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A Case of Idiopathic Pulmonary Fibrosis Diagnosed with Progression Post-COVID-19 Pneumonia

COVİD-19 Pnömonisi Sonrası Progresyon ile Tanı Alan İdiopatik Pulmoner Fibrozis Olgusu

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Abstract

A chest tomography taken after COVID-19 revealed bilateral fibrotic foci areas, and two months later it was seen that they had been precursors to honeycomb lesions, and that the usual interstitial pneumonia (UIP) pattern associated with post-COVID pneumonia had occurred. It was noted that the fibrotic lesions in the left lung were already present before the disease. The lesions present in the patient, who had dyspnea pre-COVID-19 but had not been diagnosed with ILD, were considered to be UIP precursor lesions that progressed with the increase in fibroblast activity and the triggering of fibrotic pathways in the course of the disease. The patient was thus diagnosed with Idiopathic Pulmonary Fibrosis (IPF). We suggest that if a UIP appearance develops in COVID-19 patients with progressive fibrosis that is not relieved by anti-inflammatory treatments in long-term examinations, the possibility of IPF should be considered, and so the clinical and radiological findings of patients' pre-COVID-19 should be investigated for the early identification of IPF.

Key words: *IPF, COVID, fibrosis.*

Öz

Hastanın COVİD-19 geçirdikten sonraki akciğer tomografisinde bilateral fibrotik odaklar mevcuttu. İki ay sonraki başvurusu tomografisi ile karşılaştırıldığında fibrotik odakların bal peteği lezyonların öncülü olduğu ve COVİD pnömonisi sonrası olağan interstisyel pnömoni (UİP) paterninin meydana geldiği görüldü. COVİD-19 öncesi dispnesi olan ancak interstisyel akciğer hastalığı tanısı almayan hastada mevcut lezyonların UİP öncü lezyonları olduğu ve hastalık döneminde fibroblast aktivitesinin artışı ve fibrotik yolakların tetiklenmesi ile beraber progresyon gösterdiği düşünüldü. Hasta idiopatik pulmoner fibrozis (IPF) olgusu olarak değerlendirildi. Uzun dönem kontrollerde antiinflamatuvar tedaviler ile rahatlamayan ilerleyici fibrozis saptanan COVİD-19 hastalarında eğer UIP görünümü gelişmiş ise mutlaka İPF olasılığının düşünülmesini ve bu yönü ile hastaların COVİD-19 öncesi klinik ve radyolojik bulgularının erken IPF açısından araştırılmasını öneriyoruz.

Anahtar Sözcükler: *IPF, COVİD, fibrozis.*

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ILD (Interstitial Lung Disease) is an accepted risk factor for COVID-19 (1,2). In patients whose lesions do not regress on chest radiography after the acute phase of COVID-19 disease and whose symptoms continue, the possibility of interstitial lung disease that occurred before or after the onset of COVID-19 should also be considered (3).

CASE

A 60-year-old male patient with hypertension presented to the thoracic diseases clinic with dyspnea a year prior to admission. After a detailed medical history was taken, it was understood that the complaints had increased after the patient had contracted COVID pneumonia five months earlier. A physical examination revealed bruit in the basal parts of both lungs. Room air saturation was 97%, and the patient covered 408 meters in a six-minute walk test, after which his saturation was 83%. No pulmonary function test could be performed due to the risk of transmission during the pandemic period.

On the chest radiography shown in Figure 1, distinct increases in peripheric density were observed in the lower left zone. On the thorax tomography shown in Figure 2, intralobular and interlobular septal thickening on lower lobes and subpleural area, traction bronchiectasis, ground glass infiltrations and honeycomb appearances on lower lobes can be clearly observed.

Mixed alveolitis was detected on bronchoalveolar lavage (53% alveolar macrophages, 19% polymorphonuclear leukocytes, 17% eosinophils leukocytes, 11% lymphocytes). Lung involvement associated with collagen tissue disease was not considered based on the findings of an examination and clinical results. The patient's long-term medication (atorvastatin and acetylsalicylic acid) was causing pneumonitis, and so the medication was revised considering medication-related lung damage. Subsequently, treatment of 0.5 mg/kg/day oral methylprednisolone + methotrexate 15 mg/week was decided upon under observation, and the methylprednisolone dosage was decreased gradually.

An examination 6 months after the revision to the medication revealed clinical and radiological progression. Upon starting the oral methylprednisolone treatment, the ground glass appearances noted previously on the lower lobes disappeared, the honeycomb appearance increased and fibrotic progression was noted, as shown in Figure 3.

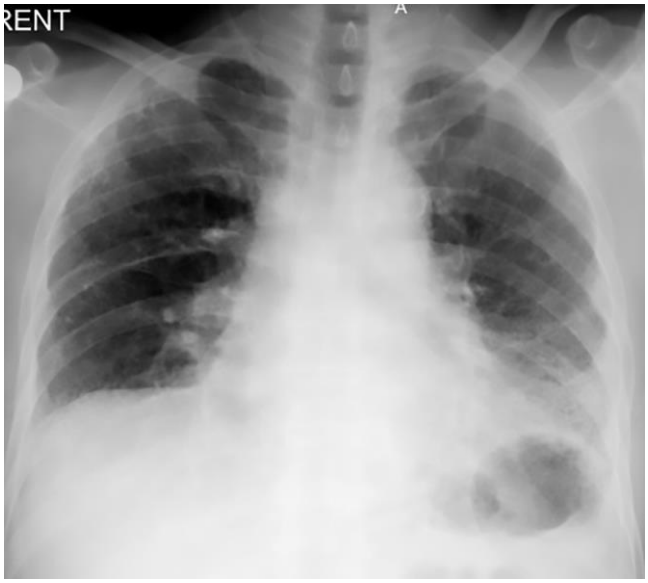

Figure 1: Admission Posteroanterior Chest Radiography

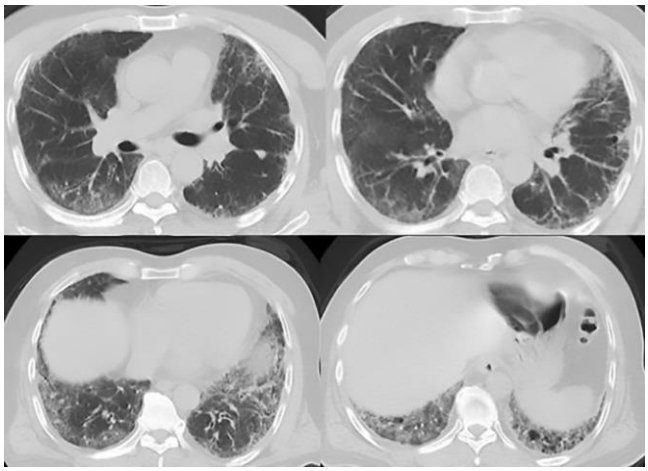

Figure 2: Admission thorax CT scan

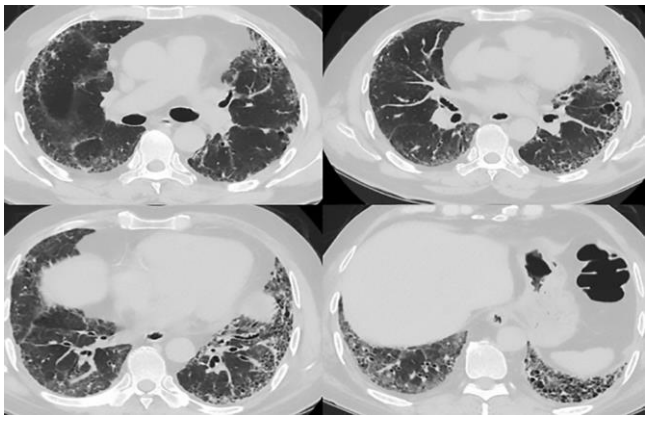

Figure 3: Thorax CT scan after medication revision

Table 1: Fibrogenic mechanisms associated with viral infection (15)

Mechanism	Summary
Viral activation of profibrotic pathways	*Altered renin-angiotensin system balance inhibition of host translation and altered cell cycle *Activation of growth factors (e.g., FGF, EGF and TGFβ) *Cytoskeletal rearrangement
Direct cellular injury	*Type II alveolar epithelial cells *Macrophages *Endothelial cells
Cytokine-induced injury	*Acute respiratory distress syndrome *Immune recruitment Neutrophil reactive oxygen species Macrophage exosomes *Aberrant wound-healing response
Mechanical injury	*Volutruma/atelectrouma *Barotrouma *Biotrouma
Age	*Altered cellular communication *Stem cell exhaustion *Extracellular matrix dysregulation

EGF, epidermal growth factor; FGF, fibroblast growth factor; TGF-β, transforming growth factor-β

The causes of progression after medication revision and treatment were questioned. The external center examinations of the patient who had a history of COVID-19 were analyzed, and a lung tomography (Figure 4) taken as a result of palpitation complaints 25 days after a positive PCR showed areas compatible with subacute COVID pneumonia and more prominent bilateral fibrotic foci in the left lung posterolateral. Compared with the tomography at the time of admission 2 months later, it was seen that the fibrotic foci were the precursors of honeycomb lesions, and the usual interstitial pneumonia pattern post-COVID pneumonia had developed. Although fibrosis is expected, as the UIP pattern is not an expected radiological appearance in the long-term post-COVID, lung roentgenograms taken before the diagnosis of COVID were examined, as shown in Figure 5, and it was observed that fibrotic lesions in the basal areas of the left lung had been present before disease onset. It was thus considered that the lesions present in the patient, who had complained of shortness of breath pre-COVID-19 but was not diagnosed with ILD, were UIP precursor lesions that had progressed with the increase in fibroblast activity and the triggering of fibrotic pathways during the course of the disease.

After additional triggering pathologies were eliminated as a potential cause, the patient was evaluated as a case of idiopathic pulmonary fibrosis diagnosed as a fibrotic process after COVID pneumonia, and was started on antifibrotic treatment.

DISCUSSION

In the radiological course of the acute phase of COVID pneumonia, the most common tomographic findings are bilateral subpleural ground glass appearances and consolidation in the inferior zones (4,5). Edema, organizing pneumonia and diffuse alveolar damage are the underlying causes of radiological findings (6,7). Approximately 7 to 10 days after the onset of symptoms, tomographic findings may appear as cobblestones that fade gradually after two weeks. In some patients, however, fibrotic streaks and bronchiectasis can be seen even on early tomography scans (8-10). It can be hypothesized that the duration of lung lesions and whether they will be permanent are related to the severity and risk factors of COVID-19 pneumonia in the acute period (11).

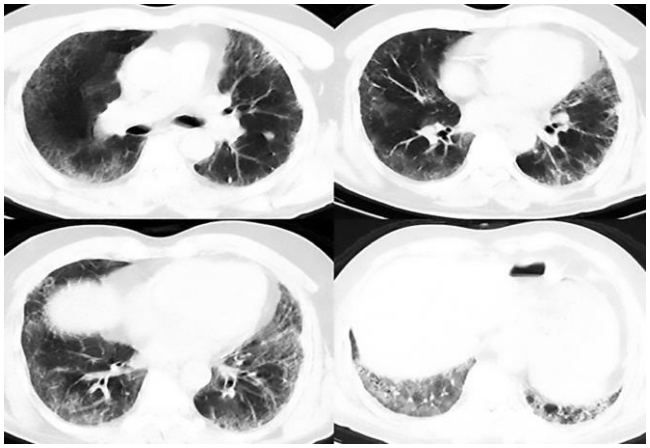

Figure 4: COVID period thorax CT scan

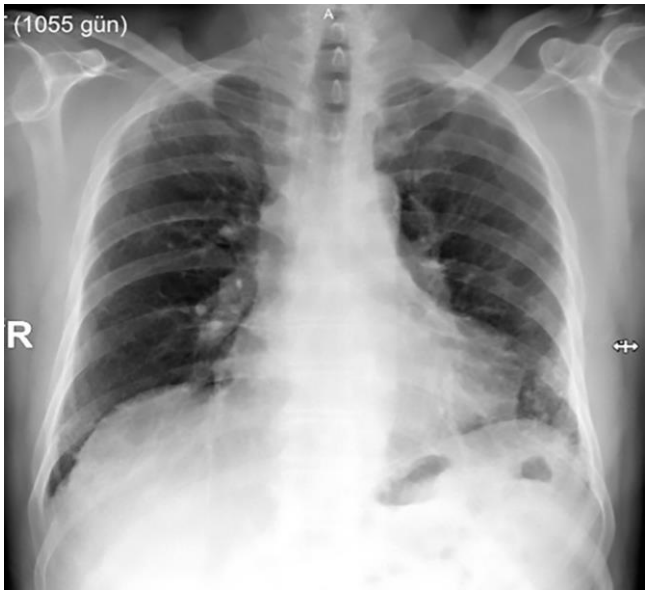

Figure 5: Pre-COVID posteroanterior roentgenogram

Fibrosis is a common outcome of chronic inflammatory diseases. In response to tissue damage, fibroblasts, mesenchymal cells and myofibroblasts can initiate wound healing and the restoration of tissue integrity. This profibrotic process generally ends with the tissue healing, although a recurring damage-repair cycle can lead to lead instability in this process and can cause a pathological accumulation of extracellular matrix protein. This is accompanied by increased myofibroblast activity, the release of proinflammatory and profibrotic cytokines and the activation of fibrosis-related pathways (12). Although potential mechanisms explaining the development of pulmonary fibrosis secondary to COVID-19 have not yet to come to light, prolonged exposure to high-flow oxygen in the treatment of respiratory failure in addition to these pathways may cause oxidative stress and contribute to the development of fibrosis (13,14). The known fibrosis mechanisms associated with viral infections are summarized in Table 1.

IPF-like radiological findings can be seen in long-term COVID-19 pneumonia, and comorbidities such as hypertension and diabetes, male sex, smoking and advanced age are common risk factors for severe COVID-19 and IPF (15). In COVID-19, unlike IPF, the cause of lung fibrosis is viral pneumonia and ARDS in which intense inflammation plays a role. Fibrosis in IPF, on the other hand, occurs as a result of chronic damage to the alveolar epithelium, and the abnormal and exaggerated response to the repair of this damage.

Repetitive micro-damages that cause an aging of the alveolar epithelium play a fundamental role in the development of the disease. Fibroblast hyperplasia and extracellular matrix deposition can be observed as a result of the imbalance between fibrotic and antifibrotic mediators. Honeycomb cysts form after progressive lung remodeling. The fibrosis seen in IPF is cell-poor, diffuse, irreversible and progressive (16). The use of antifibrotic drugs in treatment aim to slow the progression of the disease. In the explanted lungs of patients who underwent lung transplantation due to COVID-19, the main pathological characteristics identified were more severe injury with pulmonary fibrosis, acute interstitial pneumonia, organizing pneumonia, micro-thrombosis, alveolar hemorrhage, and acute bronchopneumonia resulting from secondary bacterial infection (17,18). No progressive widespread fibrosis is expected with COVID-19, as in IPF, where there may be limited squeal lesions, and so honeycomb and usual interstitial pneumonia appearances are not expected findings.

CONCLUSION

IPF is a disease that is usually diagnosed late, contributing to a high mortality rate. IPF should be considered in cases where a UIP appearance develops in COVID-19 patients with progressive fibrosis that is not relieved by anti-inflammatory treatments in long-term examinations. Accordingly, any available clinical and radiological findings of patients' pre-COVID-19 should be investigated for early IPF. COVID-19 pneumonia may accelerate the fibrotic process in early-stage IPF cases, however, a diagnosis of IPF may be masked as it may be confused with post-COVID-19 pulmonary fibrosis.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - T.Ö., A.P.; Planning and Design - T.Ö., A.P.; Supervision - T.Ö., A.P.; Funding - A.P.; Materials - T.Ö.; Data Collection and/or Processing - A.P.; Analysis and/or Interpretation - T.Ö., A.P.; Literature Review - A.P.; Writing - A.P.; Critical Review - A.P.

YAZAR KATKILARI

Fikir - T.Ö., A.P.; Tasarım ve Dizayn - T.Ö., A.P.; Denetleme - T.Ö., A.P.; Kaynaklar - A.P.; Malzemeler - T.Ö.; Veri Toplama ve/veya İşleme - A.P.; Analiz ve/veya Yorum - T.Ö., A.P.; Literatür Taraması - A.P.; Yazıyı Yazan - A.P.; Eleştirel İnceleme - A.P.

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