RESEARCH ARTICLE

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Evaluation of Patients with Organizing Pneumonia in the Post-COVİD-19 Period

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Objective: This study aimed to retrospectively evaluate the cases of healthy adults, diagnosed with histologically confirmed organizing pneumonia and had shortness of breath and fatigue persist for at least three months in the post-COVID-19 period.

Materials and Methods: Seventeen patients admitted to our hospital with shortness of breath and fatigue complaints between September 2020 and May 2021 were diagnosed with SARS-CoV-2 infection at least three months before the last admission and diagnosed with organizing pneumonia confirmed both radiologically and pathologically were included.

Results: All of the patients were previously hospitalized due to COVID-19. The median time elapsed between the diagnosis of COVID-19 and recurrent hospitalization due to organizing pneumonia was four months. Our patients had bilateral lobular; subpleural densities vary from ground glass to the middle/lower lung consolidation, which is the typical radiological feature of organizing pneumonia. Partial lobular excision of the lung was performed in all patients. İntra-alveolar exudate, characterized by granulation tissue and fibroblast proliferation in the lung parenchyma, was detected in all patients.

Conclusion: We believe that secondary organizing pneumonia should be considered among patients with COVID-19 pneumonia, especially in the case of persistent or recurrent respiratory symptoms and ongoing lung infiltrates. Thus, it will be possible to provide the proper medical approaches instead of unnecessary surgical intervention.

Key Words: *Post-COVID-19 period, organizing pneumonia, interstitial lung disease*

Post COVID-19 Sürecinde Organize Pnömoni Hastalarının Değerlendirilmesi

Amaç: Bu çalışmada, COVID-19 sonrası dönemde histolojik olarak doğrulanmış organize pnömoni tanısı alan, nefes darlığı ve yorgunluğu en az üç aydır devam eden sağlıklı erişkin olguların geriye dönük olarak değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Eylül 2020-Mayıs 2021 tarihleri arasında nefes darlığı ve halsizlik şikayetleri ile hastanemize başvuran, son başvuru tarihinden en az üç ay önce SARS-CoV-2 enfeksiyonu tanısı alan ve hem radyolojik hem de patolojik olarak organize pnömoni tanısı konan 17 hasta dahil edildi.

Bulgular: Hastaların tamamı daha önce COVID-19 nedeniyle hospitalize edilmişdi. COVID-19 tanısı ve organize pnömoni nedeniyle tekrar hastaneye yatış arasında geçen ortalama süre 4 aydı. Hastalarımızda organize pnömoninin tipik radyolojik özelliği olan buzlu camdan orta/alt akciğer konsolidasyonuna kadar değişen bilateral lobüler, subplevral dansite varlığı mevcuttu. Tüm hastalara akciğer parsiyel lobüler eksizyon işlemi uygulandı. Hastaların tamamında akciğer parankiminde granülasyon dokusu ve fibroblast proliferasyonu ile karakterize intraalveolar eksüda tespit edildi.

Sonuç: COVID-19 pnömonisi olan hastalarda, özellikle kalıcı veya tekrarlayan solunum semptomları ve devam eden akciğer infiltrate varlığında ikincil seconder organize pnömoninin düşünülmesi gerektiğine inanıyoruz. Böylece gereksiz cerrahi müdahaleler yerine doğru medikal yaklaşımların sağlanması mümkün olacaktır.

Anahtar Kelimeler**:** *COVID-19 sonrası dönem, organize pnömoni, interstisyel akciğer hastalığı*

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Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), leading to an ongoing global pandemic. COVID-19 results in respiratory tract infection symptoms in most cases and may cause clinical presentations ranging from self-limited upper respiratory tract infection to acute respiratory failure (1, 2). It is known that 143 million people were infected with the SARS-CoV-2 virus, and 3 million patients have died so far during the COVID-19 outbreak that started in late 2019 (3).

In some patients, symptoms of COVID-19 may last longer than five weeks. However, the predictors of the severity and course of COVID-19 are still not fully understood. Today, the definition of prolonged COVID-19 has not been clearly described. However, according to the guidelines on managing the long-term of COVID-19, the course of COVID-19 is divided into three periods: An acute period with signs

and symptoms lasting up to 4 weeks; an ongoing symptomatic period during which signs and symptoms of COVID-19 last 4 to 12 weeks; and post-COVID-19 period with signs and symptoms lasting longer than 12 weeks and cannot be associated with alternative diagnoses. It is emphasized in the guideline that attention should be paid primarily in the presence of new or worsening symptoms that persist for more than four weeks (4). As the COVID-19 disease continues to spread worldwide, numerous medical articles are being published as a part of scientific efforts to characterize, treat and prevent the disease current COVID-19 guidelines cover acute disease management, preventive measures, and vaccination. Limited information is available for dealing with persistent symptoms after COVID-19 (5, 6). However, the medium and long-term clinical consequences of COVID-19 infections have not yet been elucidated.

The most common lung computed tomography (CT) finding in COVID-19 patients is the image of ground-glass opacity, which may be accompanied by consolidating abnormalities consistent with viral pneumonia. In addition, the pattern of organizing pneumonia (OP) on lung CT scans has been reported mainly as a late-phase complication (7-9). Findings in subacute and chronic inflammation of the pulmonary parenchyma range from bronchiolitis obliterans with organizing pneumonia (BOOP) to extensive interstitial fibrosis. Since the BOOP pattern is highly non-specific and represents a typical tissue response to various stimuli, it is recommended to use organized pneumonia instead. Secondary organizing pneumonia (SOP) is a rare form of interstitial lung disease (ILD) called OP. OP, chronic lung injury, tissue response, is characterized by plugs of granulation tissue located in the lumens of the small airways and extending into the alveolar ducts and alveoli. These plugs consist of inflammatory cells, small vessels, and fibroblasts embedded in the myxoid matrix. Fibrous polypoid masses rising from the alveolar walls to adjacent air spaces fill the alveolar lumens. They are defined as intra-alveolar organized exudate consisting of myofibroblasts and connective tissue with interstitial inflammation. Viral infections are among the most common etiologies of SOP. In particular, there is a strong correlation between SOP and various conditions, including adenovirus, cytomegalovirus, herpes virus, human immunodeficiency virus, parainfluenza virus, and influenza virus (10). In addition, viruses that caused global epidemics, such as SARS, MERS, and influenza A in the previous years, have also been reported to cause SOP (11-14).

Although the relationship between COVID-19 pneumonia and SOP is limited to a few case reports, the similarities between these two entities are increasingly being investigated (15, 16).

Histopathology publications on COVID-19 are not at the forefront of clinical and imaging studies. Histological studies are often limited to autopsy reports of patients who died from COVID-19 infection (17).

This study aimed to retrospectively evaluate the cases of healthy adults diagnosed with histologically confirmed organizing pneumonia and had shortness of breath and fatigue persist for at least three months in the post-COVID-19 period.

Materials and Methods

Research and Publication Ethics: The procedures and retrospective study was carried out by the principles of the Declaration of Helsinki. The research was first registered in the data of the Turkish Health Ministry Scientific Research Committee, and then the protocol was approved by the Institutional Review Committee of Firat University (22.11.2021 - 5180).

Study Design, Participants, and Data Collection: Patients admitted to our hospital with complaints of shortness of breath and fatigue between September 2020 and May 2021 who were diagnosed with SARS-CoV-2 infection confirmed by real-time PCR at least three months before the last admission and diagnosed with organizing pneumonia confirmed both radiological and pathologically with lung partial lobular excision material were included in this retrospective study. The diagnosis of COVID-19 infection was made by real-time RT-PCR test positivity of nasopharyngeal swab samples. Demographic characteristics, medical history, laboratory, radiological and pathological findings of the cases were obtained retrospectively from electronic medical records.

Cases under 18 years of age, with clinical findings and/or pneumonia findings consistent with COVID-19 on Thorax CT, but negative RT-PCR test, and comorbidities such as any rheumatological disease or malignancy, or chronic drug use were excluded from the study.

Statistical Analysis: Data analysis was performed with SPSS 22 software (SPSS, Inc., Chicago, Illinois). The normal distribution of the variables was tested using visual methods (histograms, probability plots) and analytical methods (Shapiro-Wilk's test). For continuous variables with normal distribution, mean±standard deviation (SD) were provided, whereas those without normal distribution were expressed using median [interquartile range (IQR)]. Categorical variables were expressed as counts and percentages.

Results

Seventeen patients were included in the study. 16 (94.1%) of the patients were male. The mean age of the patients included in the study was 38 (±13.8), the minimum age was 21, the maximum age was 72, and the median age was 36. The cases were mostly in the 20-29 and 40-49 age groups. Age and gender distributions of the cases are given in Table 1. While 1 (5.8%) of the patients had asthma, 2 (11.7%) had a history of atelectasis, and only 1 (5.8%) male patient had a history of smoking. Other patients did not have any

comorbidity. All of the patients were previously hospitalized due to COVID-19. The time elapsed between the diagnosis of COVID-19 and hospitalization due to organizing pneumonia was four months, ranging from 3 months to 7 months. While all patients had fatigue and shortness of breath at admission, 5 (29.4%) had a high fever, and 2 (11.7%) coughed. The laboratory values were as follows: white blood cell count 10760 (min 5080-max 16200), lymphocyte count 1520 (min 850 – max 3160), erythrocyte sedimentation rate (ESH) 54 (min 19-max 98), and C-reactive protein (CRP) 43 (min 3 -max 82). The leukocyte count was >10.000/mm^3 in 11 (64.7%) of patient, whereas ESR was >20 mm/hr in 14 (82.3%) and CRP was >3 in 16 (94.1%) cases.

Table 1. Age and gender distribution of the cases

Age (year)	Female n (%)	Male n (%)	Total n (%)
20–29	0	6 (35.2%)	6 (35.2%)
30-39	0	3 (17.6%)	3 (17.6%)
40-49	0	5 (29.4%)	5 (29.4%)
50-59	1 (5.8%)	1 (5.8%)	2 (11.7%)
≥ 60	0	1 (5.8%)	1 (5.8%)
Total n (%)	1 (5.8%)	16 (94.1%)	17 (100%)

Our patients had bilateral lobular, sub-pleural densities varying from ground the ass to consolidation of the middle/lower lung, which is the typical radiological feature of OP (18). Consolidation was found in 12 (70.5%) patients, and the patient distribution according to their lung CT findings is given in Table 2.

Partial lobular excision of the lung was performed in all patients. Intraalveolar exudate with interstitial inflammation, characterized by granulation tissue and fibroblast proliferation in the lung parenchyma, was detected in all patients (Figure 1, 2).

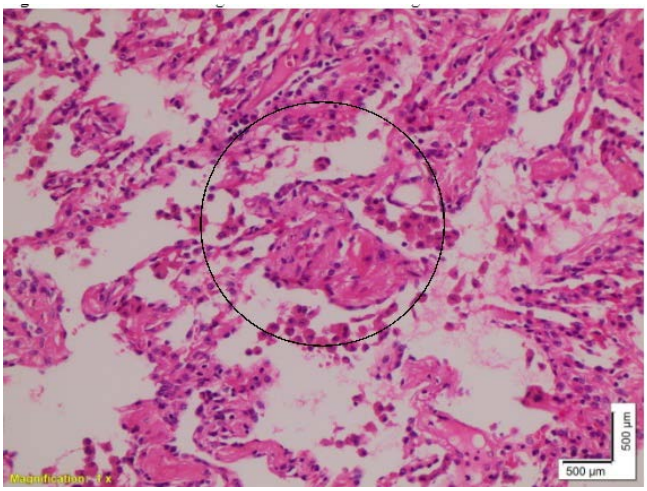

Figure 1. Alveolar duct and granulation tissue extending into alveoli

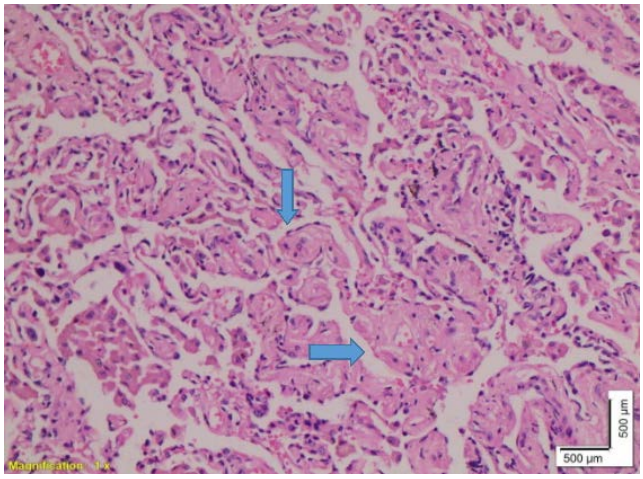

Figure 2. Fibrous plugs filling the alveoli

Table 2. Lung computed tomography findings of the cases

Distribution	Secondary organizing pneumonia n (%)
Upper zone	2 (11.7%)
Middle zone	9 (52.9%)
Lower zone	14 (82.3%)
Peripheral Distribution	15 (88.2%)
Bilateral	11 (64.7%)

Discussion

Viral pneumonia findings may develop in the course of COVID-19 disease (19). Radiological changes are expected to peak approximately ten days after symptoms and then regress (20-22). In some cases, however, ground-glass opacities gradually transform into multifocal consolidation with septal thickening from the onset of symptoms (23-25). This case indicates progression to organizing pneumonia, a typical response to lung injury (18). However, the SOP pattern has been reported mainly as a late-phase complication (8). In our study, all patients were diagnosed in the post-COVID-19 period, consistent with the literature.

Baha and Yildirim. (26) have found the mean age at OP diagnosis was 57.0+/-12.6, and the male gender was predominant. The most common symptoms were cough (71.4%), dyspnea (66.1%), and fatigue (64.3%), and dyspnea has been reported to last from 10 days to 2 years. In another study (27), the mean age at presentation was 60.46±13.57, and fatigue, cough, fever, and dyspnea were the most common symptoms. In the present study, most of the patients were in the 20-29 and 40-49 age groups, and the mean age was 38 (±13.8). These results were consistent with the age range reported by Fang et al. (28) in a study investigating COVID-19 patients with secondary OP. Our study also showed that OP was more common in males, the most common symptoms were fatigue, shortness of breath, and other symptoms included high fever and cough.

Some of the most common causes of secondary OP are medications, infections, rheumatological diseases, and malignancies. In a study, the most common causes of SOP were rheumatological diseases and malignancies (26). In another study (29), the most common cause of SOP was infection. In this study, SOP developed after the COVID-19 infection in all patients.

Many studies have unexplained the relationship between smoking and OP (26, 27, 29). Lazor et al. (30) have found that 71% of OP patients were non-smokers, and most of them were female. Only one male patient who had a smoking history in our study is compatible with this outcome.

Similar to our study, in studies evaluating the laboratory parameters of organizing pneumonia patients, the presence of high CRP and ESR are noteworthy. However, the reasons for these higher values have not been clarified (31-33). CRP synthesis from hepatocytes during inflammation increases with the influence of cytokines such as interleukin 6 (34). In the presence of OP, it has been shown that there is an increase in inflammatory cytokines (35). In addition, considering the role of acute inflammation in the etiology of SOP, increased acute phase reactants can be expected.

The most common radiological findings in patients with organizing pneumonia are consolidation and ground-glass opacities, with often bilateral-peripheral involvement. It has also been shown that the lower lung zones are more affected (36). Another study showed that middle zone involvement is prevalent (37). Our findings were consistent with the literature and showed that the predominant involvement of the lung's lower zone and the central location was detected, respectively.

Histopathological examination is the most valid method to diagnose organizing pneumonia (38). However, OP can be analyzed in appropriate clinical and radiographic findings (36). Cazzato et al. (39) have found that clinical and radiological findings usually support the diagnosis, but definitive confirmation requires histopathological examination in the diagnostic approach of patients with OP. In our study, the diagnosis was made by histopathological evaluation of all patients.

This is the first study to show the relationship between COVID-19 and SOP in a case series to the best of our knowledge. However, the study has some limitations. Our results need to be supported by well-designed, large-scale studies to determine the association between SOP and COVID-19 disease. In addition, the retrospective nature of the research and the relatively small sample size are among the limitations of the present study.

In conclusion, COVID-19 is a novel infection with severe medical conditions that have affected people worldwide for almost two years. Organizing pneumonia seen after COVID-19 pneumonia is one of the leading causes of lung injury manifested by different interstitial changes seen on CT scans. Despite few case reports to date, it has been suggested that OP is much more common in COVID-19 infection. In the light of all these findings, secondary OP, which represents an immunological process, should be considered among patients with COVID-19 pneumonia and should be evaluated to detect lung damage in the early period, especially in the case of persistent or recurrent respiratory symptoms and ongoing lung infiltrate. This study will increase clinicians' awareness of OP in the post-COVID period, resulting in reduced need for invasive mechanical ventilators and unnecessary antibiotic use and improved overall survival by enabling early diagnosis and treatment of the disease.

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Conflicts of interest: The authors have no conflicts of interest to declare

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