was listed as having the third-highest incidence of any IIP (2). The 2013 IIP Consensus of the ATS and ERS revealed COP to be the fifth most common type of IIP (3). Earlier studies found the incidence rate of OP to be 6–7 per 100,000 people (4), with COP accounting for more than half of OP cases (5). The recent incidence rate of COP was not available (6).

In the last two decades, the number of COP cases has been reported to have gradually increased, which may be related to the more frequent use of lung biopsy. In 2011, Yoo *et al.* reported 76 COP cases (7), and Yilmaz *et al.* described 100 COP cases in 2017 (8). Those studies were the most recent literature with large patient groups. The condition is called "cryptogenic" because in most cases, the cause is unknown. Studied have shown that there are many possible causes including radiation therapy, exposure to certain chemicals, post respiratory infections, as a side-effect of organ transplantation or as a side effect from taking certain medications (9-12). Therefore, COP is only diagnosed when all other possible causes of pneumonia have been eliminated.

This study retrospectively analyzed the clinical data of 1,346 patients with OP who were diagnosed by lung biopsy in our hospital between January 1, 2000, and December 31, 2013. After undergoing strict CRP diagnostic consideration, 176 patients were confirmed to have COP and followed up to December 31, 2017. We aim to summarize the clinical, imaging, pathological, and prognostic characteristics of 176 patients with confirmed COP. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4490).

Methods

Study design

This was a retrospective observational study. *The study was conducted in accordance with the Declaration of Helsinki*. The study protocols were approved by the Institutional Review Boards of Shanghai Pulmonary Hospital (Approval No: k15-192). Because of the retrospective nature of the research, the requirement for informed consent was waived.

Diagnostic criteria

COP was diagnosed according to the 2013 ATS guidelines (3). The diagnosis of COP requires multidisciplinary CRP consideration, known causes of OP to be eliminated, and other possible diseases, such as infectious/non-infectious granulomatous diseases, connective tissue diseases, allergic pneumonia, tumors, and occupational pneumoconiosis (examined by polarized light microscopy), to be excluded. If secondary causes of OP were identified during follow-up, the diagnosis was promptly revised. Patients who showed symptoms such as Raynaud phenomenon, heliotrope rash, mechanic hands, erosive arthritis, telangiectasias calcinosis, erosive Gottron's papules, or periungual erythema, were referred to the Department of Rheumatology to rule out connective tissue disease.

Study participants

A total of 1,346 patients with a confirmed diagnosis of OP who were treated in Shanghai Pulmonary Hospital between January, 2000, and December, 2013, were screened. The clinical presentations, imaging examination results, pathological features, and laboratory test results of each patient were independently reviewed by 3 pulmonologists, 3 radiologists, and 3 pathologists. The patient screening process is displayed in *Figure 1*. A total of 207 cases were diagnosed as COP. Each case was followed up by telephone or clinic visits. Among them, 31 patients were found to have secondary OP during the follow-up and thus were excluded. Therefore, only 176 patients were diagnosed with COP and were followed up until December 31, 2017.

Imaging examination

The patients underwent chest X-ray and chest CT examination. Each patient had at least two imaging examinations: one before treatment and at least one after treatment.

Pulmonary function test

Pulmonary ventilation function was estimated using the percentage of the first second forced expiratory volume (FEV1) over the predicted value (FEV1%). Lung capacity was estimated using the percentage of residual gas volume over the total lung volume. Diffusion function was estimated using the percentage of diffusion of carbon monoxide (DLCO) over the predicted value (DLCO%).

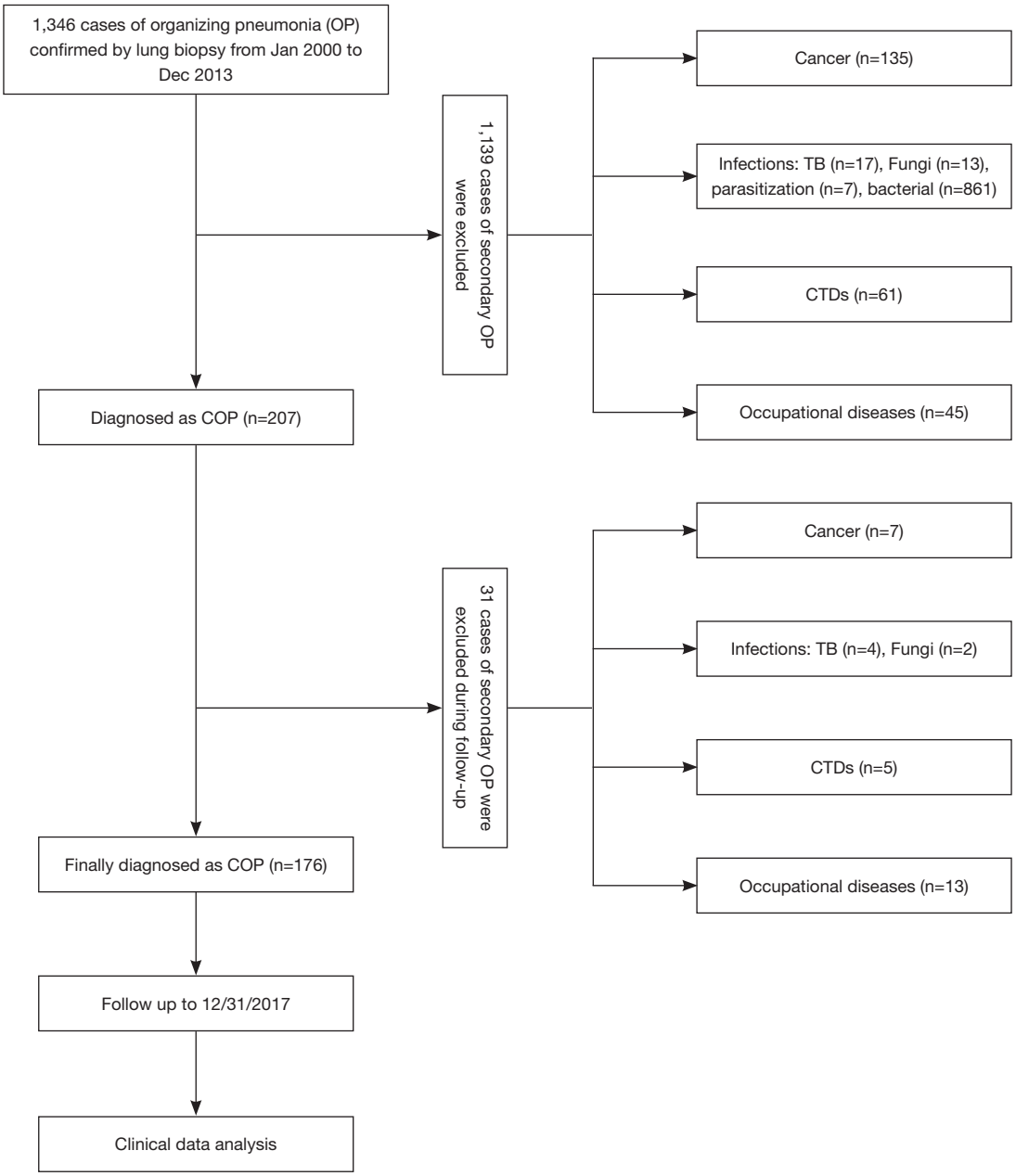

Figure 1 Flow chart.

Arterial blood gas analyses

The arterial partial pressure of oxygen (PaO_2), arterial carbon dioxide partial pressure ($PaCO_2$), arterial oxygen saturation (SaO_2), and blood pH (pH) of the patients were measured.

Blood tests

The patients regularly underwent routine blood tests, blood biochemical examinations, rheumatoid factor tests, and other autoimmune antibody tests and the result were negative. [Including anti-centromere antibodies, perinuclear

and cytoplasmic anti-neutrophil cytoplasmic antibodies, indirect immunofluorescence anti-nuclear antibody detection, immunoblotting to detect ENA polypeptide antibodies (anti-Sm antibody, anti-U1RNP antibody, anti-Scl-70 antibody, anti-ribosomal antibody), anti-cardiolipin antibody, and serum immunoglobulin electrophoresis].

Other tests

Sputum and bronchoalveolar lavage fluid (BALF) samples were sent for cytologic evaluation and culture to exclude tuberculosis, tumor, and other potential infectious diseases. And all of the results were negative.

Pathology

All lung specimens underwent hematoxylin and eosin (H&E) staining, and the pathological changes associated with OP were observed under light microscopy. The specimens also underwent special acid staining, hexamine silver staining, reticular fiber staining, and Periodic Acid-Schiff (PAS) stain for observation under a polarized light microscope.

Treatment and criteria for therapeutic efficacy evaluation

Treatments included glucocorticoid treatment (*Figure 2*) and other supplementary therapies. All patients were followed up after surgery.

In 80 cases, the patient showed no obvious symptoms at the time of disease onset but lung lesions were detected by high-resolution chest CT during routine physical examination. These patients underwent video-assisted thoracoscopic surgery (VATS) for complete resection of their lesions (77 cases of unilateral resection and 3 cases of bilateral resection). OP was confirmed by surgical pathology.

There were 96 patients [6 cases of unilateral lesions (ULs) and 90 cases of bilateral lesions (BLs)] who underwent partial resection of their lesions. These patients underwent surgery, transbronchial lung biopsy (TBLB), or percutaneous needle lung biopsy (PNLB). Of these 96 cases, 43 (6 ULs and 37 BLs) cases presented with no prominent symptoms. The post-treatment residue lesions of these patients involved a limited area, and they were followed up after surgery. The other 53 patients had BLs and presented with apparent symptoms or had extensive lesions shown on chest CT. These patients underwent steroid therapy after partial resection: 36 out of 53 patients began steroid therapy immediately after diagnosis, and 17 cases whose condition was shown by CT examination or pulmonary function tests to have progressed commenced steroid therapy during follow-up.

Statistical analyses

All data were analyzed using the IBM SPSS Statistics 20.0 (SPSS, Inc., Chicago, IL). Continuous variables were presented as mean ± standard deviation (SD) and were compared using Student's *t*-test. The chi-square test was used for the categorical variables. A P value of <0.05 was considered to be statistically significant.

Results

General clinical data

The general clinical information of the patients is displayed in *Tables 1* and *2*. Of the 176 patients with COP (103 men, aged 19–78 years), 160 underwent thoracoscopy or VATS, and 9 had PNLB and 7 had TBLB. All pathological specimens were re-examined by pathologists to exclude secondary OP. Of the patients, 17 patients had an exposure history to industrial dust, 26 had a history of allergies, and 55 had a smoking history. The patients had an extremely diverse range of occupations. The duration from the onset of symptoms to confirmed diagnosis ranged from 1–72 months (average: 4.0±9.4 months; median: 1.5 months, *Table 1*). The length of hospital stay ranged from 7–96 days (average: 20.2±16.2 days). The follow-up time ranged from 51–215 months. There were 31 patients who were originally diagnosed with COP who were found to have secondary OP during follow-up; their diagnoses were subsequently amended to secondary OP (*Table 2*).

Imaging presentations

All of the patients in this study received chest X-ray and chest CT. Chest CT examination of the patients with COP showed diverse patterns (*Figure 3*). The most common patterns were patchy ground-glass opacity (63.6%), consolidation (with or without air bronchogram, 56.8%), nodules (39.8%), and fibrous stripes (39.2%), and 6.8% (12/176) had a reversed halo sign (*Table 3*). Also, 65.3% of the patients showed mixed patterns. Patchy ground-glass lesions, fibrous stripes, and mixed types of lesions were seen more commonly in cases with BLs than in cases with ULs.

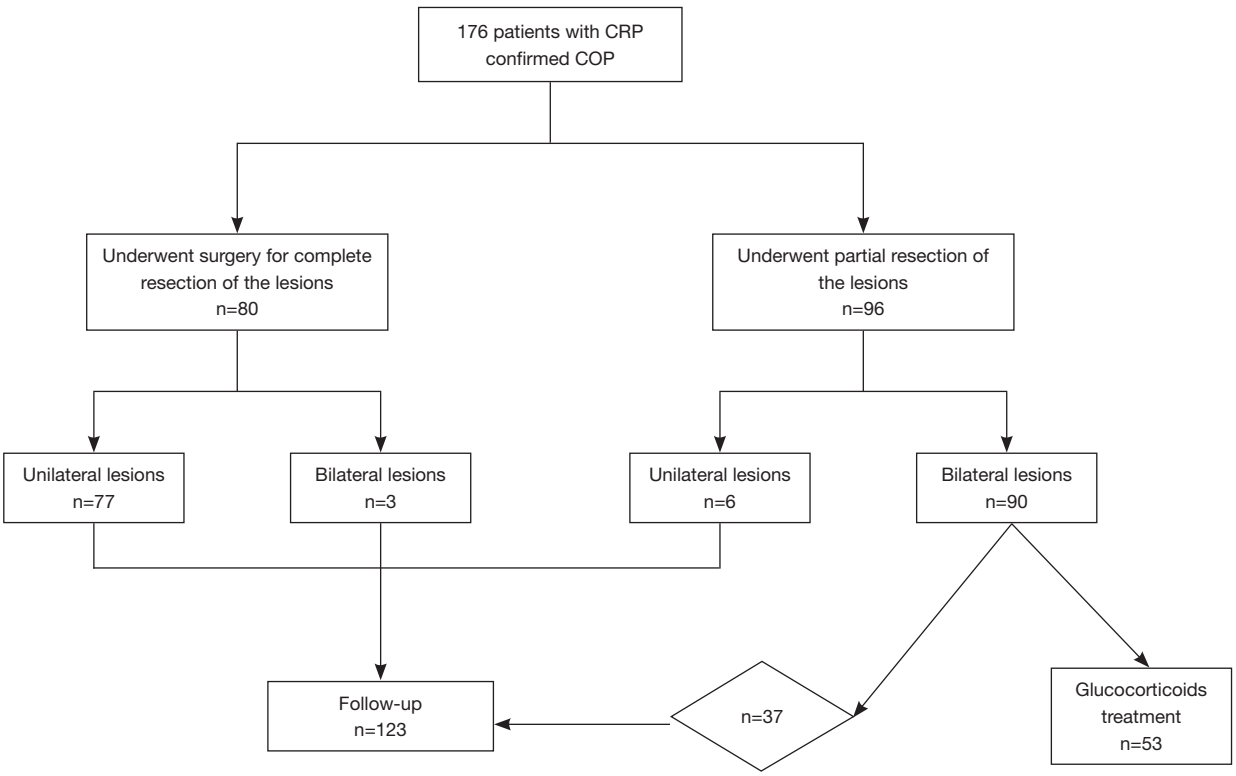

Figure 2 Treatments and Criteria for Therapeutic Efficacy Evaluation of the 176 patients with COP. Glucocorticoids were administered by intravenous drip (dosage: methylprednisolone 1–2 mg/kg/d for 1–2 weeks) followed by oral tablet (dosage: prednisone tablet or methylprednisolone tablet 30–40 mg/d with gradually reducing dosage for a minimum of 12 months). The patients were followed up. Steroid dosage was adjusted promptly when recurrence was found. Of the hospitalized patients, only one underwent non-invasive ventilation because of severe respiratory failure, other patients with hypoxemia received nasal oxygen administration or other supportive therapies. Therapeutic efficacy evaluation was based on clinical symptoms, physical signs, improvements in imaging presentations, and arterial blood gas status. The last follow-up date was December 31, 2017. Therapeutic efficacy was evaluated at the following 4 categories: (I) cured. All the clinical symptoms and abnormalities disappeared and imaging examinations showed normal. (II) Improved. The clinical symptoms and abnormalities were attenuated significantly, and imaging examinations also showed substantial improvements but not completely normal yet. (III) Recurrent. The clinical symptoms and abnormal imaging presentations recurred after steroid therapies were stopped or when steroid dosage was reduced, but was attenuated rapidly after steroid dosage was increased. (IV) Deteriorated or died. The clinical symptoms and abnormal imaging presentations were aggravated. COP, cryptogenic organizing pneumonia.

Cases with ULs comprised 47% of the study population, which might be attributable to the majority of cases being identified by lung biopsy.

Lesions were found in the upper, middle, and lower lungs of the patients; however, upper lung lesions were 38.7% (117/302). The distribution of lesions was not substantially different between the left and the right lung. Half of the patients had involvement of the pleura, which was more common in cases with BLs than in cases with ULs. Most of the lesions (59.5%, 50/84) were migratory, especially in patients with BLs (84%, 42/50).

Histopathology

Light microscopy revealed that the most typical pathological change was patchy granulomatous polypoid hyperplasia in the distal airways and alveolar cavity along the small airways (*Figure 4A*). The contents of the alveoli were composed of loose collagen and fusiform cells, and the alveoli had clear boundaries. The tissue surrounding the alveoli showed chronic inflammatory cell infiltration (*Figure 4B*). Lymphocyte and plasma cell infiltration was observed in the interalveolar space of the lesion area. Type II alveolar epithelial hyperplasia was also seen. Some cases exhibited

Table 1 Clinical characteristics of the 176 patients with COP

Characteristics	Unilateral, N=83	Bilateral, N=93	P value
Sex			
M (n=103)	62	41	<0.01
F (n=73)	21	52	
Total	83	93	
Age (mean ± SD)	55.9±9.4	55.8±10.0	NS
Days in hospital (mean ± SD)	13.9±4.2	25.5±20.2	<0.01
Smoking history			
M (n=103)	34	18	
F (n=73)	0	3	
Total	34	21	<0.01
Drug-allergy history	5	19	<0.01
Biopsy			
VATS or open chest	82	78	<0.05
TBLB	1	6	
PNLB	0	9	
Total	83	93	
Occupation			
Teacher	0	4	<0.01
Textile worker	0	4	
Foundry casting worker	0	1	
Turner welding worker	1	3	
Leather manufacturing worker	0	1	
Livestock farmer	0	1	
Warehouse bookkeeper	0	2	
Public sanitation worker	0	1	
Driver	0	2	
Health care professional	0	3	
Banker clerk	0	2	
Cook	0	1	
Farmer	0	4	
Office worker	82	64	
Duration from onset to confirmed diagnosis (months)	1.8±2.1	6.0±12.5	<0.01

COP, cryptogenic organizing pneumonia; VATS, video-assisted thoracic surgery; TBLB, transbronchial lung biopsy; PNLB, percutaneous lung biopsy; SD, standard deviation.

Table 2 The causes of secondary OP in the 31 patients who were originally considered as COP but were found to have OP during follow-up

Cause for secondary OP	Number of cases	Missed diagnosis	Reasons for missed diagnosis	Diagnosed during follow-up	Reasons for the diagnosis during follow-up
Tumor	7*	7	The original diagnosis was OP based on TBLB or PNLB. The patients did not respond to the treatment. Surgical pathology was performed again and OP was confirmed	0	
Infection	6	0		6	Two cases were positive for anti-fungal antibodies and responded well to anti-fungal treatment. Four cases showed positive tuberculosis culture results
Connective tissue disease	5	0		5	The results of rheumatism immunology test were positive. Skin and joint symptoms appeared
Occupational hazard exposure	13	13	The patients did not provide occupational exposure history at the initial diagnosis§	0	
Total	31	20		11	

*, include 1 case of hematological malignancy, 1 case of lung carcinoid tumor, and 5 cases of lung cancer; §, include 4 foundry casting workers, 3 textile workers, 3 assembly line workers, 2 turner welding workers, and 1 patient with a history of long-term exposure to glass dust. OP, organizing pneumonia; COP, cryptogenic organizing pneumonia; TBLB, transbronchial lung biopsy; PNLB, percutaneous lung biopsy.

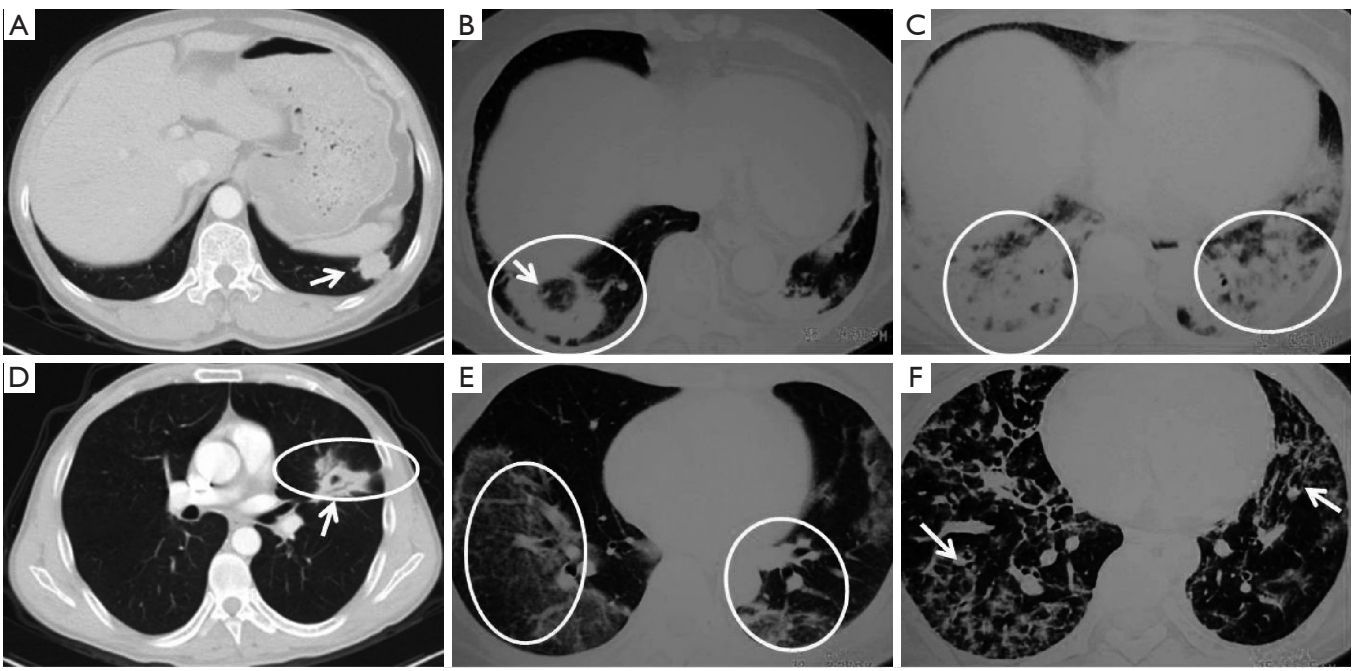

Figure 3 Lesion types on chest CT of patients with COP. Patients with COP showed diverse types of lesions on Chest CT, including nodules (A, arrow), reversed halo sign (B, arrow), diffuse consolidation (C), lung consolidation with air bronchogram (D, arrow), patchy ground glass (E), fibrous stripes (F, arrow). COP, cryptogenic organizing pneumonia.

Table 3 The CT findings of the 176 COP cases

Lesions	Unilateral[$], N=83 (47%)	Bilateral, N=93 (53%)	Percentage, N (%)	P
Lesion type*				
Nodules	20	50	70 (39.8)	<0.01
Consolidation	57	43	100 (56.8)	
Patchy ground glass	29	83	112 (63.6)	
Fibrous stripes	10	59	69 (39.2)	
Mixed pattern	28	87	115 (65.3)	
Reversed halo sign	6	6	12 (6.8)	
Distribution 1*				
Upper/middle/lower	45/8/32	72/60/85	117/68/117	<0.01
Left/right	35/48	93/93	128/141	NS
Distribution 2*				
Underneath the pleura	36	41	77 (43.8)	NS
Bronchovascular bundle	28	25	53 (30.1)	
Random	19	27	46 (26.1)	
Involvement in other tissues				
Mediastinal lymphadenopathy	11	28	39 (22.2)	NS
Pleural involvement	26	62	88 (50.0)	<0.01
Migratory/possible migratory[#]	8/34	42/50	50/84 (59.5)	<0.01

[$], unilateral lesions represent that lesions involved only one side of the lung; *, some patients showed multiple types of lesions; therefore, the total number of lesions was higher than the total number of patients; [#], patients with migratory lesions presented migratory lesions on chest CT in at least three follow-up examinations. Of the 84 patients with possible migratory lesions, 8 of the 34 patients with ULs had migratory lesions; 42 of the 50 patients with BLs showed migratory lesions. COP, cryptogenic organizing pneumonia; Uls, unilateral lesions; BLs, bilateral lesions.

fibrous tissue hyperplasia to varying degrees. However, severe fibrosis and honeycomb lung were rarely seen.

Acid-fast staining, hexamine silver staining, reticular fiber staining, and PAS staining were performed on all of the tissue specimens. Then, the specimens were examined with polarized light microscopy and showed no significant dust particle deposition. Tuberculosis, fungal infection, and tumors were ruled out. One patient with severe COP presented clinical and radiographic changes similar to those of usual interstitial pneumonia (UIP); however, the patient's biopsy showed characteristics typical of OP. The histopathology of this patient also revealed fibrosis and honeycomb lung.

Pulmonary function and arterial blood gas status

The baseline lung function test results showed mild airway dysfunction. The mean FEV1% was 77.4%±1.7%, and there was no statistical difference between the patients with ULs and BLs. The patients with BLs had significantly lower DLCO% (P<0.05, *Figure 5A*), lower PaO_2 (77.3±1.2 mmHg, P<0.05, *Figure 5B*), and lower SaO_2% (P<0.05, *Figure 5C*) than the patients with ULs. The other parameters were similar in the two groups. For the 53 patients who received steroid therapies, the DLCO% was improved after the treatment (83.4%±6.0% *vs.* 51.8%±6.4%, P<0.05, *Figure 6A*), as were their PaO_2 (90.7±4.1 *vs.* 75.2±1.8 mmHg, P<0.05, *Figure 6B*) and SaO_2% (96.8%±0.3% *vs.* 94.7%±0.4%, P<0.05, *Figure 6C*).

Rheumatology blood test, BALF, and other test results

The results of an autoimmune antibody test were negative for all patients. BALF samples were cultured and used for

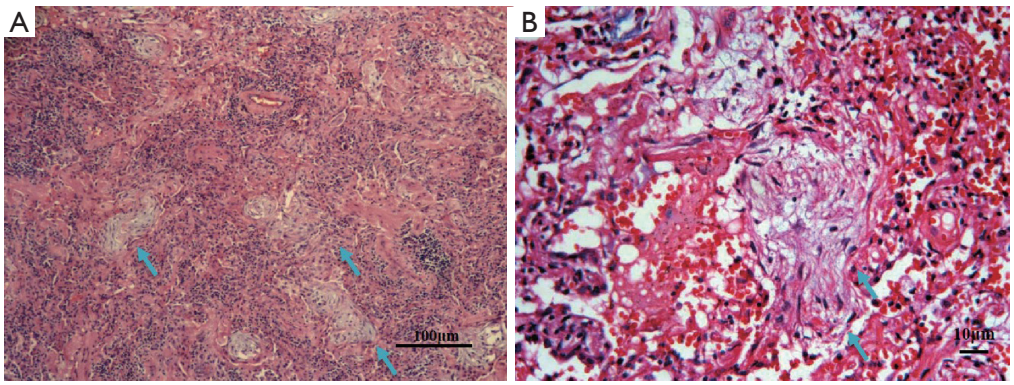

Figure 4 Pathological characteristics of patients with COP. (A) Image (×100) showing H&E staining. The lung tissue section showed a large amount of stained granulation tissue in alveoli and alveolar septum. (B) Image (×400) showing H&E staining. The contents inside alveoli were loose collagen and fusiform cells, and alveoli had clear boundaries. The tissue surrounding alveoli showed chronic inflammatory cell infiltrates. COP, cryptogenic organizing pneumonia.

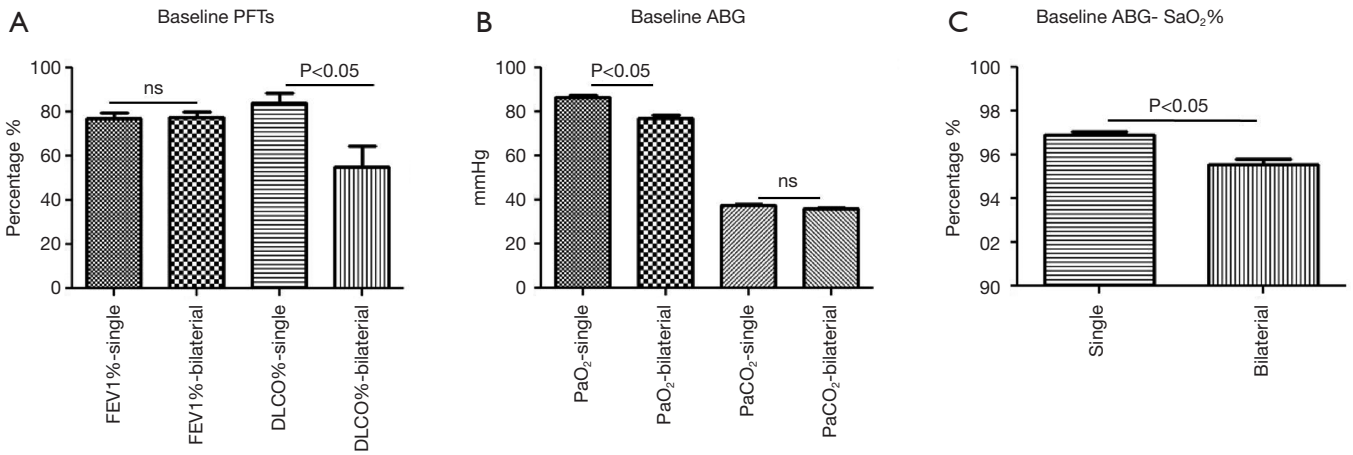

Figure 5 Pulmonary function. (A) FEV1% was similar in patients with unilateral and patients with bilateral lesions. Patients with bilateral lesions had significantly reduced DLCO% (55.1%±9.4%) than patients with unilateral lesions (84.1%±4.5%), P<0.05. B. Patients with bilateral lesions has significantly lower PaO_2 (77.3±1.2 mmHg) than patients with unilateral lesions (86.4±1.1 mmHg), P<0.05. C. Patients with bilateral lesions showed significantly lower SaO_2% (95.5%±0.1%) than patients with unilateral lesions (96.9%±0.1%), P<0.05. FEV1, forced expiratory volume in one second; DLCO, carbon monoxide diffusing capacity.

smear tests. No tumor cells, tubercle bacilli, or fungi were found, and the smear tests were all negative. Lymphocyte subtype, serum immunoglobulin, urine, fecal examination, and routine blood biochemistry tests produced normal results. No acid-fast bacilli or cancer cells were found in the sputum samples.

Therapeutic outcomes

The therapeutic outcomes of the patients are displayed in *Table 4*. All 80 patients who received complete resection were radically cured. Of the 96 patients who received partial resection, the follow-up examination results showed that 43 had been cured. The remaining 53 patients were treated with steroids and their conditions improved to various extents within one week after the treatment. Of these 53 patients, 35 had COP recurrence when the dose of steroid was reduced or stopped, and unfortunately, 3 patients died. The overall 5-year survival rate of our patient cohort was 98.3%.

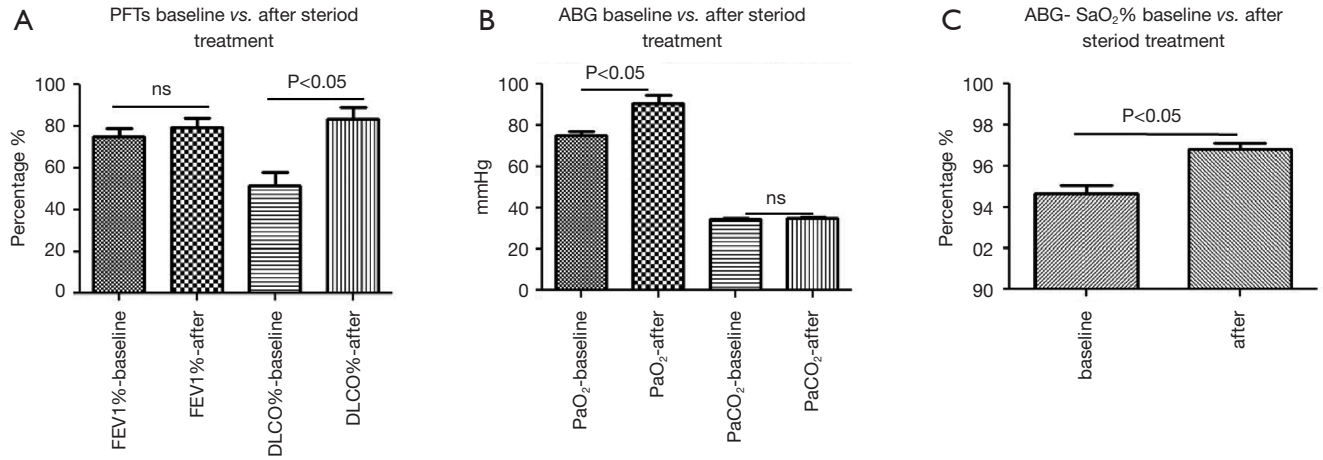

Figure 6 Lung function after glucocorticoid therapy. After glucocorticoid therapy, patient DLCO% [(A) 83.4%±6.0% *vs.* 51.8%±6.4%, P<0.05], PaO_2 [(B) 90.7±4.1 *vs.* 75.2±1.8 mmHg, P<0.05], and SaO_2% [(C) 96.8%±0.3% *vs.* 94.7%±0.4%, P<0.05] improved significantly compared with the baseline values.

Discussion

Pathological biopsy is not commonly performed in patients with COP, and it is challenging to clinically distinguish COP from the secondary OP. Consequently, COP is often misdiagnosed as pulmonary infection, tuberculosis, or cancer (7). The increasing application of pathological biopsy in current practice may leads to the increasing number of COP cases. In 2017, Yilmaz *et al.* conducted a comparative study on a group of 65 patients with pathologically confirmed secondary OP and 100 patients with COP (8). They retrospectively compared the clinical and imaging characteristics of the two patient groups and concluded that COP and secondary OP display similar imaging features on CT scan. However, their study was limited by a lack of follow-up data, treatment information, and outcome results. In 2011, Yoo *et al.* also reported a comparative study of 76 cases of COP and 24 cases of connective tissue disease-related OP (CTD-OP). Their findings suggested that the clinical features and prognosis of CTD-OP are similar to COP, however, lower complete recovery rate with a tendency towards higher recurrence rate in CTD-OP compared with COP (7).

The current study included 1,346 cases of the pathologically diagnosed OP, of which 176 cases of COP were diagnosed by the CRP method. Although it is a retrospective study, to our knowledge, the current study involved the largest patient group from a single-center with the longest follow-up time.

The majority of the patients in our study were male, which is consistent with the previous report (1), and were aged in the range of 50–60 years old. Some the patients had histories of drug allergies (26/176), exposure to industrial dust (17/176), and smoking (52/176), which indicated that COP initiation might be associated with dust, allergy, and smoking. Various conditions or factors can cause the pathological changes associated with OP or BOOP (13); these include infection (fungus, tuberculosis, parasites, and viruses), drugs, occupational hazard exposure, chest radiotherapy, organ transplantation, connective tissue diseases, and tumors. Furthermore, COP initiation has been increasingly found to be associated with environmental factors (9-12).

In our study, 207 COP cases were initially identified; however, during follow-up, 31 of them were diagnosed with secondary OP. It included 7 cases of pulmonary tumor, 4 cases of pulmonary tuberculosis, and 2 cases of pulmonary fungal infection. Meanwhile, 13 cases had occupational diseases and 5 cases had connective tissue disease. Among the 176 cases of COP, 17 patients had a history of exposure to industrial dust. These findings suggest a possible correlation between occupational hazard exposure and COP. Our results indicate that COP could be a self-limiting condition, and to confirm its diagnosis, patients may require long-term follow-up to exclude secondary OP.

COP onset in our patients was mostly subacute. The initial diagnosis for most of these patients was a pulmonary infection for which antibiotics were ineffective. No unique patterns were revealed in the patients' clinical presentations,

Table 4 Treatments and prognosis of the 176 patients with COP

Outcomes	Complete resection (with steroid/ without steroid)	Partial resection* (with steroid/ without steroid)	Total
Unilateral, N=83			
Cured	0/77	0/6	83
Improved	0/0	0/0	0
Relapsed	0/0	0/0	0
Died	0/0	0/0	0
Total	0/77	0/6	83
Bilateral, N=93			
Cured	0/3※	12/34	49
Improved	0/0	7/3	10
Relapsed	0/0	31/0	31
Died	0/0	3$/0	3
Total	0/3	53/37	93

*, including surgical biopsy, transbronchial lung biopsy, and percutaneous lung biopsy; ※, the 3 cases underwent unilateral lobectomy and also had wedge resection to remove nodules or small nodules in the opposite side of the lung. Surgical pathology confirmed OP; $, at the initial diagnosis, the 3 patients all showed bilateral diffuse patchy ground-glass opacity, fibrous stripes, and grid lesions on chest CT, all underwent VATS lung biopsy to confirm COP, and all received steroid treatment. One patient received steroid treatment 1 month after their COP diagnosis, but the patient's condition progressed continuously and they died 4 months after the biopsy surgery. The second mortality occurred 12 months after the steroid therapy. The third case had COP combined with diabetes and heart disease and died 44 months after the COP diagnosis because of respiratory failure and heart failure. OP, organizing pneumonia; COP, cryptogenic organizing pneumonia; VATS, video-assisted thoracic surgery.

which is consistent with the report by Cordier (1). In our patient cohort, 53% had bilateral lesions and the imaging characteristics of these lesions were multiple, polymorphic (patchy, consolidation, lumps, and/or fibrous strips), migratory, and recurrent, which was consistent with the lesions described in previous studies (1,4,5). Nodules with a reversed halo sign were seen in 12 of 176 cases. Moreover, 47% of our patients had ULs, which was relatively higher than the percentage previously reported (14). The possible reason for the discrepancy may be related to the increasing use of surgical biopsy in patients with such lesions. The ULs were mostly focal consolidation and some were hollow. The majority of the patients with such lesions underwent surgery for suspected lung cancer or tuberculosis and were later confirmed as OP through a surgical biopsy. Usually, the lesions were not migratory and were rarely recurrent. The low recurrence rate could be associated with most of the patients with ULs receiving complete resection.

Glucocorticoids are often used to treat COP. Steroid therapy can be low dosage and short course (1) or high dosage and long course (13). There is no consensus on the issue of glucocorticoid therapy for COP are unavailable. In the current study, 53 patients received intravenous methylprednisolone followed by oral prednisone. The clinical symptoms of the other patients alleviated within 1–3 days of the treatment except for one patient with late-stage COP who responded poorly. For the majority of the patients, chest X-ray performed one week after steroid treatment revealed substantial remission of the lesion and after two weeks of treatment, chest X-ray and CT showed that most of the lesions had disappeared. The patients were followed up closely, and the dosage of oral prednisone was personalized and reduced as patients' condition improved. Oral steroid treatment was continued until the lesions were completely resolved. Most of the patients accepted 1-year steroid therapy for COP. In this study, 35 patients experienced reoccurrence when the oral prednisone dosage was reduced to 5–15 mg/d but eventually showed an improvement when the dosage was increased to 30 mg/d. Therefore, the premature termination of steroid therapy could increase the risk of recurrence. If patients have already developed severe fibrosis and honeycomb lung, steroid therapy should be extended to a minimum of 6 months after the disease becomes stable.

COP is reported to have a good prognosis (1,15). The 5-year survival rate of our patients was 98.3%, which is similar to the survival rates previously reported (range, 73–98%) (16,17). Some patients can achieve spontaneous remission (18,19). In the current study, 43 (44.8%) of the 96 patients who received partial resection had spontaneous remission after the surgery, and the 80 patients who underwent complete resection did not experience any recurrence during follow-up. Furthermore, 35 of the 53 patients (66%) who received steroid therapy had recurrence when the steroid dosage was reduced or the steroid therapy was stopped.

Conclusions

Among 1,346 cases of confirmed OP, the majority (86.9%)

were secondary OP, and COP only accounted for 13.1% (176/1,346) of cases. ULs were common in our COP patients. CRP diagnosis and continuous follow-up may be the key for the accurate diagnosis of COP.

Acknowledgments

The authors thank Dr. Y. Huang (The Center of Thyroid Diseases, the Shanghai Tenth People's Hospital, Tongji University, School of Medicine, Shanghai, China) for her helpful discussions. We also thank our patients for their cooperation, and all of the authors who contributed their time and effort.

Funding: This study was funded by the National Science Foundation of China (No: 81500052, 81730002, 81670055, 81670056, 91442103 and 81570057), Ministry of Science and Technology of the People's Republic of China (2016YFC1100200, 2016YFC1100204), National Science Foundation of Shanghai (18ZR1431400) and Shanghai Hospital Development Center (16CR3054A).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-4490

Data Sharing Statement: http://dx.doi.org/10.21037/atm-20-4490

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-4490). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocols were approved by the Institutional Review Boards of Shanghai Pulmonary Hospital (Approval No: k15-192). Because of the retrospective nature of the research, the requirement for informed consent was waived.

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(English Language Editor: J. Reynolds)

Cite this article as: Zhang Y, Li N, Li Q, Zhou Y, Zhang F, Chen T, Shen L, Su Y, Hu Y, Li H. Analysis of the clinical characteristics of 176 patients with pathologically confirmed cryptogenic organizing pneumonia. Ann Transl Med 2020;8(12):763. doi: 10.21037/atm-20-4490

