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Disease Course, Treatment Response and Relapse in a Group of Patients with a Primary Diagnosis of Cryptogenic Organizing Pneumonia: A Cohort Study

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Background: Cryptogenic organizing pneumonia (COP) is a rare lung condition affecting the bronchioles and alveoli. This study aimed to determine the course of the disease and response to treatment in a group of COP patients.

Materials and Methods: In a cohort study, patients' data including demographic features, chest imaging, spirometry, and blood tests, were recorded. Inclusion criteria were radiological features compatible with COP, confirmed tissue biopsy, and the absence of underlying diseases at the time of presentation. All patients received the same steroid-based regimen (oral prednisolone with a dosage of 1 mg/kg tapered to none within 6 months). They were followed for 3 years.

Results: Sixteen patients were included, 43.75% were male. The mean age was 56 ± 15 years. Nobody experienced recurrence. Reversed halo sign and ground-glass opacity were the most common radiological findings. ESR decreased significantly after treatment ($P<0.005$). Forced vital capacity increased significantly after treatment ($P<0.005$), the same was true for oxygen saturation ($P<0.005$). On three years of follow-up, 5 patients developed signs and symptoms of connective tissue diseases and malignancy. There was no significant association between the final diagnosis and radiological findings at presentation ($P>0.05$).

Conclusion: Standard treatment in patients with early diagnosis of COP was associated with an appropriate therapeutic response and no recurrence of pulmonary symptoms. Proper treatment can lead to optimized oxygenation parameters and a decreased inflammatory index. Lower response to treatment among corticosteroid-treated COP patients may suggest secondary causes of organizing pneumonia.

Keywords: Pneumonia; Cryptogenic organizing pneumonia (COP); Corticosteroid

INTRODUCTION

Cryptogenic organizing pneumonia (COP) is a rare interstitial lung disease (ILD) affecting the bronchioles and alveoli (1). The exact etiology is not known but organizing pneumonia might develop in response to various insults whether localized or widespread, or secondary to connective tissue disease, hematological disease, malignancy, or medications. The term "COP" is used when there is no definite etiology for organizing pneumonia (2). Patients frequently complain of a subacute course of dry cough and shortness of breath. Other symptoms include fever and exhaustion (3). Granulation tissue within the

small airways and alveoli characterizes cryptogenic pneumonia pathologically. Chest computed tomography (CT) scan commonly shows bilateral patchy consolidations with subpleural and lower lung orientation.

Corticosteroid treatment is effective in patients with cryptogenic organ pneumonia (4). Before ultimate diagnosis, most COP patients are treated for other conditions such as unresolved bacterial pneumonia, various kinds of ILD, and heart failure. As a result, there is a 20-day to 2-year delay between the development of symptoms and the initiation of corticosteroid medication (3).

Although individuals with organizing pneumonia respond well to corticosteroid therapy, recurrence is prevalent when corticosteroid dosages are discontinued or reduced rapidly. Risk factors for illness recurrence include the burden of intra-alveolar fibrin deposits and the number of involved lung zones (5). Some studies evaluated parameters such as C-reactive protein (CRP) in COP patients with and without recurrence (4,5,6) while others looked at the HRCT results of patients with COP and how they changed during therapy. They also compared CT scan results in individuals with organizing pneumonia associated with connective tissue diseases to those in patients with cryptogenic organizing pneumonia. Despite many investigations on COP patients, there is currently not enough evidence and systematic study that assess the course of therapy, responsiveness to treatment, ultimate diagnosis, and follow-up of patients with cryptogenic pneumonia.

This study aimed to evaluate the course of the disease, response to treatment, recurrence rate, and final diagnosis (if any) in a group of COP patients followed for three years.

MATERIALS AND METHODS

In this cohort study, demographic information including age, sex, smoking rate, time from onset of symptoms to treatment, clinical examination findings such, CT scan findings such as unilateral or bilateral involvement, and paraclinical indicators including spirometry and blood tests were recorded in questionnaires. Inflammatory index of erythrocyte sedimentation rate (ESR) and forced vital capacity (FVC) were recorded before and after treatment.

Inclusion criteria were radiological infiltration in favor of organizing pneumonia along with a confirmed tissue biopsy based on organizing pneumonia and the absence of underlying diseases such as hematologic malignancies and connective tissue diseases at the time of presentation. Tissue biopsies were obtained mostly by Cryo-transbronchial lung biopsies. Surgical lung biopsy or CT-guided transthoracic biopsy was done in a few patients.

Those patients whose follow-up files were incomplete were excluded from the study process.

All the patients received the same treatment under the supervision of expert clinicians. Treatment was started in all patients with oral prednisolone at a dose of 0.75-1 mg/kg daily (maximum: 100 mg daily) according to the British Thoracic Society Guideline (6). It was administered over 4-6 weeks, depending on the clinical dose. Prednisolone was converted to 0.5 mg/kg and then gradually tapered within 6 months of starting prednisolone treatment. Eventually, the dose was reduced to zero within the first 6 months. The patients were followed monthly. Then, they were followed every 3 months for one year and then yearly for two years. Follow-up included history taking, physical exam, pulmonary function tests, and if needed inflammatory blood tests and chest imaging.

Pulmonary function tests were done with MIR Spirolab Spirometer II(UK,2012) according to the American Thoracic Society Guideline. FVC and ESR were measured once before the start of treatment (NO.1) and 6 weeks after treatment (NO.2).

Outcome

Within a 3-year follow-up period, five out of 16 patients developed signs and symptoms of other diseases, and were diagnosed with rheumatoid arthritis (2 cases), lymphoma

(1), giant cell arthritis (1), and mixed connective tissue disease (1). These five patients did not have any underlying disease (including rheumatological and hematologic diseases) at the time of first presentation and diagnosis of organizing pneumonia lung disease (like the remaining eleven patients). Therefore, to compare the data of these patients with other patients who did not show symptoms of underlying diseases in the follow-up period, patients were divided into two groups: secondary organizing pneumonia and cryptogenic organizing pneumonia. Finally, the data related to these two groups was compared and statistically analyzed.

Sample size and statistical analysis

Information from the medical records of all patients with a primary confirmed diagnosis of COP who met the inclusion criteria was collected between 2016 and 2020. The significance level of the data was considered less than 5%. All the statistical analysis was performed by SPSS 26 software. The Chi-square test (or Fisher's exact test) was used to examine the relationship between qualitative and nominal variables. The Wilcoxon test was also used to differentiate the mean rank of variables before and after treatment.

RESULTS

A total of 16 patients were included, 43.75% were male. The average age was 56 ± 15. None of the patients experienced recurrence. A summary of the patient's medical history is provided in Table 1.

Initially, ten patients were diagnosed with transbronchial lung cryo-biopsy (TBLC), four patients by open lung biopsy (OLB) done after non-diagnostic TBLC, one patient by open lung biopsy (OLB), and one with CT scan-guided transthoracic biopsy (CTB). Preliminary results of the chest imaging showed a reversed halo sign (Atoll) in 8 patients, unilateral GGO in 4 patients, bilateral GGO in 3 patients, and a crazy paving pattern in one. After administration of treatment, 5 patients developed complications. Two of them developed diabetes mellitus, one hypertension, one oral thrush, and another one fungal otitis. The results of Fisher's exact test did not show a significant association between primary diagnosis and radiological findings (P>0.05).

There were two types of pneumonia in this study: secondary organizing pneumonia (SOP) and cryptogenic organizing pneumonia (COP). Five patients who initially were diagnosed and treated as cryptogenic organizing pneumonia were finally diagnosed as secondary OP during the follow-up period and eleven patients remained as cryptogenic organizing pneumonia. It was found that there is an association between radiological imaging pattern and the type of organizing pneumonia ($\chi 2$=9.40, Cramer's V=0.76, p=0.012) so that 72.7% of COP patients had ATOLL pattern and 60% of secondary OP patients had GGO patterns. It should be noted that the magnitude of the effect of this relationship indicates a strong association. Descriptive clinical and laboratory of patients are provided in Table 2.

The independent comparison between SOP and COP patients for variables before and after treatment was performed to understand any significant differences in terms of variables before and after treatment, independently (Table 3).

The results of independent comparisons revealed that COP patients had higher FVC before and after treatment in comparison to secondary OP patients (p<.05). Furthermore, COP patients had higher oxygen saturation both before and after treatment (p<.05). Although there was a reduction trend in terms of ESR in both groups of patients, there were no statistically significant differences either before or after treatment. To compare the mean of variables before and after the treatments, Paired T-test was performed (Table 4).

As it is vividly apparent in Table 3, the mean of ESR significantly decreased after the treatment (P < 0.005). The mean average of FVC significantly increased after the treatment (P<0.005). Oxygen saturation also increased significantly after the treatment. Also, there is a positive correlation between these variables before and after treatment (Figure 1, 2).

Table 1. Summary of patients' data

Sex	Age years	Imaging	Symptom duration before diagnosis	ESR 1 Mm/h	ESR 2 Mm/h	FVC 1 liter	FVC 2 liter	SpO_2(%) 1	SpO_2(%) 2	Ultimate Diagnosis
F	53	Bilateral GGO	3 months	42	38	1/62	1/87	81	96.00	RA 3 years later
F	68	Bilateral GGO	3 weeks	68	42	1/24	1/55	85	96.00	_
F	81	Bilateral GGO	4 weeks	40	36	1/13	1/34	87	97.00	_
M	38	ATOLL	6 weeks	54	32	2/23	2/89	91	98.00	_
F	54	ATOLL	2 weeks	51	32	1/41	1/75	87	96.00	_
F	31	GGO	2 weeks	38	21	1/21	1/36	85	96.00	RA 3 years later
F	51	GGO	2 weeks	36	32	0.830	1/1	73	95.00	MCTD 6 month later
M	63	ATOLL	3 weeks	82	40	2/14	2/85	88	96.00	_
F	48	ATOLL	4 weeks	70	32	2/13	2/52	88	97.00	_
F	31	GGO	4 weeks	34	21	1/71	2/11	90	98.00	_
M	51	ATOLL	4 weeks	91	54	2/36	2/7	83	97.00	_
M	72	ATOLL	4 weeks	104	74	1/58	1/91	73	96.00	_
F	51	ATOLL	6 weeks	65	35	2/69	3/01	90	99.00	_
M	72	GGO	2 weeks	47	34	1/08	1/56	73	96.00	Next year GCA
M	63	ATOLL	3 weeks	91	48	2/22	2/45	88	98.00	_
M	78	Crazy paving	6 weeks	78	51	1/42	1/6	84	97.00	Lymphoma

GCA: giant cell arteritis, MCTD: mixed connective tissue disease, RA: rheumatoid arthritis

ESR1: before treatment, ESR2: after treatment. FVC1: before treatment, FVC2: after treatment

GGO: ground glass opacities. ATOLL sign: central GGO surrounded by denser consolidation of crescentic shape or complete ring of at least 2mm in thickness, reversed halo sign

Table 2. Descriptive clinical data of patients

	Minimum	Maximum	Mean	Std. Deviation
ESR1(mm/hour)	34.00	104.00	61.93	22.42
ESR2(mm/hour)	21.00	74.00	38.87	13.11
FVC1(Litr)	1.08	2.69	1.70	0.52
FVC2(Litr)	1.10	3.01	2.03	0.62
SPO_2 (1)	73.00	91.00	84.12	6.11
SPO_2 (2)	95	99	96	1.06
Duration of symptoms before (Weeks)	2.00	12.00	4.18	2.50

Table 3. ESR, FVC, and oxygen saturation in COP and SOP patients before and after treatment

Variable	COP	SOP	P – value
ESR1	68.18±22.33	48.20±17.18	0.10
ESR2	40.54±14.18	35.20±10.84	0.53
FVC1	1.89±0.50	1.28±0.23	0.027
FVC2	2.28±0.57	1.49±0.28	0.027
SPO_2 (1)	86.36±4.98	79.2±5.84	0.016
SPO_2 (2)	97.07±1.04	96±0.7	0.056
Duration (Weeks)	3.9±1.22	4.8±4.38	0.56

Table 4. ESR, FVC, and oxygen saturation in patients before and after treatment

Variable	Before treatment	After treatment	r*	P – value
ESR	61.93 ± 22.42	38.87 ± 13.11	0.848	0.000
FVC	1.70 ± 0.52	2.03 ± 0.62	0.967	0.000
SPO_2	84.12 ± 6.11	96 ± 1.06	0.691	0.003

*Correlation

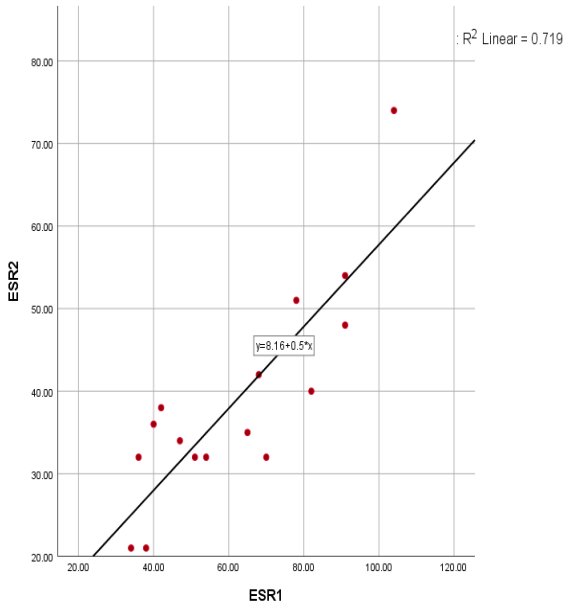

Figure 1. Scatter plot chart of the correlation between ESR 1 & ESR 2

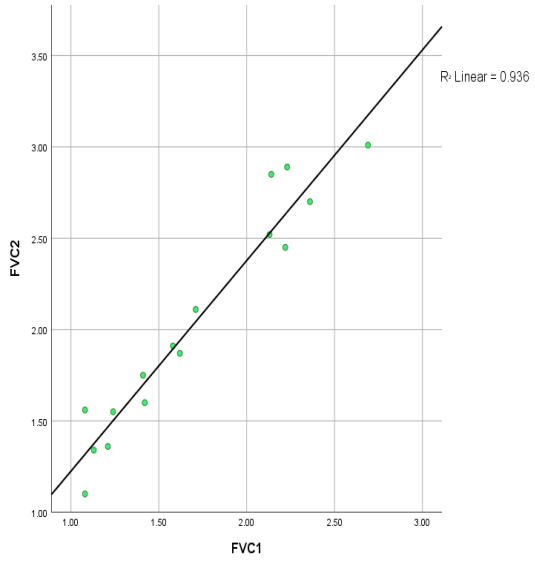

Figure 2. Scatter plot chart of the correlation between FVC 1 & FVC 2

An ANCOVA was performed to examine the mean differences in post-intervention ESR and FVC concentration among males and females after adjusting for ESR and FVC before treatment. The results indicated that the post-intervention ESR and FVC did not significantly differ among the two groups after controlling for gender (P>0.05) (Figure 3, 4). Also, post-treatment ESR and FVC did not significantly differ after controlling for the pneumonia type (P>0.05)

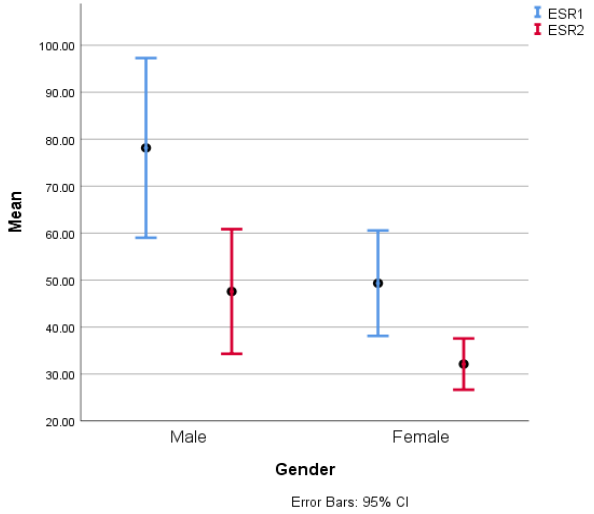

Figure 3. Comparison of ESR 1 & ESR 2 in each gender

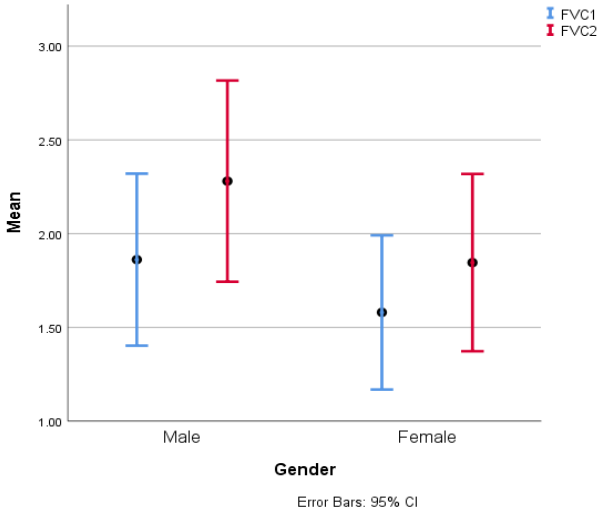

Figure 4. Comparison of FVC 1 & FVC 2 in each gender

DISCUSSION

In this study, we prospectively examined the course of the disease and the response to treatment in a group of patients with a primary diagnosis of cryptogenic organizing pneumonia (COP). The diagnosis of COP was made based on a histopathology study of lung biopsy in patients whose pulmonary symptoms and chest imaging were compatible with COP and had no secondary cause for organizing pneumonia at the time of the first presentation of the respiratory symptoms.

The results of our study showed a significant increase in FVC and a significant decrease in patients' ESR during

the 6-month follow-up period which can be a sign of appropriate response to treatment. In a study in India, Sen and Udwadia reported a clinical profile of 34 cases of hospitalized COP. The response rate to corticosteroid therapy in patients was reported to be about 79%. One of the possible reasons for not responding to treatment is the late diagnosis of the disease and delay in the onset of treatment with corticosteroids (7).

In our study, the recurrence rate was zero within 3 years from primary diagnosis and standard treatment. In the study of Zhou et al., the disease course of seventy-three patients with a primary diagnosis of COP was evaluated; the relapse rate was 31.5%. They showed increasing CRP and decreasing DLCO were associated with COP recurrence (8). Extensive pulmonary involvement as consolidation of more than 10% of lung parenchyma and the presence of bronchiectasis were reported to be associated with more COP recurrence after treatment; patients with connective tissue disease-op (CTD-OP) had a higher risk of recurrence than COP patients (9). A retrospective study in 2019 examined factors associated with COP recurrence after treatment and showed some early patterns of pulmonary involvement such as bilateral lung involvement and traction bronchiectasis may predict future COP recurrence (10). In a study by Niksarlıoğlu et al. (11), the medical records of seventeen patients with a confirmed pathological diagnosis of COP were reviewed. CT scan findings, early signs, response to treatment, and follow-up of patients were evaluated. The most common radiological finding was lower lobe consolidation. The discrepancy between the relapse rate in our study and previous studies might be justified by early diagnosis, treatment, and regular follow-up. In addition, none of our patients had extensive consolidation or traction bronchiectasis. However, the small number of patients was a great limitation in our study.

During the follow-up period, two patients showed joint symptoms and were diagnosed with RA. Also, one patient was diagnosed with lymphoma, one with MCTD, and one with giant cell arthritis (GCA). There are reports that some cases of patients who were initially treated as COP were eventually diagnosed with secondary OP (8). Rheumatoid arthritis, lupus, Sjogren, and even scleroderma were reported as the ultimate diagnosis (12). This may indicate that some cases that are initially treated with a COP diagnosis will, over time, be diagnosed as secondary OP, which raises the need for careful examination and follow-up.

The ultimate diagnosis in one of our patients was GCA. Organizing pneumonia has been reported in vasculitis syndrome such as Behçet's disease and granulomatosis with angiitis but it was not reported as the initial manifestation of GCA (13,14). In a study conducted by Baha et al. (15), it was shown that there is no significant difference between the general radiological findings of COP and SOP patients. In our study, comparing the data between patients in the secondary OP group with patients in the COP group, it was shown that there is a significant relationship between the primary radiological findings on chest CT scans of patients at the time of the first presentation of the disease and their final diagnosis. ATOLL sign pattern was detected in 72.7% of COP patients, but 60% of SOP patients had a GGO pattern on their primary chest CT scan. The association between the initial pattern of CT scans and the final diagnosis of patients was significant. It should be considered in future studies with higher sample sizes in such patients.

Also, in the statistical analysis between the COP and OP groups, it was shown that COP patients had higher FVC and SPO_2 at the time of diagnosis, and the rate of increase in FVC and SpO_2 was higher than patients in the SOP group following treatment with corticosteroid. It should be noted that although both groups of COP and OP patients responded to corticosteroid therapy, this response was more significant among the COP group. It is important to know that the lower response to treatment regarding FVC and SpO2 may be used as an index for the possibility of secondary causes of organizing pneumonia; although, accurate knowledge of this relationship requires studies with larger sample sizes.

During the follow-up period, one of the patients who initially had type 2 diabetes developed fungal otitis, which may indicate side effects of corticosteroid therapy, especially in diabetic patients. Given that the dose of corticosteroid given to all patients was the same in this study, this can be challenging. So, the question is whether the dose and duration of corticosteroids can be reduced in some patients who are at higher risk for corticosteroid complications without increasing the risk of COP recurrence. To answer this question, more studies with larger sample sizes are needed.

Limitations

The present study had two major limitations. First, the sample size is too small to enable us to draw definitive conclusions. Second, parameters such as drug histories, and rheumatological blood tests like Rheumatoid Factor (RF) and Anti-cyclic citrullinated peptides (anti-CCP) were not assessed in this study. It is recommended to be considered in the future research.

CONCLUSION

Even though the majority of COP cases have been diagnosed late, standard treatment according to British Thoracic Society guidelines appears to be effective in preventing recurrence. Appropriate treatment can lead to optimized oxygenation parameters and a decreased inflammatory index. The FVC (functional residual capacity) and SpO_2 were higher in the COP group at the first presentation of the disease and had more increase after corticosteroid treatment in comparison to secondary OP group patients. Lower response to treatment (with FVC and Spo_2 parameter) among corticosteroid-treated COP may suggest secondary causes of organizing pneumonia, especially RA and other rheumatologic disorders. Reversed halo sign (ATOLL) and GGO are the most common radiological findings in COP patients. ATOLL sign is the most common radiological finding in COP patients and GGO is more common in patients who are finally diagnosed as a secondary OP at their follow-up period. Throughout the treatment with corticosteroids, patients should be screened for complications like diabetes and opportunistic infections.

Highlight of the study

- 6-month corticosteroid treatment is effective in patients with a primary COP diagnosis and can prevent relapse of the disease in follow-up.
- Some patients who were primarily diagnosed as COPs (cryptogenic organizing pneumonia) presented signs and symptoms of underlying hematological and rheumatologic diseases at the time of follow-up.
- Secondary causes of organizing pneumonia (secondary organizing pneumonia) should be considered in the follow-up of patients with a primary diagnosis of COP.
- It is proposed that a lower level of FVC at the first presentation of the organizing pneumonia disease and after treatment in comparison to other patients (who remained as COPs) can lead physicians to reevaluate patients with a primary diagnosis of COP for secondary causes of OP, particularly hematological disease, and rheumatoid arthritis.

Conflict of interest

There is no conflict of interest to declare.

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