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COVID-19-Associated Diffuse Alveolar Hemorrhage: A Case Report

COVID-19'a Bağlı Diffüz Alveoler Hemoraji: Olgu Sunumu

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Abstract

Diffuse alveolar hemorrhage is a syndrome characterized by cough, hemoptysis, diffuse pulmonary infiltrates, anemia, and hypoxemic respiratory distress, and lung infections also play a role in its etiology. The restricted use of bronchoscopy in COVID-19 patients due to the risk of infection has led to the poor recognition of diffuse alveolar hemorrhage in COVID-19. We present here the case of a 35-year-old patient with laboratory, radiological and bronchoscopic evidence of diffuse alveolar hemorrhage who was diagnosed with COVID-19 by bronchial lavage. The restrictions on the use of bronchoscopy during the pandemic due to the high risk of infection has led diagnoses of COVID-19 to be mistakenly excluded in immunosuppressive patients with a negative SARS-CoV-2 polymerase chain reaction test, and the under-recognition of conditions such as diffuse alveolar hemorrhage and secondary infection in patients with a positive SARS-CoV-2 PCR.

Key words: COVID-19, Diffuse alveolar hemorrhage, ground-glass opacities.

Öz

Diffüz alveoler hemoraji, öksürük, hemoptizi, yaygın pulmoner infiltratlar, anemi ve hipoksemik solunum sıkıntısı ile karakterize bir sendromdur. Etyolojisinde akciğer enfeksiyonları da rol oynamaktadır. Enfeksiyon riski nedeniyle COVID-19 hastalarında bronkoskopi kullanımının kısıtlanması, diffüz alveoler hemorajinin COVID-19'da yeterince tanınamamasına neden olmaktadır. Burada SARS-CoV-2 bağlamında laboratuvar, radyolojik ve bronkoskopik olarak diffüz alveoler hemoraji kanıtı olan 35 yaşındaki hastada SARS-CoV-2 için nasofarengeal sürüntü polymerase chain reaction (PCR) testi negatif saptanmış, COVID-19 tanısı bronş lavajı ile konulabilmiştir. Yüksek enfeksiyon riski nedeniyle pandemi döneminde bronkoskopi kullanımının kısıtlanması, SARS-CoV-2 PCR testi negatif immünsupresif hastalarda COVID-19 tanısının yanlışlıkla dışlanmasına veya SARS-CoV-2 PCR pozitif hastalarda diffüz alveoler hemoraji ve sekonder enfeksiyon gibi durumların yeterince tanınamamasına neden olmaktadır.

Anahtar Sözcükler: *COVID-19, Diffüz alveolar hemoraji, buzlu cam opasiteler.*

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with a broad range of clinical presentations, from mild upper respiratory tract symptoms to progressive life-threatening viral pneumonia. Clinically, severely ill patients experience shortness of breath and progressive hypoxemia. Peripheral lung ground-glass opacities are observed on thorax computed tomography (CT) imaging in most patients with severe pneumonia, while acute respiratory distress syndrome (ARDS) meets the Berlin criteria. Histologically, pulmonary edema and diffuse alveolar damage are observed in patients (1). Diffuse alveolar hemorrhage (DAH) is a syndrome that is characterized by the accumulation of intra-alveolar red blood cells that originate mostly from alveolar capillaries and less frequently from precapillary arterioles or postcapillary venules. DAH is characterized by acute or subacute cough, hemoptysis, diffuse radiographic pulmonary infiltrates, anemia, and signs and symptoms of hypoxemic respiratory distress (2). We present here the case of an immunosuppressed patient with rapidly developing hypoxemic respiratory failure and evidence of DAH in the context of SARS-CoV-2.

CASE

A 35-year-old female patient with a diagnosis of Psoriatic Arthritis was taking Methotrexate and Secukinumab as treatment for her current disease. The patient, who admitted to the emergency department with complaints of malaise, myalgia and shortness of breath, was admitted to the isolation ward with a preliminary diagnosis of COVID-19 pneumonia. At the time of admission, the patient's body temperature was 36.7°, pulse 90 beats/min, respiratory rate 25 breaths/min, blood pressure 120/70 mmHg, and peripheral oxygen saturation 90% (with 15 liters of oxygen support). Laboratory parameters were hemoglobin 12.5 g/dL (12-16), leukocyte 8.25 x 103 /μL (4.5-11), Platelet 230 x 103 /μL (150-400), Lymphocyte 2.05 x 103 /μL (1-4), Eosinophil 0.024 x 103 /μL (0-1), Neutrophil/Lymphocyte ratio 2.85 , Sedimentation 71 mm/h (0-25), Monocyte 0.293 x 103 /μL (0-1), CRP (turbidimetric) 108 mg/L (0-5), Procalcitonin <0.12 μg/L (<0.12), D-Dimer 0.5 mg/L (<0.44), Prothrombin Time (PT) 11.1 seconds (10-14.5), APTT 22.8 seconds (21-35), PTZ INR 0.96 (0.8) -1.2), Ferritin 174 μg/L (4.6-204), Glomerular Filtration Rate (CKD - EPI) 60 ml/min/1.73m2 (>60), BUN 10 mg/dL (6-19), Creatinine 0.66 mg/ dL (0.50-1.2), ALT 18 U/L (0-55), AST 30 U/L (5-34), Mass CK-MB 0.3 μg/L (0-3.4) and Hs Troponin-I 3 ng/ L (<16). There was no growth in the urine culture, while in a complete urinalysis, Erythrocyte was 5 (0-8) in each field and protein was 300 mg/dL (0-30). A computed tomography (CT) of the thorax taken at the time of admission reported "the trachea and both main bronchi are open, mediastinal and hilar-located pathological lymph nodes are absent, heart size is increased, areas of dense infiltration containing air bronchograms commonly observed in both lung parenchyma are thought to be associated with diffuse alveolar hemorrhage or interstitial pneumonia". A CT image of the patient is presented in Figure 1. The patient was started on Favipiravir (1600 mg 2x1 loading dose followed by 600 mg 2x1 maintenance dose, 10 days), Ceftriaxone 1x2gr and Dexamethasone 6mg/day. The immunosuppressive drugs were discontinued by rheumatology and 2x200 mg Plaquenil was given (5 days). SARS-CoV-2 Reverse Transcriptase PCR tests performed upon admission and 24 hours after admission were both negative. During follow-up, the patient recorded a decrease in hemoglobin and an increase in oxygen demand, and so was provided breathing support with a high-flow oxygen device (FiO_2 53 / Flow 40). The steroid dose was increased to 100 mg/day and the patient was followed up in the intensive care unit (ICU). Steroid therapy at a dose of 100 mg/day was continued for 3 days, and then reduced to 1 mg/kg/day. A bronchoscopy performed due to an increase in oxygen demand after the treatment revealed abundant hemorrhagic-looking secretions from the bilateral bronchial system, and increasing amounts of hemorrhagic lavage fluid was obtained at each lavage. The patient's bronchial lavage fluid sample obtained during Fiberoptic Bronchoscopy is shown in Figure 2. A polymerase chain reaction (PCR) test for SARS-CoV-2 was performed on a sample of the patient's bronchial lavage fluid and the result was positive, while acid-fast staining was negative, a PCR test for tuberculosis was negative and no bacterial growth was observed. Reactive bronchial epithelial cells, alveolar macrophages, lymphocytes and erythrocytes can be seen in the bronchial lavage cytology (Figure 3). The patient, whose general condition improved and who had no oxygen requirement was discharged with antibiotic treatment after 15 days of hospitalization.

DISCUSSION

DAH is a severe and life-threatening syndrome with acute or subacute onset of hypoxemic respiratory failure, hemoptysis, anemia and diffuse pulmonary infiltrates (2,3). In the case presented here, acute onsets of hypoxemic res-

piratory failure, hemoptysis, anemia and diffuse pulmonary infiltrates were observed, and a hemorrhagic bronchial lavage obtained via bronchoscopy confirmed alveolar hemorrhage. The criteria for alveolar hemorrhage were thus met. Recurrent episodes of hemorrhage in DAH lead to collagen deposition and fibrosis in the small airways, and the subsequent continuation of respiratory failure in the later stages. DAH can develop due to Wegener's granulomatosis, microscopic polyangiitis, Goodpasture syndrome, connective tissue disorders, antiphospholipid antibody syndrome, infectious or toxic exposures, and neoplastic conditions (4), however, no such factors were detected in the patient, and other causes that play a role in the etiology of DAH were excluded. DAH should be differentiated from localized pulmonary hemorrhage attributable to chronic bronchitis, bronchiectasis, tumor or localized infection (2). In our case, no chronic bronchitis, bronchiectasis, tumor or localized infection were detected. Lung infections (viruses, bacteria, fungi and parasites) also play a role in its etiology (2,5,6), while pulmonary infections, especially viral diseases such as influenza A, are considered as possible triggers for DAH (7). In our case, the infectious agent SARS-CoV-2 was detected in a Reverse Transcriptase PCR test leading to a diagnosis of COVID-19 pneumonia, supported by radiological and laboratory tests. There are two reports in literature of COVID-19-associated DAH in immunosuppressed patients, similar to our case (3).

Reports of hemoptysis in patients with COVID-19 infection are rare (8). Guan et al. (9) reported hemoptysis to be a rare symptom of COVID-19, with varying rates of 0.6% in non-severe cases and 2.3% in severe cases. Diffuse alveolar damage with perivascular T-cell infiltration has been observed in autopsy studies of COVID-19 patients, along with distinctive vascular features such as severe endothelial damage associated with the presence of an intracellular virus and impaired cell membranes. Diffuse thrombosis with microangiopathy has been observed in a histological analysis of pulmonary vessels in COVID-19 patients.

Alveolar capillary microthrombi were found to be nine times more common in patients with COVID-19 than in patients with influenza. In lung samples from COVID-19 patients, neovascular growth was observed to be 2.7 times greater than in patients with influenza, predominantly through an intussusceptive angiogenesis mechanism. These findings suggest that SARS-CoV-2 infection causes pulmonary endothelitis, leading to thrombotic microangiopathy, and in turn causing DAH (1).

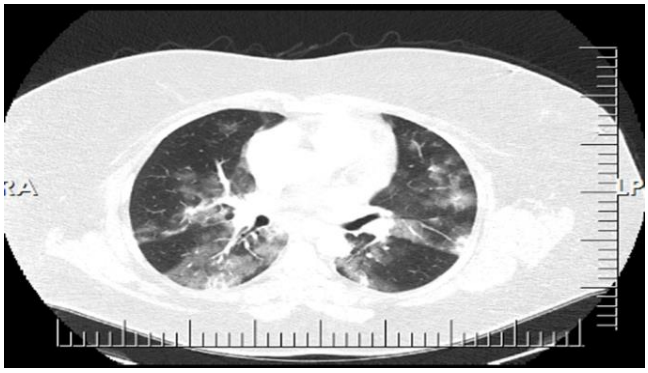

Figure 1: *The patient's Computed Tomography image*

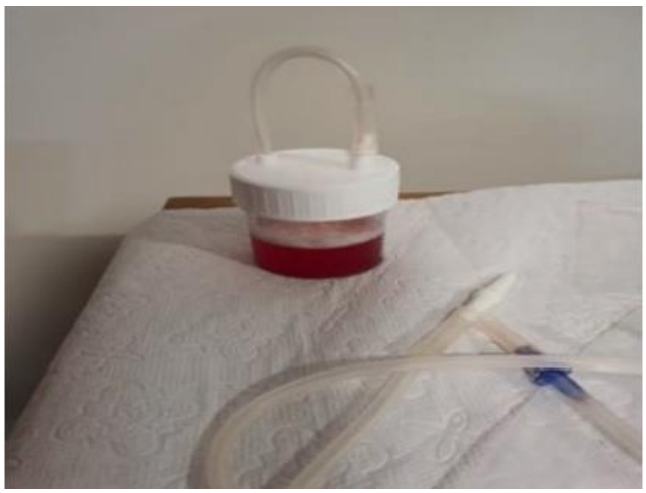

Figure 2: *The patient's bronchial lavage fluid sample obtained through fiberoptic bronchoscopy*

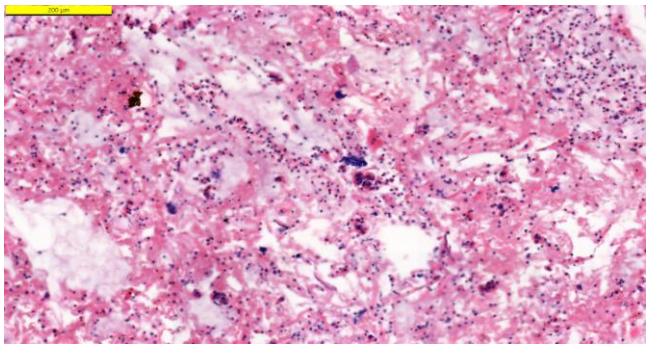

Figure 3: *Reactive bronchial epithelial cells, alveolar macrophages, lymphocytes and erythrocytes seen in the bronchial lavage cytology (H&E, x40)*

Diffuse alveolar injury (DAD) has been observed in COVID-19-related deaths in inpatients, and it is also believed that medical interventions, especially high oxygen therapy, can cause lung damage in cases of COVID-19. In an autopsy study of COVID-19 patients who died in the hospital after treatment and those who died untreated in a community setting, DAD was detected in both groups. The fact that DAD was the primary histological manifestation of severe lung disease in COVID-19 patients who died both in a hospital and in a community

setting without treatment proves that the development of DAD in cases of COVID-19 pneumonia is not caused by high-dose oxygen, anticoagulant, antiviral or steroid therapy, but by mechanisms directly related to the disease. The same study reported the presence of focal perivascular inflammation/endothelitis in SARS - CoV - 2 positive patients (10). DAH is a potentially life-threatening syndrome that generally has a poor prognosis, with in-hospital mortalities reported in the 20 – 50% range. The prompt initiation of appropriate treatment is important for the prevention of acute respiratory failure and death. Classic treatment regimens include corticosteroids and immunosuppressive agents, although have the potential to be harmful when DAH is due to infection, and so its use at appropriate times and only in appropriate cases is important (11). In our case, the patient responded well to high-dose steroid treatment.

CONCLUSION

Our case report corroborates the diagnosis of COVID-19-associated DAH in an immunosuppressed patient. The limited use of bronchoscopy due to the risk of COVID-19 infection can lead to a diagnosis of COVID-19 being mistakenly excluded in patients whose nasopharyngeal swabs are PCR-negative for SARS-CoV-2, and the under-recognition of conditions such as DAH or secondary infection in PCR-positive patients for SARS-CoV-2. In this group of patients, bronchoscopy should be performed using the appropriate personal protective equipment when necessary, and targeted therapies should be applied without delay.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - G.D.Y., M.Ş.A., D.E., K.H., M.T.; Planning and Design - G.D.Y., M.Ş.A., D.E., K.H., M.T.; Supervision - G.D.Y., M.Ş.A., D.E., K.H., M.T.; Funding - G.D.Y., K.H., M.T.; Materials - G.D.Y., D.E., M.T., K.H.; Data Collection and/or Processing - G.D.Y., D.E., K.H., M.T.; Analysis and/or Interpretation - G.D.Y., M.Ş.A.; Literature Review - G.D.Y., M.Ş.A.; Writing - G.D.Y.; Critical Review - G.D.Y., M.Ş.A., D.E., M.T., K.H.

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