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Original Article

Cryptogenic and Secondary Organizing Pneumonia: Clinical Presentation, Radiological and Laboratory Findings, Treatment, and Prognosis in 56 Cases

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Abstract

OBJECTIVES: Organizing pneumonia is an important disease that is associated with non-specific clinical findings and radiographic appearance. Our aim was to examine the clinical and radiological features, laboratory findings, diagnostic approach, and response to therapy in subjects with cryptogenic (COP) and secondary organizing pneumonia (SOP).

MATERIALS AND METHODS: Patients' medical records were retrospectively reviewed between 2010 and 2016 in our hospital. We analyzed the symptoms, radiological features, pulmonary function tests, laboratory data, bronchoalveolar lavage findings, treatment, and prognosis.

RESULTS: Thirty-seven patients were diagnosed with COP and 19 patients with SOP. The most common causes of SOP were determined as rheumatologic diseases. The most common symptoms were cough (71.4%) and dyspnea (66.1%). Bilateral symmetrical consolidations were the most prominent radiological appearance in both COP and SOP. The general radiographic findings were not different in COP and SOP. However, pulmonary lesions were located rather in the central (p=0.023) and middle (p=0.001) zones in patients with SOP. Corticosteroid (CS) therapy was administered to 34 (60.7%) patients. Two patients showed deterioration despite CS therapy.

CONCLUSION: The clinical and radiographic findings, treatment response, prognosis were similar in patients with COP and SOP.

KEYWORDS: Cryptogenic organizing pneumonia, secondary organizing pneumonia, clinical radiological laboratory features, prognosis

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INTRODUCTION

Organizing pneumonia (OP) is defined histopathologically by intra-alveolar buds of granulation tissue, consisting of intermixed myofibroblasts and connective tissue. This condition can be cryptogenic OP (COP) or secondary OP (SOP) to other known causes [1].

The bronchiolitis obliterans with OP (BOOP) terminology was abandoned because the main event is OP, and bronchiolitis obliterans is only a minor finding [1]. The presenting symptoms, radiographic findings, and laboratory data are usually non-specific [2]. SOP has a characteristic pathological pattern, but it is associated with known diseases or situations. Some of these entities include connective tissue diseases, infections, malignancies, drugs, radiation, transplantation, and aspiration. COP is diagnosed in the appropriate clinical, radiographic, and pathological setting after excluding situations associated with SOP [3].

The aim of the present study was to examine the etiological factors; clinical, laboratory, and radiological features; treatment response; and prognosis in patients with COP and SOP.

MATERIALS AND METHODS

The medical records of the patients from 2010 to 2016 were retrospectively reviewed. Demographic characteristics, radiological examinations, laboratory data, pulmonary function tests (PFTs), and follow-up data were collected retrospectively through the hospital information management system.

The diagnosis of OP was based on the following criteria:

1. Abnormal chest radiograph and/or thorax high-resolution computed tomography (HRCT) ranging from multiple acinar/nodular shadows,

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2. Histopathologically, the presence of intraluminal fibrotic buds within the alveoli and alveolar ducts with or without bronchiolar involvement and infiltration of chronic inflammatory cells in the alveolar septa with preservation of the alveolar structure,
3. Negative microbiological analysis on bronchoalveolar lavage (BAL) fluid, and
4. A well-documented improvement that was either spontaneous or after exclusive corticosteroid (CS) treatment.

Multidisciplinary approach was used in the diagnosis, treatment, and follow-up of the patients. Patients who were not diagnosed histopathologically were diagnosed according to clinical and radiological features. The diagnosis of OP was supported by the response to CS treatment in these patients. No pathogen was detected in the BAL examination of patients.

PFTs (SensorMedics Vmax Series 20C Respiratory Analyzer; SensorMedics Corp., Yorba Linda, CA, USA) were performed according to the American Thoracic Society guidelines. Arterial blood gases were measured at rest (Radiometer ABL 735 blood gas analyzer; Radiometer, Copenhagen, Denmark).

Fiberoptic bronchoscopy (FOB) (Olympus EVIS LUCERA CV-260; Olympus, Tokyo, Japan) was performed to obtain BAL and transbronchial biopsy (TBB). BAL was applied according to the guidelines. HRCT was used to detect the most affected area. The right middle lobe or lingula was used in the presence of diffuse involvement. At least three aliquots of 40 mL sterile saline at room temperature were instilled through FOB and gently retrieved by mechanical suction. Only the second aliquot was used for BAL analysis [4]. The following technique was used for biopsy. With the bronchoscope in the appropriate segmental bronchus, the forceps, with a biopsy cup of 2×4 mm, is passed into the bronchus and advanced until resistance is met. It is withdrawn at 2 cm, opened, and again advanced until resistance is met. The patient breathes out, and the forceps is closed and withdrawn with the biopsy specimen. After fixation in formol saline, the tissue is prepared by the Millipore filter technique and processed by conventional methods [5].

Table 1. Clinical variants of OP in the study population (n=56)

	Patients	
OP variants	**n**	**%**
COP	37	66.1
SOP	19	33.9
Rheumatoid arthritis	4	7.1
SLE	1	3.6
Sjogren syndrome	3	5.4
Lymphoma	2	3.6
Ovary cancer	1	1.8
Lung cancer	2	3.6
Nasopharynx cancer	1	1.8
Psoriasis	1	1.8
HBV	1	1.8
Stevens-Johnson syndrome	1	1.8
POEMS	1	1.8

OP: organizing pneumonia; COP: cryptogenic organizing pneumonia; SOP: secondary organizing pneumonia; SLE: systemic lupus erythematosus; HBV: hepatitis B virus; POEMS: polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes

Patients were evaluated at 1, 3, and 6 months and 1 year of diagnosis and examined in four categories according to their follow-up status: stable, remission, progression, and exitus.

Stable patient was defined as a patient whose symptoms, functional status, and radiological findings remain unchanged. Remission was defined as a patient whose symptoms, functional status, and radiological findings remain recovered. Progression was defined as a patient whose symptoms, functional status, and radiological findings remain worsened.

Approval of the ethics committee was not obtained because the study was designed retrospectively. The authors declare that there is no conflict of interests regarding the publication of this paper.

Statistical Analysis

The SPSS (Statistical Packege for Social Sciences) version 21.0 (IBM Corp.; Armonk, NY, USA) software was used for statistical analysis. Continuous data for normal distribution are expressed as mean±standard deviation (SD). A $p<0.05$ was considered as significant. In descriptive statistics, frequency and percentage were used for discrete data, and mean±SD were used for continuous variables. The normality test was performed by the Kolmogorov-Smirnov and Shapiro-Wilk methods. The Mann-Whitney U test and t-test were used to compare the differences between the groups.

RESULTS

Table 1 shows the clinical types of OP and the associated diseases of SOP. The most common causes of SOP were determined as rheumatologic diseases and malignant diseases, respectively.

Table 2 shows the demographic features and symptoms. The most common symptoms were cough (71.4%), dyspnea (66.1%), and malaise (64.3%). Cough was usually non-productive. Dyspnea lasted from 10 days to 2 years. Both COP and SOP did not differ with regard to demographic findings and symptoms.

X-ray findings included consolidation in 29 (51.8%) patients that was bilateral in 68.0% and unilateral in 32.0% of the patients. Migratory alveolar infiltrates were observed in 8 (14.3%) patients. A diffuse reticulonodular pattern was present in 15 (26.8%) patients and mass-like lesions in 13 (23.2%) patients. There was no difference between the groups in consolidation, migratory infiltration, reticulonodular pattern, and mass-like lesion. The SOP group had more middle zone infiltration ($p=0.025$) and central localization ($p=0.049$) in chest X-ray.

On HRCT scan, a reverse halo sign was not detected in patients. None had honeycomb changes. The distribution of the infiltrates was more frequent in the lower and peripheral

Table 2. Clinical characteristics of patients with COP and SOP

Variable		OP n=56	COP n=37	SOP n=19	p
Age, mean±SD, years		57.09±12.68	57.38±12.04	56.53±14.15	0.789
Age, range, years		28-83	35-83	28-75	-
Male		29 (51.8%)	20 (54.1%)	12 (63.2%)	0.267
Female		27 (48.2%)	17 (45.9%)	7 (36.8%)	
Smoking					
Smokers		33 (58.9%)	22 (59.5%)	11 (57.9%)	0.775
Non-smokers		21 (37.5%)	13 (35.1%)	8 (42.1%)	
Missing data		2 (3.6%)	2 (5.4%)	0 (0%)	
Antibiotic use	Yes	31 (55.4%)	20 (54.1%)	11 (57.9%)	0.948
Before diagnosis	No	22 (44.6%)	14 (37.8%)	8 (42.1%)	
Cough	Yes	40 (71.4%)	25 (67.6%)	15 (78.9%)	0.747
	No	14 (25.0%)	10 (27%)	4 (21.1%)	
Sputum	Yes	20 (35.7%)	12 (32.4%)	8 (42.1%)	0.769
	No	34 (60.7%)	23 (62.2%)	11 (57.9%)	
Hemoptysis	Yes	4 (7.1%)	3 (8.1%)	1 (5.3%)	0.657
	No	47 (83.9%)	20 (81.1%)	17 (89.5%)	
Dyspnea	Yes	37 (66.1%)	23 (62.2%)	14 (73.7%)	0.760
	No	17 (30.4%)	12 (32.4%)	5 (26.3%)	
Fever	Yes	24 (42.9%)	16 (43.2%)	8 (42.1%)	0.775
	No	28 (50.0%)	17 (45.9%)	11 (57.9%)	
Chest pain	Yes	7 (12.5%)	5 (13.5%)	2 (10.5%)	1.000
	No	46 (82.1%)	30 (81.1%)	16 (84.2%)	
Loss of appetite	Yes	25 (44.6%)	16 (43.2%)	9 (47.4%)	0.939
	No	27 (48.2%)	17 (45.9%)	10 (52.6%)	
Malaise	Yes	36 (64.3%)	24 (64.9%)	12 (63.2%)	0.541
	No	16 (28.6%)	9 (24.3%)	7 (36.8%)	
Weight loss	Yes	14 (25.0%)	8 (21.6%)	6 (31.6%)	0.515
	No	39 (69.6%)	27 (73.0%)	12 (63.2%)	
Crackles	Yes	31 (55.4%)	20 (54.1%)	11 (57.9%)	0.869
	No	24 (42.9%)	16 (43.2%)	8 (42.1%)	
Wheezing	Yes	2 (3.6%)	2 (5.4%)	0 (0%)	0.539
	No	53 (94.6%)	34 (91.9%)	19 (100%)	
Clubbing	Yes	1 (1.8%)	0 (0%)	1 (5.3%)	0.333
	No	53 (94.6%)	37 (100%)	17 (89.5%)	
Cyanosis	Yes	5 (8.9%)	2 (5.4%)	3 (15.8%)	0.327
	No	50 (89.3%)	34 (91.9%)	16 (84.2%)	
Bronchial breath sounds	Yes	2 (3.6%)	2 (5.4%)	0 (0%)	0.539
	No	53 (94.6%)	34 (91.9%)	19 (100%)	
NPEF	Yes	23 (41.1%)	15 (40.5%)	8 (42.1%)	0.975
	No	32 (57.1%)	21 (56.8%)	11 (57.9%)	

COP: cryptogenic organizing pneumonia; SOP: secondary organizing pneumonia; NPEF: normal physical examination findings

zones. Middle zone involvement (p=0.001) and central localization (p=0.023) in the SOP group were significantly higher than those in the COP group (Table 3).

Erythrocyte sedimentation rate (ESR) was >20 mm/h in 38 (67.8%) patients. The mean C-reactive protein (CRP) level in the total patient population was 34.5±32.6 mg/L. There was no difference between the groups in CRP levels (p=0.868). The leukocyte count was >10,000/mm^3 in 18 (32.1%) patients. A slight eosinophilia was observed in 18 (32.1%) patients. There was no difference between the groups with regard to laboratory parameters (Table 4).

Table 3. CT scan and HRCT findings in 56 patients with COP and SOP

Variable		OP n=56	COP n=37	SOP n=19	p
Distribution					
Upper zone	Yes	16 (28.6)	12 (32.4)	4 (21.1)	0.365
	No	38 (67.9)	23 (62.2)	15 (78.9)	
Middle zone	Yes	23 (41.1)	9 (24.3)	14 (73.7)	0.001
	No	31 (55.4)	26 (70.3)	5 (26.3)	
Lower zone	Yes	38 (67.9)	26 (70.3)	12 (63.2)	0.534
	No	16 (28.6)	9 (24.3)	7 (36.8)	
Peripheral distribution	Yes	35 (62.5)	22 (59.5)	13 (68.4)	0.771
	No	19 (33.9)	13 (35.1)	6 (31.6)	
Central distribution	Yes	25 (44.6)	12 (32.4)	13 (68.4)	0.023
	No	29 (51.8)	23 (62.2)	6 (31.6)	
Bilateral alveolar	Yes	31 (55.4)	20 (54.1)	11 (57.9)	0.958
	No	23 (41.1)	15 (40.5)	8 (42.1)	
Reticular	Yes	15 (26.8)	8 (21.6)	7 (36.8)	0.345
	No	39 (69.6)	27 (73.0)	12 (63.2)	
Mass-like lesion	Yes	13 (23.2)	9 (24.3)	4 (21.1)	0.705
	No	41 (73.2)	26 (70.3)	15 (78.9)	
Cavitation	Yes	2 (3.6)	0 (0)	2 (10.5)	0.053
	No	52 (92.9)	35 (94.6)	17 (89.5)	
Migratory lesions	Yes	8 (14.3)	4 (10.8)	4 (21.1)	0.431
	No	46 (82.1)	31 (83.8)	15 (78.9)	

Table 4. Laboratory data in patients with COP and SOP

Variable (no. of COP/SOP)	OP±SD	COP±SD	SOP±SD	p
WBC, 10^3/mL (26/14)	7.960±2.631	6.959±4.449	6.959±4.449	0.207
Hb, g/dL (26/14)	12.8±1.86	12.61±1.91	13.16±1.76	0.309
Plt, 10^3/mL (26/14)	270.0±1.48	295.45±1.39	223.00±1.57	0.089
ESR, mm/h (26/14)	48.97±37.71	50.56±40.05	45.95±33.65	0.666
CRP, mg/dL (26/14)	34.57±24.56	35.32±23.24	33.20±28.40	0.868
Eosinophilia, % (26/14)	2.8±1.4	3.38±2.48	1.75±1.70	0.178
ANA	3/56	0/37	3/19	-
Anti-dsDNA	2/39	0/37	2/19	-
RA	2/39	0/37	2/19	-
ANCA	1/39	0/37	1/19	-
Anti-Ro	3/39	0/37	3/19	-
Anti-La	2/39	0/37	2/19	-
Viral hepatitis markers	3/40	1/37	2/19	-

SD: standard deviation; WBC: white blood cell; Hb: hemoglobin; Plt: platelet; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ANA: antinuclear antibody; RA: rheumatoid arthritis; ANCA: antineutrophil cytoplasmic antibody

PFT was available for 49 patients, and diffusion capacity for carbon monoxide (DLCO) test was available for 43 patients (Table 5). Eleven (22.4%) patients had pure-restrictive defect, and 7 (14.3%) patients had obstructive defects. DLCO was reduced (<60%) in 15 (34.9%) of 43 patients. Normal PFT was determined in 30 (61.2%) of 49 patients (Table 5).

BAL analysis was completed in 38 (67.8%) patients. Neutrophilia >5% in BAL fluid was observed in 20 (52.6%) patients. The BAL neutrophil count was higher in the SOP group than in the COP group (16.85±5.35% vs 5.71±5.01) (p=0.044). Lymphocytes were 28.6% of the total cells. A lymphocytosis of >25% was identified in 12 (31.6%) patients. There was no difference between the groups in terms of spirometric mea-

Table 5. PFTs and BAL findings in patients with COP and SOP

Variable (no. of COP/SOP)	OP±SD	COP±SD	SOP±SD	p
FEV_1, % (32/17)	82.77±19.32	81.50±20.21	85.18±17.88	0.526
FVC, % (32/17)	86.11±18.59	83.76±19.55	90.12±16.63	0.263
FEV_1/FVC, % (32/17)	77.81±9.06	76.65±8.97	80.06±9.07	0.220
DLCO, % (26/17)	67.73±13.98	68.11±13.29	67.06±15.56	0.817
DL ADJ, % (26/17)	68.79±14.84	69.24±13.76	68.00±17.13	0.802
DLCO/VA, % (26/17)	80.18±13.60	77.44±13.34	85.07±13.12	0.093
DL/ADJ/VA, % (26/17)	80.31±14.57	78.28±14.36	84.23±14.73	0.232
Lymphocytes (mean±SD) (24/14)	17.52±16.42	16.58±14.85	19.15±19.03	0.643
Lymphocytes (>20% of total BAL cells, n) (24/14)	16 (28.6%)	10 (41.67%)	6 (42.86%)	1.000
Neutrophils (mean±SD) (25/14)	9.52±6.16	5.71±5.01	16.85±5.35	0.044
Neutrophils (>5% of total BAL cells) (25/14)	19 (33.91%)	12 (50%)	7 (50%)	1.000
Eosinophils (mean±SD) (25/14)	4.68±4.63	5.48±4.18	3.15±2.35	0.305
Eosinophils (>2% of total BAL cells) (25/14)	14 (25%)	10 (41.67%)	4 (28.57%)	1.000
Macrophages, % (25/14)	51.68±26.66	57.24±26.05	41.00±25.41	0.075

DLCO: diffusion capacity for carbon monoxide; DL ADJ, DLCO adjusted for hemoglobin; DLCO/VA, DL (CO) to alveolar ventilation (DLCO/VA)

surement and eosinophil and lymphocyte counts. Table 5 shows the other BAL findings.

Thirteen (23.2%) patients were diagnosed with OP (COP: 8 (14.3%) patients and SOP: 5 (8.9%) patients) clinically and radiologically, after exclusion of all other possible etiologies. Clinical and radiological improvement in patients using corticosteroid (CS) treatment with OP pre-diagnosis supported the diagnosis of OP. Twenty-four (42.9%) patients were diagnosed with OP (COP: 17 (30.4%) patients and SOP: 7 (12.5%) patients) using TBB. Seventeen (30.4%) patients were diagnosed with OP (COP: 10 patients and SOP: 7 patients) using video-assisted thoracoscopy (VATS). Two (3.6%) patients were diagnosed with COP using CT-guided percutaneous transthoracic needle biopsy (PTNB).

Oral CS was administered to 37.5% (n=21) of the patients with COP and 23.2% (n=13) of the patients with SOP. Eight (14.3%) patients were not treated because of the lack of specific symptoms or functional and physical limitations. In addition, 6 (10.7%) patients (4 (7.1%) with COP and 2 (3.6%) with SOP) underwent surgery for removal of a solitary pulmonary nodule due to suspected carcinoma. Treatment of patients with COP and SOP was similar.

In-hospital mortality and a 1-year mortality in patients with OP were 2.5% and 0%, respectively. One patient (who had SOP-Hodgkin lymphoma) who used CS treatment had a rapidly progressive respiratory failure requiring mechanical ventilation; the patient died.

Overall, 34 patients underwent CS therapy. Table 6 shows the information about the prognosis of the disease at 1, 3, and 6 months and 1 year of follow-up of the patients. Eight patients were followed up without any treatment, and 5 patients were treated surgically. Table 6 shows the features of these patients.

The response to CS treatment was not different between those with lymphocyte dominance and those with neutrophil dominance (p=0.6). However, the response to CS treatment was different between those with ground glass opacity and those without ground glass opacity patterns in high resolution computed tomography (HRCT) (p=0.002). In the ground glass opacity group, 9 of the patients with CS therapy at 3 months were in remission, and 12 at 6 months were in remission. However, none of the patients without ground glass opacity in HRCT were in remission at 3 months of CS treatment, and 3 were in remission at 6 months.

DISCUSSION

The classification of OP is very important because the treatment and follow-up of patients with SOP include not only the treatment of OP but also the management of underlying diseases. The most common causes of SOP include drugs, infections, rheumatologic diseases, malignancies, and their treatments [6]. In our study, 37 patients were COP, and 19 were SOP. Rheumatologic diseases and malignancies were the most common causes of SOP.

OP is most common in the 5-6 decades of life [7,8]. In our study, patients were between 28 and 83 (mean age: 57.09±12.68) years. Studies that examined the distribution of patients with COP and SOP according to gender have shown no significant difference between the two groups [6,8]. Our results were similar to previous studies.

The association of smoking with OP has been controversial [9]. In our study, 58.9% of all patients had a smoking background, and there was no statistically significant difference between COP and SOP (p=0.775). These results were similar to studies by Sveinsson [6] and Drakopanagiotakis [2]. In the study by Lazor et al. [9], 71% of the patients were non-smokers, and most of the patients who were non-smokers were women. Researchers thought that smoking could be protective against COP development in women [9].

Table 6. Prognosis for patients

	Values (no. of treatment/total patients)	n	%
Prognosis for patient on corticosteroid treatment	1 month (27/34) (missing data=7)		
	Stable	27	79.4
	3 months (26/34) (missing data=1)		
	Stable	17	65.4
	Remission	8	30.8
	Progression	1	3.8
	6 months (21/34) (missing data=5)		
	Stable	6	28.6
	Remission	13	61.8
	Progression	1	4.8
	Exitus	1	4.8
	1 year (19/34) (missing data=2)		
	Stable	2	10.5
	Remission	17	89.5
	Progression	-	-
Prognosis for patient on no treatment	1 month (8/56)		
	Stable	8	100
	3 months (8/56)		
	Stable	7	87.5
	Remission	1	12.5
	6 months (8/56)		
	Stable	2	25
	Remission	6	75
	1 year (8/56)		
	Remission	8	100
Prognosis for patient on surgical treatment	1 month (6/56)		
	Remission	5	83.3
	Missing data	1	16.7
	3 months (5/56)		
	Remission	4	83.3
	Missing data	1	16.7
	6 months (4/56)		
	Remission	4	100
	1 year (4/56)		
	Remission	4	100

OP is characterized by non-specific symptoms, such as flu-like illness [10-13]. Most of our patients had flu-like symptoms. Non-specific symptoms of malaise, cough, fever, and dyspnea occurred in more than two-thirds of the patients [9,14]. Hemoptysis was previously described to be uncommon in many studies. The hemoptysis rate in our patients was 7.1%. Our results were similar to previous studies [8,15,16]. Hemoptysis could occur as a result of underlying diseases, such as malignancies but not OP.

The most common radiological findings in patients with OP are consolidation and ground glass opacities, and these are usually bilateral-peripheral [1]. Our findings were consistent with the literature; however, centrally located lesions were more frequent in SOP than in COP (p=0.023). A previous study showed a predominance of lesions in the lower lung areas in 55% of the patients [1]. Another study showed a predominance of lesions in the middle zone in 91.7% of the patients [7]. We detected involvement in the lower lobes in the general patient population, but the most common middle lobe was affected in SOP (p=0.001). Only 14.3% of the cases had migratory infiltrates. This number is significantly lower than previous reports [13,17]. Although a solitary opacity is an uncommon presentation in OP that is known as focal OP, and 10%-15% of the patients are focal OP [15]. We found 23.4% of mass-like lesions.

An elevated ESR was common in patients. This was similar to previous studies [1,14,18,19]. The majority of cases have been reported to have elevated CRP [20]. The cause of elevated acute phase reactants (APRs; such as CRP and ESR) in patients with OP is not well known. Elevated APRs have been defined in several studies. However, no explanation was given as reason [6,20]. APRs are synthesized from liver cells during inflammation, most often with the effect of cytokines (especially interleukin 6). They are elevated in acute infections and autoimmune, rheumatologic, and granulomatous diseases and are used in the course of active disease [21,22]. Previous studies have shown increased inflammatory cytokines in OP [23,24]. APRs may be elevated by the increase of cytokine in OP. In addition, most of the known causes of SOP are associated with acute inflammation. It is thought that elevated APRs may develop secondary to these diseases.

OP normally presents a restrictive pattern on PFT [25]. However, our results and the study by Kavakli et al. [26] differed from previous studies. In the study by Kavakli et al. [26], normal PFT was detected in 58% of the patients, and we observed normal PFT in 33 (58.9%) patients. Nine (16.1%) of our cases had isolated restrictive defects. The mechanism of the restrictive pattern in OP is not well established yet.

BAL examination usually shows expansion of all cell lines [27]. In the study by Drakopanagiotakis et al. [2], BAL was performed in 32 of 61 patients. In 43% of the 32 patients, BAL lymphocyte was found >20%. However, in the present study, there were 21 patients in the SOP group, and only 5 had BAL lymphocyte. Of these 5 patients, 4 (80%) had a BAL lymphocyte level >20%. Possibly, the rates could have changed if there were more patients whose BAL lymphocyte levels were examined in the SOP group. In our study, a significant part of patients with SOP had BAL neutrophilia, and this was statistically significant (p=0.044). These findings were inconsistent with previous studies [1,6]. Costabel et al. [27] analyzed BAL findings in 10 patients with BOOP syndrome. All 10 of them had lymphocytosis >20%, 8 (80%) exhibited neutrophilia (>5%), and 5 (50%) exhibited eosinophilia (>5%). There have been almost no explanation about the cause of the cellular distribution in previous studies.

Open lung biopsy, VATS, and CT-guided PTNB are preferred in the diagnosis of OP, whereas TBB often fails to obtain a large and adequate piece of lung tissue [28]. However, by the proper clinical and radiographic findings, TBB and BAL may be diagnosed with OP [1,27]. Moreover, OP can be diagnosed by clinical findings and compatible imaging (especially in patients who are too frail) [1]. Cazzato et al. [29] investigated the clinical and radiological features at onset, outcome, and diagnostic approach in subjects with OP. They found that although clinical and radiological findings usually suggest the diagnosis, a definitive confirmation requires TBB and BAL. In our study, 13 (23%) patients were diagnosed with OP by clinical and radiological findings. Of these patients, 10 were >65 years old, and the patients did not accept TBB or VATS. TBB has been used for diagnosis in many studies [1,14,29,30]. According to Cazzato et al. [29], from a diagnostic perspective, TBB (together with BAL) should be the first diagnostic step. They diagnosed 74% of the patients with TBB and determined that although the sensitivity of BAL was found to be lower than that of TBB, the combination of the two procedures improved the diagnostic yield (sensitivity 86%) [29]. In our study, approximately 43% of the patients had pathological diagnosis by TBB.

VATS allow biopsy of the lung in well conditions of security. Currently, VATS is a safe procedure that may be used in many patients [30]. Seventeen (30%) patients were diagnosed by VATS.

Two patients were diagnosed by CT-guided PTNB. These patients had peripheral located consolidation in thorax CT. PTNB is a rare diagnostic method in the literature [26].

There are no sufficient studies available to make recommendation CS, and length of treatment is not known [6]. In accordance with previous studies, we applied CS treatment to most of our patients (34 of 56 patients) [1,7]. Of the patients who were followed up for 1 year, 89% were fully recovered with CS therapy. Only one patient relapsed, and one patient died. All patients with focal lesions underwent surgery for both diagnosis and treatment, and there was no relapse in any patient. Relapses were frequently reported in the literature, but in our patients, it was negligible. However, approximately half of our patients were lost during follow-up.

The response to CS treatment has not been evaluated in subgroups, such as neutrophil predominance group and lymphocyte predominance group, in HRCT pattern in previous studies [6,7]. These subgroups were evaluated in our study. We found that in patients with ground glass opacity in HRCT, the response to CS treatment is better. Ground glass opacities also respond better to CS treatment in other interstitial lung diseases. However, we do not know how to respond to CS treatment in nodular OP because these patients are usually patients with surgical resection with malignancy pre-diagnosis and did not use CS therapy.

In conclusion, the clinical and radiological findings in patients with both COP and SOP are similar. The most common complaints were cough and dyspnea. The most common radiological appearance was peripheral consolidation area. Lesions tended to predilect the central part of the middle zone in SOP. COP and SOP have similar treatment response and prognosis.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

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