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Physiotherapy on a Patient Supported by Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome: Short- and Long-Term Follow-up

Akut Respiratuar Distres Sendromu Sebebiyle Ekstrakorporeal Membran Oksijenasyon Tedavisindeki Bir Hastada Fizyoterapi: Kısa ve Uzun Dönem Takip

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Abstract
In recent years extracorporeal membrane oxygenation (ECMO) has been used to maintain adequate gas exchange in patients with Acute Respiratory Distress Syndrome (ARDS). The aim of this case report is to share our center’s experience with physiotherapy in patients with ARDS on ECMO, to support the use of physiotherapy and to relate the long-term functional outcomes of the patient at six months after discharge. We present here the case of a 28-year-old female who was referred to our intensive care unit with a diagnosis of ARDS being supported by ECMO. While on ECMO, she received physiotherapy interventions including passive techniques, and participated in an active mobility program following ECMO. Her long-term outcomes, including functional level, exercise capacity, dyspnea, muscle strength, anxiety, depression and quality of life, assessed six months after discharge, were at a very good level. We consider that participation in the early physiotherapy and mobility program may contribute to short- and long-term functional improvements in an ECMO patient.

Key words: ARDS, ECMO, physiotherapy.

Özet
Son yıllarda Akut Respiratuar Distres Sendromu (ARDS) olan hastalarda yeterli gaz değişimini sürdürümek için ekstrakorporeal membran oksijenasyonu (ECMO) kullanılmaktadır. Bu olgu sunumunun amacı, merkezimizin ECMO tedavisindeki ARDS’li bir hastada fizyoterapi ile ilgili deneyimini tanımlamak, fizyoterapiyi desteklemek ve taburcu olduktan altı ay sonra hastanın uzun dönem fonksiyonel sonuçlarını aktarmaktır. Burada, yoğun bakım ünitimize ARDS tanıısı ile sevk edilen ve ECMO tedavisi alan 28 yaşındaki bir kadın sunulmuştur. Hasta ECMO’da iken pasif teknikleri içeren fizyoterapi uygulamaları almış ve ECMO’nun ardından aktif bir mobilite programına katılmıştır. Taburculuk sonrası 6. ayda hastanın, fonksiyonel seviyesi, egzersiz kapasitesi, dispne, kas kuvveti, anksiyete, depresyon ve yaşam kalitesi gibi uzun dönem sonuçlarının oldukça iyi seviyede olduğu görülmüştür. Erken fizyoterapi ve mobiltite programına katılması bir ECMO hastasında kısa ve uzun vadeli fonksiyonel iyileşmeleri katkıda bulunabileceği düşünülmektedir.

Anahtar Sözcükler: ARDS, ECMO, fizyoterapi.

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With advances in intensive care medicine, patient survival has improved, but this has brought with it such morbidity problems as general decondition and functional independence (1). Skeletal muscle weakness has been shown to be associated with an increase in mortality, and to continue for years after discharge in Acute Respiratory Distress Syndrome (ARDS) patients (2). For this reason, there is a need for rehabilitation after intensive care unit (ICU), as well as certain evaluations and applications to prevent or reduce the loss of physical functionality during ICU admission.

In recent years, extracorporeal membrane oxygenation (ECMO) has been used to maintain adequate gas exchange in patients with severe respiratory failure that is refractory to even maximal ventilatory support (3). Although patients on ECMO often have many contraindications for physiotherapy, such as bleeding from the cannulation area and dislocation of the cannula, hemodynamic instability, hypoxemia and dependency on veno-venous ECMO support (4), it would seem reasonable that the benefits of early rehabilitation seen in the general ICU population apply also to patients receiving ECMO. Evidence and awareness of the emphasis of physiotherapy in ECMO patients is increasing. Literature contains case studies investigating the feasibility of physiotherapy in patients on ECMO, although there is only limited data on the assessment of long-term effects and post-intensive care syndrome (3,5,6). The present case report supports early physiotherapy interventions for patients on ECMO, and describes the long-term functional outcomes of the patient six months after discharge.

CASE
A previously healthy 28-year old woman was referred to the ICU with a diagnosis of respiratory failure and suspected Influenza A virus (H1N1). Her arterial blood gas was pH: 7.49, PaCO₂: 31.5 mmHg, PaO₂: 40.4 mmHg, HCO₃⁻: 25.3 mmol/l. BE: 1 mmol/L and SaO₂: 75.5%, and her Acute Physiologic and Chronic Health Evaluation (APACHE) II score was 14 at the time of ICU admission. Over the following 24 hours, the patient’s oxygen demand continued, despite receiving non-invasive mechanical ventilation with 100% oxygen support in the ICU, and so intubation ensued. The Intelligent Adaptive Support Ventilation (ASV) mode, which automatically sets the controls for oxygenation (positive end-expiratory pressure [PEEP], Oxygen) was used for invasive ventilatory support. The patient was paralyzed and sedated. At the first hour following intubation, values of PaO₂/FiO₂ 82.4 with 20 cmH₂O PEEP and 100% FiO₂ were recorded. The patient was diagnosed with severe ARDS based on the Berlin Criteria (7). Although many ventilation strategies for the management of ARDS were attempted, such as low tidal volumes, high PEEP and recruitment maneuvers, the hypoxemia worsened and the critical care team decided to instigate veno-venous ECMO on the second day of ICU admission (8). On the first day of ECMO treatment, H1N1 was confirmed.

On the 11th day, the ECMO was discontinued and a tracheostomy was performed to ensure airway patency, and the paralysis and sedation subsequently ceased. The patient remained on mechanical ventilation support for five more days, and support was gradually reduced and terminated. During the neurological examination, although her sedation had been ceased on the 11th day she remained unconscious until the 16th day in the ICU. Her consciousness improved progressively between days 16 and 27. Chest X-rays of the patient before admission to the ICU and at the time of discharge, as well as a thorax CT before ECMO, are presented in Figure 1.

The patient was discharged to the respiratory ward on the 27th day of hospitalization with an arterial blood gas of pH: 7.46, PaCO₂: 37 mmHg, PaO₂: 91.1 mmHg, HCO₃⁻: 26.8 mmol/l, BE: 2.5 mmol/L and SaO₂: 98.2%. A total of 650 mg rocuronium and 1760 mg steroid, which can have negative effects on skeletal muscle function, had been administered, and a total 24µg of fentanyl had been administered for analgesia. Her total ventilator time in 28 days was 330 hours (13.75 days). The patient was discharged from the ICU in a stable condition in terms of cardiac status, and she was cooperative, eating and mobile with assistance.

Physiotherapy Interventions: The characteristics of the physiotherapy program, which was implemented twice a day throughout the ICU stay of the patient, are presented in Table 1. Before the application, the patient was evaluated in terms of the safety criteria determined based on the proposed algorithm for ECMO patients (9). The patient was particularly sensitive to bleeding while receiving ECMO therapy. Her cardiopulmonary clinical stability [blood pressure, heart rate, peripheral oxygen saturation, respiratory rate, BORG score (if available)] was monitored during all treatments.

All treatment modalities were performed by the same physiotherapist in all sessions. Positioning, passive range of motion exercises and neuromuscular electrical stimulation (NMES) were applied twice daily throughout the period of unconsciousness (6).
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The patient’s active participation in the physiotherapy started on day 16, after she regained consciousness. The range of motion exercises were performed, first in an active assistive way, and then actively by the patient (10). For the mobility program, the order followed was: first in the bed, then sitting on the side of the beds, transfer to a wheelchair, standing up and walking (4,11). The patient was unable to walk without support at the time of her discharge from the ICU. Suctioning of the invasive artificial airway, as a bronchial hygiene technique, was applied by nurses until the 17th day for the clearance of secretions (12). Coughing/huffing and active breathing technique cycles were added to the program after the tracheostomy closure (1).

Table 1: Physiotherapy Interventions

| Interventions                                                                 |
|------------------------------------------------------------------------------|
| **1-11** (Sedated)                                                          |
| Bed position to maintain the feet in neutral dorsiflexion, hip in neutral rotation and keep her heels elevated off the bed |
| Passive range of motion to all major upper and lower extremity joints –except hip flexion (Repetitions: 5 times / joint) |
| Stretching of plantar flexors (20 minutes)                                   |
| NMES (Duration: 60 minutes, Frequency: 45 Hz.)                               |
| Aspiration for airway clearance                                             |
| **11-16** (ECMO discontinued, sedation stopped, awake but not following commands) |
| Passive range of motion to all major upper and lower extremity joints (5 times / joint) |
| Stretching of plantar flexors (20 minutes)                                   |
| Sitting with the bed in the chair position (Duration: Changed according to the patient tolerance) |
| NMES (Duration: 60 minutes, Frequency: 45 Hz.)                               |
| Aspiration for airway clearance                                             |
| **16-27** (Alert, following commands)                                        |
| Active / Active assistive range of motion of all major upper and lower extremity muscle groups (Repetitions: 8-10, Intensity: BORG:11-13) |
| Active range of motion of all major upper and lower extremity muscle groups against gravity or resistance by physiotherapist or small free weights (Repetitions: 8-10, Intensity: BORG:11-13) |
| Sitting edge of the bed / Sitting in wheelchair / Standing and walking with assistance (Duration: Changed according to the patient tolerance) |
| Breathing control, Diaphragmatic breathing, thoracic expansion exercises (Repetitions: 8-10, Intensity: BORG:11-13) |
| Incentive spirometer training (Repetitions: 8-10/ 2 hour)                    |
| Huffing and cough for airway clearance                                      |

Figure 1: Chest X-ray of the patient on the first day in the ICU (a), chest X-ray of the patient upon discharge from the ICU (b), thorax CT before ECMO (c)
| Examination                          | Days 1-11 (Sedated) | Day 12 | Day 13 | Day 14 | Day 15 | Day 16 | Day 17 | Day 18 | Day 27 (Discharge) |
|-------------------------------------|---------------------|--------|--------|--------|--------|--------|--------|--------|-------------------|
| Consciousness (RASS)                | (-5)                | (-4)   | (-3)   | (-3)   | (-2)   | (-1)   | (0)    | (0)    | (0)               |
| Cooperation (S5Q)                   | 0                   | 0      | 1      | 1      | 2      | 3      | 4      | 5      | 5                 |
| Muscle Strength (MRC)               | -                   | -      | -      | -      | -      | -      | 21/60  | 33/60  | R:12 L:18         |
| Hand grip (kg)                      | -                   | -      | -      | -      | -      | -      | R:18   | L:22   |                   |
| PFIT Score                          | -                   | -      | -      | -      | -      | -      | -      | 1/12   | 5/12              |
| Walking distance with assistance (meter) | -                   | -      | -      | -      | -      | -      | -      | -      | 120               |
| Modified BORG Scores at the end of walking | -                   | -      | -      | -      | -      | -      | -      | -      | Dyspnea: 2(before) 6(after) |
|                                     |                     |        |        |        |        |        |        |        | Fatigue: 2(before) 8(after) |
|                                     |                     |        |        |        |        |        |        |        | *Vital signs stable |

RASS: Richmond Agitation Scale, S5Q: Standardized Five Questions, MRC: Medical Research Council, PFIT: Physical Function in ICU Test (Higher score means higher physical function), R: Right extremity, L: Left extremity.
DISCUSSION

This report details the in-patient and out-patient follow-up care applied to an ARDS patient supported by the newly-implemented ECMO treatment in our ICU. Consensus reports and case series of ECMO use have witnessed a steady increase, however there has as yet been no report in literature on the clinical presentation before, and after six months in a patient based on the assessment parameters used herein. One of the leading motivations behind this study was the desire to provide data relevant to Turkey in terms of functionality to address the long-term process in ECMO patients. The consensus report recommends that ECMO patients should be included in the physiotherapy program (5). The biggest problem with mobility among ECMO patients is the potential for femoral cannula dislocation, although Abraham et al. suggests that femoral cannula is not an absolute contraindication for mobility, and reporting that their patient had walked around 1.2 meters (18). We did not encounter any side effects in the patient during physiotherapy interventions.

Post-intensive care syndrome is defined as the physical, cognitive and mental effects on patients after being discharged from the ICU (3). Studies have shown that preventive strategies shown to have a positive impact in the prevention of the long-term functional impairments associated with this syndrome include encouraging early mobility in ICU patients (3). Within the first year following ECMO, the physical outcomes experienced by patients are greater than those that are mental in nature, with the risk of mental problems having been reported to be 2–3 times greater than the expected rate, leading to frequent hospital admissions (19). In another study, after undergoing ECMO treatment, 75% of patients were able to return to their daily life and 25% returned to work, while mobility impairment was experienced by 50% (20). There was no evidence of post-intensive care syndrome in our patient at the 6-month evaluation, which may be due to the participation of the patient in a physiotherapy rehabilitation program from the earliest stages and the consequent rapid return of physical independence, the training of the patient and their family, family support and personal motivation.

One of the limitations of the study center is that we are unable to offer our patient rehabilitation after discharge, being a hospital with a specialization in chest diseases.
The patient had to be directed to an external center after discharge, as our hospital contains no rehabilitation center for ICU survivors. Most of the patients in our country are unable to access adequate rehabilitation after an ICU stay, and so clinical researches and funding are needed for the development of rehabilitation programs for ICU survivors.

CONCLUSION
This case study report suggests that physiotherapy and early mobilization in ECMO patients are effective and have been concluded to be safe, and can reduce the effects of post-intensive care syndrome. Future studies are needed for the formal evaluation of the long-term outcomes of ECMO patients and to explore the risks factors for post-intensive care syndrome.

CONFLICTS OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
Concept - İ.N., Ö.E., C.K.; Planning and Design - İ.N., Ö.E., C.K.; Supervision - İ.N., Ö.E., C.K.; Funding - İ.N., Ö.E., C.K.; Materials - İ.N., Ö.E., C.K.; Data Collection and/or Processing - İ.N., Ö.E., C.K.; Analysis and/or Interpretation - İ.N.; Literature Review - İ.N.; Writing - İ.N.; Critical Review - İ.N., Ö.E., C.K.

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REFERENCES
1. Gosselink R, Bott J, Johnson M, Dean E, Nava S, Norrenberg M, et al. Physiotherapy for adult patients with critical illness: recommendations of the European Respiratory Society and European Society Of Intensive Care Medicine Task Force on physiotherapy for critically ill patients. Intensive Care Med 2008; 34:1188-1199. [CrossRef]
2. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saadi F, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003; 348:683-93. [CrossRef]
3. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med 2012; 40:502-9. [CrossRef]
4. Lowman JD, Kirk TK, Clark DE. Physical therapy management of a patient on portable extracorporeal membrane oxygenation as a bridge to lung transplantation: a case report. Cardiopulm Phys Ther J 2012; 23:30-5. [CrossRef]
5. Eden A, Purkiss C, Cork G, Baddeley A, Morris K, Carey L, et al. In-patient physiotherapy for adults on venovenous extracorporeal membrane oxygenation-United Kingdom ECMO Physiotherapy Network: A consensus agreement for best practice. Intensive Care Soc 2017; 18:212-20. [CrossRef]
6. Polastri M, Loforte A, Dell’Amore A, Nava S. Physiotherapy for patients on awake extracorporeal membrane oxygenation: a systematic review Physiother Res Int 2016; 21:203-9. [CrossRef]
7. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012; 307:2526-33. [CrossRef]
8. Fanelli V, Vlachou A, Ghannadian S, Simonetti U. Acute respiratory distress syndrome: new definition, current and future therapeutic options. J Thorac Dis 2013; 5:326-34. [CrossRef]
9. Ko Y, Cho YH, Park YH, Lee H, Suh GY, Yang JH, et al. Feasibility and safety of early physical therapy and active mobilization for patients on extracorporeal membrane oxygenation. ASAIO J 2015; 61:564-8. [CrossRef]
10. Adler J, Malone D. Early mobilization in the intensive care unit: a systematic review. Cardiopulm Phys Ther J 2012; 23:5-13. [CrossRef]
11. Sommers J, Engelbert RHH, Detting-Ilhenfeldt D, Gosselink R, Spronken PE. Physiotherapy in the intensive care unit: an evidence-based, expert driven, practical statement and rehabilitation recommendations. Clin Rehabil 2015; 29:1051-63. [CrossRef]
12. Cork G, Barrett N, Ntoumenopoulos G. Justification for chest physiotherapy during ultra-protective lung ventilation and extra-corporeal membrane oxygenation: a case study. Physiother Res Int 2014; 19:126-8. [CrossRef]
13. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O’Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care patients. Am J Respir Crit Care Med 2002; 166:1338-44. [CrossRef]
14. Fan E, Ciesla ND, Truong AD, Bhoopathi V, Zeger SL, Needham DM. Inter-rater reliability of manual muscle strength testing in ICU survivors and simulated patients. Intensive Care Med 2010; 36:1038-43. [CrossRef]

15. Ali NA, O’Brien JM Jr, Hoffmann SP, Phillips G, Garland A, Finley JC, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. Am J Resp Crit Care Med 2008; 178:261-8. [CrossRef]

16. Denehy L, de Morton NA, Skinner EH, Edbrooke L, Haines K, Warrillow S, et al. A physical function test for use in the intensive care unit: validity, responsiveness, and predictive utility of the physical function ICU test (scored). Phys Ther 2013; 93:1636-45. [CrossRef]

17. Sukantarat KT, Williamson RC, Brett SJ. Psychological assessment of ICU survivors: a comparison between the hospital anxiety and depression scale and the depression, anxiety and stress scale. Anaesthesia 2007; 62:239-43. [CrossRef]

18. Abrams D, Javidfar J, Farrand E, Mongero LB, Agerstrand CL, Ryan P, et al. Early mobilization of patients receiving extracorporeal membrane oxygenation: a retrospective cohort study. Crit Care 2014; 27:18:R38. [CrossRef]

19. Tramm, R, Ilic D, Sheldrake J, Pellegrino V, Hodgson C. Recovery, risks, and adverse health outcomes in year 1 after extracorporeal membrane oxygenation Am J Crit Care 2017; 26:311-9. [CrossRef]

20. Camboni D, Philipp A, Rottenkolber V, Zerditzki M, Hollzamer A, Floerchinger B, et al. Long-term survival and quality of life after extracorporeal life support: a 10-year report Eur J Cardiothorac Surg 2017; 52:241-7. [CrossRef]
Cinnamon Stick Aspiration in a Patient with Asthma: A Case Report

Asthım Tanılı Hastada Tarçın Çubuğu Aspirasyonu: Olgu Sunumu

Sefa Semih Atal¹, Omer Ayten¹, Cengiz Özdemir², Tayfun Caliskan¹, Bengü Şaylan¹, Oguzhan Okutan¹, Zafer Kartaloglu¹

Abstract

Foreign body aspiration into the tracheobronchial system, which is more common in children than adults, can have serious consequences, leading even to mortality and morbidity, and may be diagnosed only after a delay. A foreign body was detected during a flexible bronchoscopy due to stenosis in the left main bronchus in the chest computed tomography of a 59-year-old female patient being followed up for asthma. A cinnamon stick identified in the left main bronchus was removed with rigid bronchoscopy, revealing the asthma to be a misdiagnosis.

Key words: Tracheobronchial system, foreign body aspiration, cinnamon stick, asthma, rigid bronchoscopy.

Özet

Trakeobronşiyal sisteme yabancı cisim aspirasyonu, çocukların erişkinlere göre daha sık görülen, ciddi sonuçlara ve hatta mortalite ve morbiditeye neden olabilecek tani, ancak bronşogramda sol ana bronş daralma olması nedeniyle yapılan fleksible bronkoskopide yabancı cisim saptanmıştır. Hastaya yanlıslıkla astım tanısı konmuştur.

Anahtar Sözcükler: Trakeobronşiyal sistem, yabancı cisim aspirasyonu, tarçın çubuğu, astım, rijid bronkoskopii.

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Foreign body aspiration into the tracheobronchial system is a life-threatening emergency, and early removal and detection are very important if acute and chronic complications are to be avoided. The condition is more common in children, and is a major cause of sudden upper respiratory tract obstruction (1,2). Foreign body aspiration is a significant health problem that is frequently encountered in clinical practice. It can lead to serious consequences, requiring urgent interventions in some cases, and rapid clinical recovery is observed once the foreign body is removed (2). The removal of the foreign body following early diagnosis ensures fewer complications will be encountered, while delays in diagnosis and intervention may lead to serious morbidity and even mortality, and may have clinical and radiological consequences such as recurrent pneumonia, lung abscess and bronchiectasis (3). Foreign body aspiration most commonly involves the right main bronchus (71.5%) in adults, and was located in the left main bronchus in 22.8% and the trachea in 5.7% of the cases in the review article by Ramos et al. (4). There is a more equal distribution between the two systems in children, but foreign bodies are more common in the intermediate bronchi (27%) and right lower lobe (33%). The aspirated objects are affected by the geography, sociodemographic characteristics, eating habits and other cultural characteristics of the country in question, and can be quite diverse, ranging from edible organic materials, such as hazelnuts and peanuts, to inorganic materials such as toy pieces, earrings and pins (5,6). More rarely, objects such as garlic, cinnamon sticks, razor blades and voice prostheses have also been reported (7-9).

CASE

A 59-year-old female patient was admitted to the pulmonology department with complaints of shortness of breath, cough, fever and weakness. A computed tomography (CT) of the thorax revealed cavitary images, the largest of which was 18 mm thick in the lateral segment of the left upper lobe and narrowing in the left main bronchus (Figure 1a and b). The patient had a diagnosis of diabetes mellitus, essential hypertension and asthma, the asthma diagnosis being made 9 years earlier. A previous pulmonary function test (PFT) had shown no obstruction and reversibility was positive. The patient was using inhaled corticosteroid and a long-acting beta-antagonist combination, long-acting muscarinic antagonist, a combination of short-acting beta-antagonists and muscarinic antagonists in nebulized form, and oral corticosteroids for asthma treatment. She stated that although she had used her medicines properly and regularly, she had experienced frequent hospital admissions and several hospitalizations due to pneumonia within the 9-year period. She did not smoke and had no known allergies. While in our care, a PFT was repeated and reversibility was observed to be negative. The PFT results were; FVC: 1.49 lit (61%), FEV1: 1.23 lit (60%) and FEV1/FVC: 83; and the postbronchodilator results were FVC: 1.76 lit (72%), FEV1: 1.29 lit (63%) and FEV1 FVC: 74. The patient was thus found to have been misdiagnosed with asthma. She was also using gliclazide, metformin and valsartan for hypertension, and had no history of tuberculosis or contact with patients with tuberculosis.

The laboratory parameters were reported as glucose: 279 mg/dL, urea (serum): 18 mg/dL, Lactic Dehydrogenase: 162 U/L, creatinine: 0.55 mg/dL, sodium: 137 mmol/L, C-reactive protein: 131.29 mg/L, sedimentation: 120 mm/hour, ferritin: 75.68 ng/mL, N-terminal Pro Brain Natriuretic Peptide: 1958 ng/L, White blood cell count: 13.61x10^3/mm³, hemoglobin: 7.8 g/dL, hematocrit: 25.7%, platelet count: 450x10^3/mm³, procalcitonin: 0.151 ng/mL and high sensitive troponin: 17.78 ng/L in the blood taken from the patient.

An internal medicine consultation was requested due to anemia. Since the patient’s iron, folic acid and vitamin B12 levels were low, hemoglobin electrophoresis, fecal occult blood test, gastroscopy and colonoscopy were recommended.

The culture of the sputum sample taken from the patient was compatible with the upper respiratory tract flora. Sputum acid-resistant bacilli (ARB) direct examination and Mycobacterium tuberculosis sputum polymerase chain reaction (PCR) were negative. A 2019 nCoV Real-Time PCR was negative. Antibiotherapy was initiated with ceftriaxone 1000 mg 2x1 IV and clarithromycin 500 mg 2x1 pod.

![Figure 1: Stenosis of the left main bronchus on computed tomography of the lung (a) and thick-walled consolidated areas and an image of cavitation in the left hemithorax (b)](image-url)
Cinnamon Stick Aspiration in a Patient with Asthma: A Case Report | Atal et al.

A flexible bronchoscopy (FOB) was planned for the patient, whose lung computed tomography showed stenosis in the left main bronchus. The left main bronchus entrance was found to be narrowed by 80% in bronchoscopy, and the purulent secretions in the proximal part were aspirated. A foreign body surrounded by granulation tissue was noted in the proximal of the left main bronchus (Figure 2), and a fiberoptic bronchoscope was unable to access distal to the left main bronchus, and was lavaged. Following the bronchoscopy, when the patient was questioned about possible foreign body aspiration, it was learned that the patient had accidentally swallowed a cinnamon stick that she had added to her tea 9 years earlier, after which he applied to the emergency department with intense cough and shortness of breath but no cyanosis, and was discharged after undergoing bronchodilator treatment. It was decided to perform rigid bronchoscopy to remove the foreign body, which was surrounded by granulation tissue in the proximal left main bronchus. The foreign body was removed as a whole from the granulation tissue with rigid bronchoscopy (Figure 3). The removed foreign body was a cinnamon stick, approximately 10 cm in length, which had preserved its integrity. There were no complications during or after the procedure.

A growth of Klebsiella oxytoca was identified in the non-specific lavage culture, while other cultures and tests were negative, and there were no findings in favor of malignancy observed in a cytological examination. In accordance with the culture antibiogram, amoxicillin /clavulanic acid 1000 mg 2x1 pod was prescribed to the patient, and after regression in the infection parameters and improvement in the patient’s clinical course, she was discharged from the hospital. A control thorax computed tomography and FOB was planned for the first month after the procedure, and the left main bronchus was observed to be completely open, and the size of the cavitary lesions associated with the bronchial structures in the subpleural areas in the left upper lobe and lower lobe basal-posterior segment had decreased in the control chest computed tomography performed 1 month after the rigid bronchoscopy (Figure 4). Flexible bronchoscopy revealed the left main bronchus to be open.

**DISCUSSION**

Early admission to the hospital is important for a patient with a history of foreign body aspiration, as this will improve the success rate of the removal procedures (2). At the same time, the rate of complications that may develop with early diagnosis, and the possibility of false diagnoses in the future, will also decrease (2). Our case was being followed for asthma for many years, and it was observed that pneumonic infiltrates progressed to cavitary lesions in the lung parenchyma over time. The patient's
quality of life decreased and there were frequent hospital admissions and hospitalizations, clarifying the importance of early diagnosis and intervention. Although foreign body aspirations are more frequently seen in childhood, they can occur in all age groups. They are most common in children aged 0–3 years and later in those over 75 years of age (2). The most common foreign body aspiration materials in children are hazelnuts, peanuts, sunflower seeds, chickpeas, pencil caps and watermelon seeds (10), while the most common foreign body aspiration materials in adult individuals in our country are pins (11). Among the organic objects, it is mostly nuts that are aspirated (2). In cases of aspiration of large-sized inorganic objects, such as dental prostheses, money, bone fragments and beads, a complete occlusion of the tracheobronchial system may develop that may result in death (9,12). Foreign body aspirations in adults have been found to be most common (71.5%) in the right main bronchus (4), while in our case, a foreign body that was located in the proximal left main bronchus that caused an almost 80% obstruction was detected. There have been a number of case series published involving interesting objects, and the aspiration and removal of a cinnamon stick was reported in only one case in a review of studies of 25,998 bronchoscopies performed for foreign body aspiration in adults (9). Our case is thus an extremely rare and interesting example of foreign body aspiration. The most common clinical finding with foreign body aspirations is the cough crisis that occurs due to the foreign body irritating the tracheobronchial system. When the patient’s anamnesis is taken, it is commonly stated that sudden coughing attacks start immediately after the object is aspirated as a result of such activities as laughing, sneezing and speaking when there is a foreign body in the mouth (2). Aside from this, clinical findings such as respiratory distress, tachypnea, wheezing, stridor, hemoptysis, sputum production, vomiting and fever can also be seen in patients (12,13). Stridor is seen especially when the aspirated object does not completely occlude the main bronchus or trachea, although the patient may rarely be asymptomatic. Although similar clinical findings are observed in children, most parents describe a sudden onset of severe cough and bruising (2). Our patient presented with complaints of long-term shortness of breath and cough, and she stated that her complaints had continued, despite bronchodilator treatment. In tracheobronchial foreign body aspirations, the patient’s anamnesis – taken from the parents if the patient is a child – is often sufficient for diagnosis, and so should be questioned to the smallest detail. Radiological examinations and bronchoscopic evaluations are also required for diagnosis in patients with suspected foreign body aspiration with anamnesis. For this, if the patient’s vitals are stable and the general condition is good, the first thing that should be requested is an anterior-posterior and lateral chest radiography, followed by a thorax CT. Radiopaque substances can be easily detected during imaging studies (needles, money, other metal objects, etc.). If the object is not radiopaque, a diagnosis can be made based on secondary changes that may occur as a result of the aspiration. For example, if there is a foreign body completely obstructing a lobe or segment bronchus, signs of atelectasis or obstructive pneumonia may be detected in the distal of the obstruction, such findings being frequently encountered in patients who present a few days or weeks after foreign body aspiration. In patients with suspected foreign body aspiration, normal radiological images do not exclude aspiration, and therefore, bronchoscopy should be evaluated. Rigid bronchoscopy should be performed quickly in case of deterioration in the general condition of the patient, desaturation in room air or under oxygen support, cyanosis or upon an increase in respiratory distress. If an early diagnosis cannot be made, over time, secondary conditions may develop secondary to chronic inflammatory processes, such as obstructive pneumonia, lung abscess, bronchiectasis and cavitary lesions due to infections (2). Foreign bodies that are not removed for a long time become covered with granulation tissue, and can resemble an endobronchial mass with the potential for misdiagnosis as bronchial carcinoma (14). In our case, who could not be diagnosed and was treated for asthma for many years, pneumonia and cavitary lesions due to foreign body aspiration were observed, and the body had in time become covered with granulation tissue as a result of the endobronchial interventional processes. Bronchoscopic procedures have an important place in both the diagnosis and removal of tracheobronchial foreign bodies. Rigid bronchoscopy is the most common approach to the removal of aspirated foreign bodies from the tracheobronchial system, which, being performed under general anesthesia, has disadvantages when compared to fiberoptic bronchoscopy. On the other hand, a detailed evaluation of the distal airways can be made by sending a FOB through the rigid bronchoscope (2). In our case, a FOB was first performed, and the foreign body was found to be surrounded by granulation tissue. After being evaluated to be organized, it was decided to
remove the foreign body through rigid bronchoscopy. Under general anesthesia, the cinnamon stick that our patient had aspirated into her tracheobronchial system nearly 9 years earlier, was successfully removed in one piece, and without complications either during or after the procedure.

Tracheobronchial foreign body aspiration is a significant health problem in which rapid clinical recovery can be observed with early diagnosis and treatment. A detailed anamnesis is often diagnostic. After an anamnesis is taken and a physical examination has been performed, the patient with a suspected foreign body should be evaluated quickly through a radiological examination and bronchoscopic procedures. Although symptoms secondary to foreign body aspiration are usually seen acutely, it should be kept in mind that respiratory system symptoms may develop in cases of foreign bodies aspirated a long time ago, as in the patient in the present study.

CONFLICTS OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
Concept - S.S.A., Ö.A., C.Ö., T.Ç., B.Ş., O.O., Z.K.; Planning and Design - S.S.A., Ö.A., C.Ö., T.Ç., B.Ş., O.O., Z.K.; Supervision - S.S.A., Ö.A., C.Ö., T.Ç., B.Ş., O.O., Z.K.; Funding - S.S.A., Ö.A., C.Ö., T.Ç.; Materials - S.S.A., Ö.A., C.Ö., T.Ç.; Data Collection and/or Processing - S.S.A., T.Ç.; Analysis and/or Interpretation - T.Ç., B.Ş., O.O., Z.K.; Literature Review - S.S.A., T.Ç.; Writing - S.S.A., T.Ç.; Critical Review - S.S.A., T.Ç., B.Ş., O.O., Z.K.

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REFERENCES
1. Salih AM, Alfaki M, Alam-Elhuda DM. Airway foreign bodies: A critical review for a common pediatric emergency. World J Emerg Med 2016; 7:5-12. [CrossRef]
A Rare Complication of Endobronchial Ultrasonography-transbronchial Needle Aspiration: Endobronchial Nodule

Endobronşiyal Ultrasonografi-Transbronşiyal İğne Aspirasyonunun Nadir Bir Komplikasyonu: Endobronşiyal Nodül

Kemal Can Tertemiz¹, Nurcan Güler¹, Volkan Karaçam², Aylin Ozgen Alpaydın¹

Abstract

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a safe procedure with high diagnostic yield. However, complications related to EBUS-TBNA procedures are increasingly being reported. Common complications of EBUS-TBNA include infectious complications, pneumothorax, bleeding, and pneumomediastinum. Although the frequency of complications varies among studies, complication rates are quite rare (0.15 - 1.44%). One of the rare complications of EBUS-TBNA is the appearance of nodular lesions at the tracheobronchial puncture sites following EBUS-TBNA, namely “tracheobronchial puncture site nodular reaction” (TPNR). Here, we present three cases of TPNR, two of which were diagnosed with granulation tissue and one with malignancy. A biopsy must be taken in cases presenting with nodular lesion after EBUS.

Key words: Endobronchial ultrasonography, endobronchial nodular lesions, endobronchial granulation.

Özet

Endobronşiyal ultrason kilavuzluğunda transbronşiyal iğne aspirasyonu (EBUS-TBİA) yüksek tanısal verime sahip güvenli bir prosedürdür. Bununla birlikte, EBUS-TBİA prosedürleri ile ilgili komplikasyonlar giderek daha fazla rapor edilmektedir. EBUS-TBİA yaygın komplikasyonları arasında, enfeksiyöz komplikasyonlar, pnömotoraks, kanama ve pnömomediastinum yer almaktadır. Komplikasyon sıklığı çalışmalar arasında değişmekle birlikte komplikasyon oranları oldukça nadirdir (% 0.15 - % 1.44). EBUS - TBİA'nın nadir komplikasyonlarından biri, EBUS-TBİA'yi takiben trakeobronşiyal delinme bölgelerinde nodüler lezyonların ortaya çıkmasıdır. “Trakeobronşiyal ponksiyon bölgesi nodüler reaksiyonu” (TPNR) olarak tanımlanır. Burada, tanısal ikside granülasyon dokusu, birinde malignite olan TPNR gelişen üç olguyunun sunuuyoruz. EBUS sonrası nodüler lezon ile başvuran olguda mutlaka biyopsis alınmalıdır.

Anahtar Sözcükler: Endobronşiyal ultrasonografi, endobronşiyal nodüler lezyonlar, endobronşiyal granülasyon.
Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a highly effective, minimally invasive procedure for the sampling of mediastinal lymph nodes and central pulmonary masses (1). The importance of EBUS in the evaluation of mediastinal diseases has witnessed a gradual increase (2). The use of EBUS-TBNA sampling for the diagnosis and staging of mediastinal lesions has emerged as an alternative to mediastinoscopy, as the standard optimum approach to the preoperative staging of lung cancer (3). Despite the advantages of minimally invasive procedures, EBUS-TBNA has some complications, such as pneumothorax, hemorrhage and infection (4). Recently, a rare complication of EBUS-TBNA has been defined known as tracheobronchial puncture-site nodular reaction (TPNR) (5). We present here three cases of TPNR development following EBUS-TBNA.

CASE

Case 1: A 60-year-old male patient presented with three-month of hoarseness. A left upper-lobe mass lesion and left hilar lymphadenopathy (11L) were detected on a thorax computed tomography (CT). An FDG (fluorodeoxyglucose)-PET (positron emission tomography)-CT scan revealed an FDG avid mass in the left upper lobe along with FDG avid left paratracheal (4L) and hilar (11L) lymph nodes. An EBUS-TBNA of the lymph node stations was performed using an EBUS-530US bronchoscope (Fuji-film, Corporation, Tokyo, Japan) with a 22-gauge aspiration needle (Medi-Globe, Germany). The pathological diagnosis was atypical cells with suspicion of adenocarcinoma, and so a second EBUS-TBNA was performed three weeks later when biopsies were again taken from the 4L and 11L stations, and the final diagnosis was adenocarcinoma. During the procedure, a polypoid lesion was observed on the left lower lateral wall of the trachea where the TBNA was performed (4L station) (Figure 1), and a biopsy of the polypoid lesion revealed granulation tissue. The patient experienced no bleeding, fever or infection after the procedure. Systemic chemotherapy was initiated on the patient, who remains on oncological follow-up.

Case 2: A 62-year-old male patient was referred to our clinic for EBUS-TBNA. The patient had a history of lung squamous cell carcinoma and a right lower lobectomy. After four cycles of chemotherapy and radiotherapy, a thorax CT performed for the evaluation of treatment response revealed multiple progressive lymph nodes located in the right lower paratracheal (4R) and subcarinal (7) regions. A standard 22-gauge needle was used for the EBUS-TBNA procedure (Medi-Globe, Germany), and the resulting biopsies taken revealed reactive lymph nodes. The patient was admitted 2 months later with increased dyspnea, and thorax CT revealed progression in mediastinal lymph nodes as well as an irregularity and increased thickness (invasion?) between the 4R lymph nodes and the right lateral wall of the trachea. Metabolic progression was detected in 4R and 7 regional lymph nodes on a PET-CT, and a second EBUS-TBNA was planned. During the procedure, a polypoid lesion was observed on the right lower lateral wall of the trachea and a biopsy was taken (Figure 2) that was reported as granulation tissue. The patient experienced no bleeding, fever or infection after the procedure. One year later, significant regression was noted in the lymph nodes on a thorax CT. Follow-up of the patient is continuing in our oncology clinic.

Figure 1: The appearance of the 4L lymph node in the patient’s first EBUS-TBNA procedure (a), view of the second EBUS-TBNA 4L station 3 weeks later (b), endobronchial nodule in the left lower lateral tracheal wall (c)

Figure 2: 4R station CT image (a), progression of the lymph node, irregularity in the tracheal wall (b), lymph node regression after systemic therapy (c), PET image (d), a sonographic image of EBUS (e), polypoid lesion in the wall of the trachea (f)
Case 3: A 38-year-old male active smoker for 30 pack years presented with complaints of cough and weight loss for the previous 3 months. A thorax CT revealed a pulmonary nodule in the right upper lobe and lymphadenopathy in the 4R and 7 stations. Biopsies were taken from the lymph nodes with a 22-gauge needle for the EBUS-TBNA procedure (Medi-Globe, Germany), which revealed non-small cell lung carcinoma. The patient experienced no bleeding, fever or infection after the procedure. Systemic chemotherapy was initiated, and the patient was admitted 2 months later with hemoptysis, and progression in the mediastinal lymph nodes and the mass lesion in the right upper lobe. Furthermore, a mass lesion of soft tissue density protruding into the right main bronchus, as well as a polypoid lesion, was seen on the anterior wall of the trachea on thorax CT. Flexible bronchoscopy revealed a nodular lesion in the area where the EBUS-TBNA was taken. A tracheobronchial stent was placed with rigid bronchoscopy and a biopsy was taken (Figure 3) revealing squamous cell carcinoma, and so the chemotherapy was continued. The patient died during follow-up from respiratory failure, four months after the last operation.

**DISCUSSION**

EBUS-TBNA remains as the first-line option when sampling mediastinal lymph nodes for histopathological diagnosis and for the staging of suspected lung cancer (6), and is known to be a reliable method based on its widespread use in recent years. Major complications after EBUS-TBNA (infection, pneumothorax, bleeding and perforation) were found in only 0.05% of cases in a meta-analysis of 190 studies, and no mortality (7). In a multicenter retrospective study, of the 3,123 patients evaluated, five had serious complications (0.16%), determined as fever exceeding 24 hours, bronchogenic cyst infection, mediastinal abscess, pericarditis and pneumomediastinitis with empyema (8).

TPNR was detected in three of the 1,067 patients who underwent EBUS-TBNA between 2016 and 2020 in our clinic, although an accurate number of TPNR cases cannot be reported since repeat bronchoscopies or EBUS were rare. For our first and second cases, we opted for follow-up since the pathological diagnosis was granulation tissue and the cases were asymptomatic. In the third case, on the other hand, endobronchial treatment was started for the newly developed nodular lesion due to dyspnea and hemoptysis.

The frequency of nodular lesion development after EBUS-TBNA is as yet unknown. Among the publications on this subject in the form of case reports (9–12), some describe the implantation of a tumor or infection after a bronchoscopic procedure. Lee et al. reported on a case with tuberculous lymphadenitis who developed a new granuloma with a sinus tract after EBUS-TBNA. (12). Hu et al. (13) reported on a case of nasopharyngeal metastasis of lung cancer after bronchoscopic interventions, and Kim et al. (11) presented a case of TPNR development after EBUS-TBNA, the pathology of which squamous metaplasia and granulation tissue. The current knowledge of tumor seeding due to EBUS-TBNA is as yet insufficient, and there is thus a need to share further experiences on this subject.

The use of EBUS-TBNA is becoming more common with the increasing number of cancer cases recently, which may result in the identification of previously undefined complications in the future. We recommend a biopsy to distinguish between malignant benign granulation tissue in patients presenting with TPNR, as a recently defined rare complication of EBUS-TBNA. The course of cases with complications after EBUS-TBNA is a new research topic in this field.
CONFLICTS OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
Concept - K.C.T., N.G., V.K., A.O.A.; Planning and Design - K.C.T., N.G., V.K., A.O.A.; Supervision - K.C.T., N.G., V.K., A.O.A.; Funding -; Materials -; Data Collection and/or Processing -; Analysis and/or Interpretation - V.K.; Literature Review - V.K.; Writing - N.G., K.C.T.; Critical Review - A.O.A.

REFERENCES
1. Bibbo M, Wilbur D. Comprehensive Cytopathology E-Book. Elsevier Health Sciences; 2014.
2. Fusó L, Varone F, Magnini D, Calvello M, Lo Greco E, Richeldi L. Ultrasonography of the mediastinum: techniques, current practice, and future directions. Respir Care 2018; 63:1421-38. [CrossRef]
3. Walker CM, Chung JH, Abbott GF, Little BP, El-Sherief AH, Shepard J-AO, et al. Mediastinal lymph node staging: from noninvasive to surgical. Am J Roentgenol AJR 2012; 199:W54-W64. [CrossRef]
4. Dhoooria S, Aggarwal AN, Gupta D, Behera D, Agarwal R. Utility and safety of endoscopic ultrasound with bronchoscope-guided fine-needle aspiration in mediastinal lymph node sampling: systematic review and meta-analysis. Respir Care 2015; 60:1040-50. [CrossRef]
5. Madan K, Tiwari P, Arava S, Hadda V, Mohan A, Gulheria R. Tracheobronchial puncture-site nodular reaction (TPNR) following endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA): Systematic review of case reports. Lung India 2017; 34:532-7. [CrossRef]
6. Leyn PD, De Leyn P, Doms C, Kuzdzal J, Lardinois D, Passlick B, et al. Revised EST5 guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardio-Thoracic Surg 2014; 45:787-98. [CrossRef]
7. Bartheld MB von, von Bartheld MB, van Breda A, Anema JT. Complication Rate of Endosonography (Endobronchial and Endoscopic Ultrasound): A Systematic Review. Respirion 2014; 87:343-51. [CrossRef]
8. Çağlayan B, Yılmaz A, Bilaçeroğlu S, Çömert SŞ, Demirci NY, Salepci B. Complications of Convex-Probe Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration: A Multi-Center Retrospective Study. Respir Care 2016; 61: 243-48. [CrossRef]
9. Gupta R, Park HY, Kim H, Um S-W. Endobronchial inflammatory polyp as a rare complication of endobronchial ultrasound-transbronchial needle aspiration. Interactive CardioVasc Thoracic Surg 2010; 11:340-1. [CrossRef]
10. Lee KM, Jong SM, Oh SY, Do Young K, Lee G, Kim A, et al. The Natural Course of Endobronchial Inflammatory Polyps as a Complication after Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration. Tuberc Respir Dis 2015; 78:419-22. [CrossRef]
11. Kim SH, Lee Y, Park S, Choi CM, Jo J, Lee JC. Endobronchial mass formation after endobronchial ultrasound-transbronchial needle aspiration mimicking implantation metastasis. Clin Case Rep 2015; 3: 983-986. [CrossRef]
12. Lee J-W, Kim W-J, Park C-W, Kang H-W, Ban H-J, Oh I-J, et al. Endotracheal tuberculous granuloma formation following endobronchial ultrasound transbronchial needle aspiration. Intern Med 2013; 52: 1207-10. [CrossRef]
13. Hu J-B, Jin M, Chen E-G, Sun X-N. Lung squamous cell carcinoma metastasizing to the nasopharynx following bronchoscopy intervention therapies: a case report. World J Surg Oncol 2014; 12: 68. [CrossRef]
Giant Primary Mediastinal Leiomyoma Diagnosed with EBUS-TBNA: A Case Report

EBUS TBİA ile Tanı Konulan Dev Primer Mediastinal Leiomyom: Olgu Sunumu

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Abstract

Mediastinal leiomyomas are usually of esophageal origin, among which primary mediastinal leiomyomas are extremely rare. The current approach to the treatment of giant primary mediastinal leiomyoma involves the removal of the mass by thoracic surgery. We present here a case with leiomyoma of the posterior mediastinum that was compressing the trachea, and that was diagnosed via EBUS TBNA.

Key words: EBUS-TBNA, leiomyoma, mediastinal mass.

Özet

Mediyastinal leiomyomlar genellikle özefagus kökenlidir. Primer mediastinal leiomyom ise oldukça nadir görülmektedir. Dev primer mediastinal leiomyomun tedavisi torasik cerrahi ile kitlenin çıkarılmasıdır. Bu yazıda EBUS TBİA ile tanı konulan ve trakeaya bası yapan arka mediastende leiomyomu olan olguyu sunduk.

Anahtar Sözcükler: EBUS-TBİA, leiomyom, mediastinal kitle.

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Leiomyomas generally occur in the uterus, urinary tract or gastrointestinal tract. Primary Mediastinal Leiomyomas (PML) can rarely be seen in the intrathoracic area, developing from the smooth muscle (1,2). We describe here a rare case of a giant PML, diagnosed histopathologically by Endobronchial Ultrasonography guided transbronchial needle aspiration (EBUS-TBNA).

CASE
A 42-year-old male presented to our chest disease clinic with progressive chest pain and shortness of breath that had been ongoing for 6 months. The patient had no gastrointestinal tract problem symptoms, and clinical examination and laboratory tests were normal. A fixed airflow obstruction was detected in a respiratory function test.

Figure 1 shows an irregularity at the heart's borders with the lung, and linear atelectasis in the left hemidiaphragm on a posteroanterior chest radiograph. The computed tomography of lung shows a 31x45x32 mm soft tissue mass in the subcarinal area (Figure 2). A hypermetabolic appearance [maximum standardized uptake value (SUVmax): 8.9] was noted on positron emission tomography (PET-CT). Endobronchial USG revealed a large mass (49 mm × 29 mm) compressing the trachea (Figure 3), samples of which were obtained for histopathological examination through EBUS-TBNA. No associated mediastinal lymph node enlargement was detected on PET-CT. The patient was consulted with thoracic surgery and taken into operation. The mass, which started from the lower end of the esophagus and filled the subcarinal area, was removed surgically. It had no connection with esophagus or the great vessels, and all retrieved lymph nodes were clear. A cytological examination of the mass revealed no cytological atypia and no evident mitotic activity. The cells showed diffuse and strong staining for Desmin, SMA, Caldesmon, while being negative for CD117, DOG-1, BCL-2, CD34, and S100 on immunohistochemistry, consistent with a spindle cell mesenchymal neoplasia, and a smooth muscle-derived mesenchymal tumor (leiomyoma). Photomicrographs of smears showing cellular tissue fragments composed of spindle cells (a, b) and cell block material (c) (a May Grümwald Giemsa, b PAP, c Hematoxylin-Eosin x100) are shown in Figure 4. In immunohistochemical studies of cell block-section, positivity is seen for Desmin (a), smooth muscle actin (b), caldesmon and (c), negativity for DOG-1 antibodies (a, b, c, d x100) in Figure 5. Low-power magnification revealed a well-circumscribed tumor composed of spindle cells (a), and at a high power magnification, intersecting fascicles of bland-looking spindle cells can easily be identified (a x40, b x100, both Hematoxylin-Eosin) in Figure 6. It was thus evaluated as PML by a pathologist and thoracic surgeon. Six month and first-year controls were normal, with no recurrence detected on chest X-ray or computed tomography. The rarity of the condition, and the selected diagnosis and treatment steps are discussed and offered together with current literature.
DISCUSSION

Leiomyomas are generally localized in the esophagus, and account for 10% of all gastrointestinal leiomyoma in the mediastinum (3). Rare benign tumors of smooth muscle PML usually occur in women between the 2nd and 5th decades. Although the pathogenesis of leiomyoma is obscure, estrogen and traumatic theories have been suggested (1,4,5). These tumors account for 1–6% of all mediastinal tumors, and are known to be slow-growing tumors with low malignancy potential. The most common symptoms are dysphagia, non-specific chest pain and retrosternal pain, and less commonly regurgitation, epigastric tenderness, shortness of breath and weight loss (3,6,7). The symptoms and age of our case were consistent with literature. Chest radiography is not sensitive or specific enough for the diagnosis of PML (8,9), but with the enlargement of the mass it may become visible on chest radiograph. Computed tomography of the lung and PET-CT has an estimated sensitivity of 91–95% for the evaluation of PML. In our case, an increase in density was noted in the left lower zone causing an irregularity at the heart borders identified on a chest radiography, and the mass was diagnosed through a computed tomography of lung and immunohistochemical staining, and was identified as a posterior mediastinal mass. The patient had no other symptoms, such as dysphagia, epigastric tenderness, fever or hematemesis. Very few cases of PML have previously been reported, and diagnosis via EBUS-TBNA is also extremely rare (5,10). EBUS-TBNA is a minimally invasive approach to the examination and staging of mediastinal lesions (11,12). The patient was referred to our clinic and was assessed with EBUS-TBNA. A gastrointestinal tract endoscopy was not preferred primarily. The surgical removal of the tumor is the classic treatment recommended for primary mediastinal leiomyoma. A review of literature revealed PMLs to be usually completely resectable, and to generally provide a cure (13). In the present case, thoracic surgery was consulted, and the tumor filling the subcarinal area was removed by thoracic surgery. No recurrence was observed in the cases in literature, and there had been no recurrence three years after the operation in the present case.

In the present case, a benign spindle-cell neoplasm was diagnosed via EBUS-TBNA before surgery. Given the age of the patient, esophageal leiomyoma or lung cancer were considered during differential diagnosis. Although rare, PML should be considered in the differential diagnosis of an unexplained mass in the mediastinum.

Figure 3: Endobronchial USG showing a hypoechoic heterogeneous mass in the subcarinal area

Figure 4: Photomicrographs of smears showing cellular tissue fragments composed of spindle cells (a,b) and cell block material (c) (a May Grünwald Giemsa, b PAP, c Hematoxylin-Eosin X100)

Figure 5: In immunohistochemical studies of cell block sections, positivity is seen for desmin (a), smooth muscle actin (b) and caldesmon (c), and negativity for DOG-1 antibodies (a,b,c,d X100)

Figure 6: At low power magnification, a well-circumscribed tumor composed of spindle cells (a), and at high power magnification, intersecting fascicles of bland-looking spindle cells can be easily identified (a X40, b X100 both Hematoxylin-Eosin)
CONCLUSION
Primary Mediastinal Leiomyoma progress slowly and have a favorable prognosis. Endobronchial ultrasonography is an effective and reliable approach to the sampling of lesions adjacent to the trachea and bronchi. We believe that given the rare occurrence of PML, the use of EBUS-TBNA for diagnosis may be of benefit to clinicians.

CONFLICTS OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
Concept - S.D., E.B.K., T.T.T., K.İ.; Planning and Design - S.D., E.B.K., T.T.T., K.İ.; Supervision - S.D., E.B.K., T.T.T., K.İ.; Funding - S.D., K.İ.; Materials - S.D., T.T.T.; Data Collection and/or Processing - S.D., E.B.K., T.T.T.; Analysis and/or Interpretation - S.D., T.T.T., K.İ.; Literature Review - S.D., K.İ.; Writing - S.D., E.B.K.; Critical Review - S.D., T.T.T.

REFERENCES
1. Li C, Lin F, Pu Q, Liu L. Primary mediastinal leiomyoma: a rare case report and literature review. J Thorac Dis. 2018; 10:E116-9. [CrossRef]
2. Haratake N, Shoji F, Kazuma Y, Okamoto T, Maehara Y. Giant leiomyoma arising from the mediastinal pleura: a case report. Ann Thorac Cardiovasc Surg 2017; 23:153-6. [CrossRef]
3. Snène H, Blibech H, Mehiri N, Ben Salah N, Louzir B. Esophageal leiomyomas presenting as a mediastinal mass. Tunis Med 2020; 98:475-9.
4. Matsuoka H, Nishio W, Sakamoto T, Harada H, Sashikata T, Tsubota N. Mediastinal Angioleiomyoma. Ann Thorac Surg 2002; 73:1653-4. [CrossRef]
5. Shaffer K, Pugatch RD, Sugarbaker DJ. Primary mediastinal leiomyoma. Ann Thorac Surg 1990; 50:301-2. [CrossRef]
6. Thakut G, Murchite SA, Kulkarni RM, Gaikwad W. Leiomyoma of esophagus-A case report. Int J Surg Case Rep 2020; 76:285-7. [CrossRef]
7. Ouadnouni Y, Achir A, Bekarsabein S, Bouchikh M, Smahi M, Msougar Y, et al. Primary mediastinal leiomyoma: a case report. Cases J. 2009; 2:8555. [CrossRef]
8. Ha C, Regan J, Çetindag IB, Ali A, Mellinger JD. Benign esophageal tumors. Surg Clin N Am 2015; 95:491-514. [CrossRef]
9. Storey CF, Adams WC Jr. Leiomyoma of the esophagus: a report of four cases and review of the surgical literature. Am J Surg 1956; 9:3-23. [CrossRef]
10. Uno A, Sakurai M, Onuma K, Yamane Y, Kurita K, Hayashi I, et al. A case of a giant mediastinal leiomyoma with long-term survival. Tohoku J Exp Med 1988; 156:1-6. [CrossRef]
11. Darwiche K, Özkan F, Wolters C, Eisenmann S. Endobronchial ultrasound (EBUS) - an update 2017. Pneumologie 2017; 71:798-812. [CrossRef]
12. Stern JB, Wyplosz B, Girard P, Validire P, Escaut L, Calandro R. Endobronchial ultrasonography (EBUS) for the internist. Rev Med Interne 2016; 37:759-65. [CrossRef]
13. Baldó X, Sureda C, Gimferrer JM, Belda J. Primary mediastinal leiomyoma: an angiographic study and embolisation of the feeding vessels to improve the surgical approach. Eur J Cardiothorac Surg 1997; 11:574-6. [CrossRef]
Hemangiolympangioma with Accompanying Interstitial Lung Disease: A Rare Case

İnterstistiyel Akciğer Hastalığı ile Seyreden Hemanjyolenfanjiyoma: Nadir Bir Olgu

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Abstract

Vascular anomalies are pathologies that occur in embryonic life that affect the lymphatic and capillary systems, and can be classified as vascular tumors or vascular malformations, according to their histological features. They are rare and are mostly detected in the first years of life. Hemangiolympangiomas are benign vascular tumors containing lymphatic and capillary-system elements with a reported incidence of 1: 12,000 in newborns. The cases reported to date have been in the head (oral cavity, orbita, etc.), neck and mediastinum regions. We presented here a case of a 17-year-old male patient who was diagnosed with hemangiolympangioma after a video-assisted lung biopsy (VATS) with accompanying interstitial lung disease. The patient, who had no history of chronic disease, presented to the outpatient clinic complaining of cough and shortness of breath for eight months. Interstitial lung features were observed in the patient’s thorax computer tomography. After the VATS procedure, the patient developed chylothorax, and the pathology results indicated hemangiolympangioma.

Key words: Hemangiolympangioma, chylothorax, interstitial, lung.

Vasküler anomaliler, embriyonik yaşamda oluşan, lenfatik ve kapiller sistemleri etkileyen patolojilerdir ve histolojik özelliklerine göre vasküler tümörler veya vasküler malformasyonlar olarak sınıflandırılır. Nadir görülenler ve daha çok yangın ilk yıllarda saptanır. Hemanjyolenfanjiyomlar da lenfatik ve kapiller sistem elemanlarını içeren, benign bir vasküler tümörüdür. Insidansı yeniləşənənənla 1/12.000 olaraq bildirlənir. Bugüne dek bildirilən oləqlər baş bölgəsi (ağş başlığı, orbita vəs., boyun və mediastin bölgələrindədir. Biz de bu makalede interstistiyel akciğer hastalığı ile seyreden ve yapılan tanısal video yardımlı akciğer biyopsis (VATS) işlemi sonrasında hemanjyolenfanjiyoma tanısi olan 17 yaşında bir erkek hastayı sunduk. Kronik bir hastalığ olmayan ve seziz aydır olan öksürük və nefes darlığı ilə poliklinikə başvuran hastaya çekilen toraks tomografisində interstistiyel akciğer özellikleri görülmüş olup; VATS işlemi sonrasıda hastada şilotoraks gelişti. Patoloji sonucu hemanjyolenfanjiyom olarak sonlandırıldı.

Anahtar Sözcükler: Hemanjyolenfanjiyom, şilotoraks, interstistiyel, akciğer.
Vascular malformations occur as a result of anomalies in the capillary, lymphatic and venous systems during embryonic life and are classified as capillary, venous, lymphatic, arterial, mixed according to their content (1). Hemangiolympangiomas are defined as rare vascular malformations that contain endothelial-lymphatic components. Its incidence is 1: 12,000 and they are discovered at a rate of 40-60% at birth and 80-90% in the first 2 years of life. In the cases reported so far, the anterior and posterior cervical triangles are the most common areas in the body where hemangiolympangiomas are seen, as well as duodenum, mediastinum, mouth, maxillofacial region, colon, bladder, testis and vertebra involvement (2).

Although clinical diagnosis can be made by physical examination, methods such as doppler ultrasonography, computed tomography (CT) and magnetic resonance (MRI) are useful (3). Although being generally nonspecific at diagnosis; chest radiographs may show diffuse interstitial pattern and sometimes pleural effusion. Septal wall thickening due to peri-bronchial edema can be seen on thorax CT. Even if there are a few cases diagnosed after transbronchial biopsy, lung biopsy is considered to be the most accurate diagnostic method. (3)

Since hemangiolympangiomas are considered benign, there is usually not much information about their prognosis, although first-line surgery is recommended as a treatment, agents such as bevacizumab and beta blockers have become prominent in recent years due to their low toxicity (4).

In most cases; hemangiolympangiomas preset at infancy. What made our case remarkable was that our patient was a 17 years old male with a complaint of cough only for one month. We presented our case in the light of the literature.

CASE
A 17-years old male patient who hadn’t had a known chronic disease admitted to our chest diseases outpatient clinic with the complaint of cough and shortness of breath for about 8 months. He had a height of 183 cm with a weight of 65 kg and had a history of neither smoking nor abusing alcohol and drugs.

In the interrogation it was learned that the patient applied to another hospital before 8 months with an ongoing cough for one month; a thorax CT was performed and interstitial lung disease (ILD) was considered as prediagnosis. A bronchoalveolar lavage (BAL) was performed through bronchoscopy and eosinophil ratio was %5 in BAL along with eosinophilia. A lung biopsy was recommended but the patient didn’t have it performed then. The patient decided to apply to our hospital 8 months later than his first visit to hospital upon getting his cough getting severe.

The patient was questioned for additional complaints, he did not describe sputum, hemoptysis, chest pain, or a recent travel history. In the physical examination, there was no pathological feature other than the fine rales heard in the lower zones, and his vital signs were normal. A posteroanterior chest radiograph was requested.

On the radiograph, bronchiectasis areas on bilateral lower lung zones and peri-bronchial edema originating from interstitial tissues of the bronchial wall were observed (Figure 1).

Figure 1: Preoperative chest radiography of the patient; bilateral bronchiectasis and the honey-comb view

Figure 2: Thorax Tomography of the patient taken in an external hospital before the operation; increases in thickness in the interlobular septum, ground glass on the right periphery
The patient's external center CT was examined; increased interlobular septal thickness in both lungs and peribronchial consolidations (Figure 2), a budding tree appearance and pneumomediastinum, were (sarcoidosis or eosinophilic lung disease) seen more prominently in the upper lobe of the left lung (Figure 3). We decided to present the patient in the surgical council for the diagnostic procedure and ILD was our prediagnosis. The respiratory function test (PFT) performed before the operation showed a restrictive pattern. FVC was 3.12 L (59%), FEV1 3.04 L (70%), FEV1 / FVC: 97%. After the surgical council, it was decided to perform a diagnostic video-assisted lung biopsy (VATS).

A wedge resection for lower and middle lobe of the right lung was performed. With double-lumen intubation under general anesthesia, ports were placed in the left lateral decubitus position, through the right 7th intercostals space midaxillary line and 5th anterior axillary line incision, and an endocamera was inserted into the thorax wall to do a thoraacoport incision. Wedge resection was performed from the right lower and middle lobes with the help of 1 endolineer stapler. Pleural effusion material was sampled for investigation. After hemostasis and aerostasis, a 28-fr drain was placed and the layers were duly closed, and the obtained biopsy material was sent to pathology. The patient's general condition and vitals remained stable after the procedure.

The day after the VATS procedure, pleural fluid sample was sent to the laboratory upon seeing chylous white liquid was seen in the chest drain tube of the patient and the results were supporting chylothorax. (Biochemical results of the fluid sample were glucose 37 mg / dl; protein 38 mg / dl; albumin 23 mg / dl; LDH 675 mg / dl, triglyceride 120 mg / dl and ph: 7.5) Since the chylothorax hadn't regressed lymphatic ligation was applied to the patient. One week after the ligation, upon being stable; the patient was discharged from the thoracic surgery ward.

The histopathological examination of the biopsy material was resulted as "proliferating dilated vascular structures, hemangiomatosis and lymphangiomatosis spreading along the pleura and interlobar septa”. Proliferation and dilatation of lymphatic and blood vessels were existing in the subpleural area. Staining results from the pathology laboratory were CD-31, D2-40 and CD-34 positive (Figure 5).

The patient was followed up with Propranolol oral therapy of 3x20 mg. PFT values at the outpatient clinic control 2 months after the operation were; FVC 3.13 L (61%), FEV1 3.08 L (72%), FEV1 / FVC: 102%, DLCO 8.93 ml/min/mmHg (86%), besides the patient had no active complaints. Not a significant change was observed at his chest x-ray though (Figure 6). The patient’s next visit to hospital was 18 months after his operation. It is learned that he had continued taking propranolol on same dose for 18 months and had no additional complaint. His physical examination as well as his vital signs were normal. A thorax CT was taken for control; in both lungs, there were polygonal views and septal nodules formed by prominent interlobular septal regular thickening in the middle lower lobe, as well as increased peribronchial nodular opacity in the subpleural area on the left in the basal and faintly circumscribed ground glass infiltrates in the upper lobes. Pleural effusion extending into the fissure at a depth of 4 cm on the right lung was observed (Figure 7). It was decided to continue the same treatment while chest surgery outpatient clinic control was recommended for his recently developed pleural effusion.

Figure 3: Tree in bud view, peripheral consolidations and pneumomediastinum prominent in left upper zone

Figure 4: Thoracic CT taken after the operation; bilateral pleural effusion, more prominent on the right, increased fibroreticular density accompanied by traction bronchiectasis, irregular and coarse pleural fibrotic shrinkage, and 17.5 mm diameter nodular infiltrates, the largest in the left lower lobe laterobasal segment in both lungs
Lymphangiomas are anomalies caused by excessive proliferation of differentiated lymphoid tissue. According to their size, they are classified into capillary, cavernous and cystic lymphangiomas. Although vascular malformations are divided into two as vascular tumors (hemangioma) and vascular malformations according to Mullikan and Glowacki classification (1982); Landing and Faber also divided lymphangiomas into four; capillary, cavernous, cystic (hygroma) and hemangiolymphangioma (5-6).

Hemangiolymphangiomas are considered to be formed as a result of excessive proliferation of vascular formations during the angiogenesis process. They are named as hemangiolymphangioma since they contain lymphatic and capillary formations. Although they are classified as benign, invasion of the peripheral tissue by the cystic lesion can be witnessed when it is large in size. Although the pathophysiology has not been fully explained, mutations in FGF-4, PDGF-b, and tyrosine kinase genes are thought to be associated with familial type hemangiomas. Even though they are generally seen sporadically, infantile hemangiomas can be inherited as autosomal dominant. Most of them are seen in infancy, and the incidence in Caucasian race has been reported between 4-10%. The most frequent regions where the lesions seen are; head and neck (59%), trunk (24%), lower extremities (10%), upper extremities (7%) having a large scale from hypopigmented macular lesion to dark macular lesion. The male: female ratio is given as 2.5:1 (6-7).

The male patient in our case was diagnosed in adolescence, not in infancy and the diagnosis was made from the lung after wedge resection, not from the head and neck region as mostly reported. Clinical symptoms can range between a simple wheezing to advanced stage respiratory failure in adults. The diagnosis can be made even clinically in cases where the tumor is on the visible areas, but this was not possible in our case. In our opinion; the young age of our patient combined with absence of chronic illness and smoking history are also effective on his mild clinical state despite his illness. The only complaints he applied to hospital with were dyspnea and cough for two months; there were no signs of clubbing, cyanosis, etc. and his oxygen saturation was normal. The only feature on physical examination was the fine cracks heard in the basals. He didn’t get diagnosed until present day since he didn’t show any symptoms.

Pulmonary function tests (PFT) may show restrictive or mixed properties in general. In our case, the PFT had a restrictive pattern with a decreased FEV1 and an increased FEV1 / FVC ratio. Chest radiographs and CTs do not reveal pathological findings specifically to hemangiolymphangioma. Similar to our case, diffuse pleural effusion, diffuse interseptal

DISCUSSION

Figure 5: 2x10 HE pleural face dilated lymphovascular vessel proliferation-pathology preparation

Figure 6: Chest x-ray taken 2 months after the operation

Figure 7: Thorax CT taken 18 months after the surgery; septal regular thickening in the middle lower lobe, as well as increased peribronchial nodular opacity in the subpleural area, pleural effusion extending into the fissure at a depth of 4 cm on the right lung
and peribronchial thickening are generally reported in CTs. In cases where fiberoptic bronchoscopy was performed, the results revealed findings such as mucosal edema, bronchial narrowing, even thin vesicles filled with chylous fluid on the bronchial walls in cases of advanced disease. In this case, diffuse interseptal and peribronchial thickening was notable on CT, and diffuse bronchiectasis honeycomb view was noted on chest radiography. It has been shown that open lung biopsy gives more accurate results in diagnosis, so the patient was evaluated in the surgical council (7-8). Since 75% of asymptomatic hemangiomas regress on their own, follow-up without treatment is recommended. The recommended treatment options are generally palliative treatment. However, if severe deformity or life-threatening dyspnea is seen, systemic glucocorticoid is recommended as the first-choice medical treatment (5). In addition; Interferon alpha is the preferred agent in the cases where beta-blocker and cortisol are ineffective. The latest publications recommend agents such as propranolol, sirolimus and bevacizumab for treatment. These agents have been shown to provide remission with less toxicity (3).

We followed our case under propranolol after surgery in line with the new recommendations. In case of pleural effusion control, therapeutic thoracentesis and pleurodesis are applied for palliative treatment. Therapeutic thoracentesis was not needed as no pleural effusion was observed in the patient's postoperative outpatient clinic controls. The postoperative chylothorax occurred in our case shows similarity to lymphangiomatosis and should be kept in mind in differential diagnosis.

**CONCLUSION**

Although pulmonary hemangiolymphangiomas occur mostly in infancy and childhood, they may rarely be seen in adults. In differential diagnosis, lung involvement of lymphangioleiomyomatosis, hemangioma, lymphangectasis, Kaposi's sarcoma should be considered. This rare disease should be considered in interstitial lung diseases along with prolonged chylothorax.

**CONFLICTS OF INTEREST**

None declared.

**AUTHOR CONTRIBUTIONS**

Concept - G.O., E.Y.D., S.O.M., N.F., E.C.S., E.Ç., M.M.; Planning and Design - G.O., E.Y.D., S.O.M., N.F., E.C.S., E.Ç., M.M.; Supervision - G.O., E.Y.D., S.O.M., N.F., E.C.S., E.Ç., M.M.; Funding - E.C.S., E.Ç., M.M.; Materials - S.O.M., E.Y.D., M.M.; Data Collection and/or Processing - G.O., E.Y.D., S.O.M., N.F., E.C.S., E.Ç., M.M.; Analysis and/or Interpretation - G.O., E.C.S., E.Ç., N.F.; Literature Review - G.O., E.C.S., E.Ç.; Writing - G.O., E.C.S., E.Ç.; Critical Review - G.O., C

**REFERENCES**

1. Manickam S, Sasikumar P, Kishore BN, and Joy S. Hemangiolymphangioma of buccal mucosa: A rare case report. J Oral Maxillofac Pathol 2017; 21(2): 282-285. [CrossRef]

2. Schwartz RA, Mancini M, Lin RL. Arterial Vascular Malformations Including Hemangiomas and Lymphangiomas Clinical Presentation. Medscape Education Global. Access date: 16 March 2021. Place of access: https://emedicine.medscape.com/article/1018071-clinical.

3. Kadakia KC, Patel SM, Yi ES, Limper AH. Diffuse pulmonary lymphangiomatosis. Can Respir J 2013;20(1):52-54. [CrossRef]

4. Martínez-Bucio V, De la Puente-Murgia R, Gallardo-Meza A, Zapata-Martínez SG, Zertuche-Coindreau JM, López-Valdés JC. Pulmonary haemangiolymphangioma as cause of hemodynamic decompensation, Revista Médica del Hospital General de México, Volume 79, Issue 4, 2016, Pages 210-215, ISSN 0185-1063. [CrossRef]

5. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 1982;69:412-22. [CrossRef]

6. Faul JL, Berry GJ, Colby TV, Ruoss SJ, Walter MB, Rosen GD, Raffin TA. Thoracic Lymphangiomas, Lymphangiectasis, Lymphangiomatosis, and Lymphatic Dysplasia Syndrome. April 2000. American journal of respiratory and critical care medicine. 161. 1037-46. [CrossRef]
7. Nakamura T, Tamanuki K, Ko, G, Oguri, M, Akita C, Kitaoka C, Nakamura T and Saikawa, Y. Chronic thromboembolic pulmonary hypertension related to hemangio-lymphangioma. Case Reports in Clinical Medicine 2014;3:36-37. [CrossRef]

8. Murphy T, Ramai D, Lai J, Sullivan K, Grimes C. Adult neck hemangiolymphangioma: a case and review of its etiology, diagnosis and management, J Surg Case Rep 2017;31:2017(8):rjx168. [CrossRef]
A Rare Coexistence of Birt-Hogg-Dubé Syndrome and Sarcoidosis

Birt-Hogg-Dubé Sendromu ve Sarkoidozun Nadir Birlikteliği

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Abstract

A pathophysiological link may exist between Birt-Hogg-Dubé syndrome (BHD) and pulmonary sarcoidosis such that the folliculin protein encoded by the FLCN gene may lead to the development of sarcoidosis through the upregulation of T-helper 1 cell activation. We present here a rare case of coexisting BHD and sarcoidosis. Enlarged mediastinal lymphadenopathy may be underdiagnosed in patients with BHD, and so both the mediastinal and lung window of a thoracic CT scan should be evaluated carefully and a biopsy should be performed if pathologic lymphadenopathies are indicated.

Key words: Birt Hogg Dubé, sarcoidosis, fibrofolliculoma, mediastinal lymphadenopathy.

Özet

Birt-Hogg-Dube (BHD) sendromuna sahip hastalarda FLCN geni tarafından kodlanan folliculin proteininin T-helper-1 hücre aktivasyonuna yol açarak sarcoidozu yol açabileceği ve bu sebeple bu iki hastalık arasında patofizyolojik bir ortaklık olabileceği düşünülmektedir. Burada nadir bir BHD sendromu ve sarcoidoz birlikteliği olgusunu sunuyoruz. BHD tanısı olan hastaların toraks bilgisayarlı tomografilerini hem parankim hem de mediasten penceresinde olası bir mediastinal lenfadenopatiyi gözden kaçırarak detail olarak incelenmesi ve patolojik boylamada biyopsi yapılması gerekmektedir.

Anahtar Sözcükler: Birt Hogg Dubé, sarkoidoz, fibrofollikuloma, mediastinal lenfadenopati.

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Birt-Hogg-Dubé (BHD) syndrome is a rare autosomal dominant disorder caused by an FLCN gene mutation, and is characterized by lung cysts, and benign skin and renal tumors (1,2). Sarcoidosis is a granulomatous disease that mostly occurs with mediastinal lymphadenopathies and lung parenchymal abnormalities. The coexistence of BHD and sarcoidosis is extremely rare, having been reported only once before, and it is still unknown whether such co-existences are coincidental, or whether a causal link between the two exists. One possible pathophysiological link is that folliculin, a product of the FLCN gene, has an effect on the upregulation of T-helper 1 cells, and leading to the granulomatous reaction seen in sarcoidosis (3). We contribute to literature here with a second case of co-existing BHD and sarcoidosis.

CASE
A 26-year-old male patient was admitted to our hospital with a complaint of intermittent chest pain for 10 years, and was diagnosed with Birt-Hogg-Dubé (BHD) syndrome after a punch biopsy revealed fibrofolliculoma/trichodiscoma in the skin-colored lesions on his face. The patient was genetically tested for BHD, and a positive heterozygote folliculin (FLCN) gene mutation (c.1285dupC) was identified. During follow-up visits, family screening for familial association produced positive results in his brother and mother. The patient was otherwise healthy and had no history of smoking. Systemic physical examination findings were unremarkable aside from multiple, skin-colored, smooth and dome-shaped papules ranging in size from 1–4 mm in diameter, covering most of his face (Figure 1). Vital signs were normal. In laboratory tests, complete blood count, electrolytes and renal function were normal, while his angiotensin-converting enzyme (ACE) level was elevated, at 54 units per liter. A chest X-ray revealed bilateral enlarged hilar shadows with no pulmonary infiltrates (Figure 2). A thorax computed tomography (CT) was performed in which multiple mediastinal lymph nodes were identified, the largest being 13 mm in diameter, in the aortopulmonary window, subcarinal, right lower paratracheal and bilateral hilar regions, but with no parenchymal abnormality (Figure 3). An Endobronchial Ultrasonography (EBUS) identified four round, homogeneous and fused lymph nodes with regular borders in the right lower paratracheal area measuring 10–15 mm in diameter, and a round and homogeneously enlarged lymph node with a maximum diameter of 10 mm in the subcarinal station was sampled. A histopathological examination revealed non-necrotizing chronic granulomatous lymphadenitis, and the patient was diagnosed with stage 1 Sarcoidosis (Figure 4). The histochemical staining panel results for Grocott-Gomori’s methenamine silver (GMS), Periodic acid–Schiff (PAS) and Acid-Fast stain (AFB) were negative, the result of a purified protein derivative (PPD) test was 0 mm, and abdominal ultrasound revealed no abnormality. Since the patient had only stage 1 Sarcoidosis and no other organ involvement, only follow-up was planned for the detection of any renal lesions that may develop. Considering all these findings, the patient was diagnosed with coexisting Birt-Hogg-Dubé syndrome and sarcoidosis.
DISCUSSION

Birt-Hogg-Dubé syndrome was first described in 1977 as a case series including 70 kindred patients with skin manifestations, including cutaneous fibrofolliculoma / trichodiscoma. BHD is a rare inherited autosomal dominant disorder that has been reported in around 200 families (1), and is caused by germline mutations in the tumor suppressor gene FLCN. Besides skin manifestations, multiple pulmonary cysts with or without pneumothorax and renal tumors of various histological types are other organ involvements (2). There is no difference in frequency in terms of gender (4). More than 80% of patients with BHD have multiple pulmonary cysts with irregular borders, and patients often present with pneumothorax in the subpleural regions, predominantly in the lower lobes (3), although some BHD patients may be diagnosed with BHD without pulmonary cysts, as in the present case. A BHD diagnosis is based on clinical features and/or the identification of the genetic germ line FLCN mutation. Menko et al. (1) defined the major diagnostic criteria (a. at least five fibrofolliculomas/trichodiscomas, at least one being histologically confirmed adult onset b. pathogenic FLCN germline mutation) and the minor diagnostic criteria (a. multiple lung cysts b. renal tumor c. a first-degree relative with BHD). Of these, one major or two minor criteria are needed for diagnosis. Our case, whose family members were positive for FLCN gene mutation, was diagnosed with BHD after meeting two major criteria.

Enlarged mediastinal lymphadenopathy is an atypical finding in patients with BHD, and the probability of concurrently having BHD and sarcoidosis is assumed to be 1 in 9.5 billion. In literature, the only reported case diagnosed with both BHD and sarcoidosis involved a 57-year-old male patient with bulky hilar lymphadenopathy and peribronchiolar consolidations, identified with multiple pulmonary cysts from thoracic CT (4). The authors hypothesized that a possible pathophysiological link may exist between the diseases in which folliculin, a protein produced by the FLCN gene, has an effect on the mammalian target of rapamycin (mTOR) pathway, and the upregulation of T-helper 1 (TH1) cells promoted AKT-mTOR enhancement in this case, leading to the concurrence of BHD and sarcoidosis. In a further study, Kumasaka et al. (5) analyzed histopathological findings from the lung parenchyma obtained during video-assisted thoracic surgery in 50 unrelated patients with BHD. Among these, a granuloma formation and a c.1285dupC FLCN gene mutation were detected together in two patients, similar to our case, while patients without granuloma formations had other FLCN gene mutations.

The coexistence of BHD and sarcoidosis has been reported to be extremely rare, although this may be due to the underdiagnosis of enlarged mediastinal lymphadenopathies. It remains unclear as to whether the coexistence is causal or incidental, and so accompanying histopathological findings should be reported to reveal whether any causal relationship. As granulomatous diseases such as sarcoidosis may accompany BHD disease, both the mediastinal and lung window of thorax CT scan should be evaluated, and a biopsy should be performed during follow-up if indicated.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - C.S., G.K., A.K., E.C.S.; Planning and Design - C.S., G.K., A.K., E.C.S.; Supervision - C.S., G.K., A.K., E.C.S.; Funding - C.S., G.K.; Materials - C.S., G.K., A.K.; Data Collection and/or Processing - C.S., G.K.; Analysis and/or Interpretation - C.S., E.C.S.; Literature Review - C.S.; Writing - C.S.; Critical Review - C.S., G.K., A.K., E.C.S.
REFERENCES

1. Menko FH, van Steensel MA, Giraud S, Friis-Hansen L, Richard S, Ungari S, et al. European BHD Consortium. Birt-Hogg-Dubé syndrome: diagnosis and management. Lancet Oncol 2009; 10:1199-206. [CrossRef]

2. Daccord C, Good JM, Morren MA, Bonny O, Hohl D, Lazor R. Birt-Hogg-Dubé syndrome. Eur Respir Rev 2020; 29:200042. [CrossRef]

3. Kuhn B, Teckchandani P, Harper R. Parsimony or poor luck: Concurrent Birt-Hogg- Dubé syndrome and sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2017; 34:194-6. [CrossRef]

4. Gupta N, Sunwoo BY, Kotloff RM. Birt-Hogg-Dubé syndrome. Clin Chest Med 2016; 37:475-86. [CrossRef]

5. Kumasaka T, Hayashi T, Mitani K, Kataoka H, Kikkawa M, Tobino K, et al. Characterization of pulmonary cysts in Birt-Hogg-Dubé syndrome: histopathological and morphometric analysis of 229 pulmonary cysts from 50 unrelated patients. Histopathology 2014; 65:100-10. [CrossRef]
A Case of Niemann-Pick type B Presented with Interstitial Lung Disease

Interstisyel Akciğer Hastalığı ile Prezente Olan Niemann-Pick Tip B Olgusu

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Abstract

Niemann-Pick disease is a rare lysosomal storage disease in which sphingolipids accumulate in reticuloendothelial cells due to acid sphingomyelinase deficiency, three forms of which have been defined to date. Since Niemann-Pick Type B has different clinical findings, the patient presentation and disease progression can differ. Lipid storage is slow and progressive and leads to deterioration in multiple organs. Patients are mostly diagnosed in adulthood and pulmonary involvement is common. In our case, a 32-year-old female patient with complaints of cough and dyspnea was on long-term follow-up with a pre-diagnosis of interstitial lung disease, but with no specific diagnosis as she declined invasive procedures. An open lung biopsy performed due to the progression of symptoms resulted in histiocytes with foamy cytoplasm. A diagnosis of Niemann-Pick Type B was subsequently reached after a large patchy, mild hypocellular bone marrow with histiocytic infiltration, compatible with storage disease, was identified from a bone marrow biopsy performed for splenomegaly and thrombocytopenia. Since storage diseases are rare they are not considered in the differential diagnosis of interstitial lung diseases, but should be considered in the presence of systemic symptoms.

Key words: Niemann-Pick, storage disease, interstitial lung disease, splenomegaly, thrombocytopenia.

Özet

Niemann-Pick hastalığı, asit sfingomiyelinaz eksikliği sonucu retiküloendotelyel hücrelerde sfingolipiderin biriktiği nadir bir lizozomal depo hastalığıdır. Üç formu tanımlanmıştır. Niemann-Pick tip B, farklı ağırlığına klinik bulgulara sahip olduğundan hastaların presentasyonu ve hastalıktaki progresyonu farklıdır. Lipit depolanma yavaş ve progressif olup multipl organa bozulma oluşturur. Hastalar çoğunlukla erişkin yaşta tanı alırlar ve pulmoner tutulum siklikla görülür. Olgumuz, 32 yaşında kadın hasta, öksürük ve öksürük ve dispne şikayetleri ile başvurdu. Sonradan spenomegalı ve trombositopeni nedeni ile yapılan açık akciğer biyopsisi, köpükşi sitoplazmal histiyositler olarak sonuçlandı. Sonrasında splenomegalı ve trombositopeni nedeni ile yapılan kemik iliği biyopsisinde geniş yama tarzında depo hastalığı ile uyumlu histiyositik infiltrasyon gösteren hafif hipo­sellüler kemik iliği görülmesi sonucu, Niemann-Pick tip B tanısı ulaşıldı. Depo hastalıkları nadir görülen bir hastalıktır ve interstisyel akciğer hastalığı ayırıcı tanısında on planda düşünülmemele birlikte sistem solunum varlığında akla getirilmelidir.

Anahtar Sözcüler: Niemann-Pick, depo hastalığı, interstisyel akciğer hastalığı, splenomegalı, trombositopeni.

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Acid sphingomyelinase deficiency (ASMD) is a rare lysosomal storage disease with autosomal recessive inheritance caused by a mutation in the SMPD1 gene, and is known also as Niemann-Pick disease (1,2). The clinical and pathological features of disease were described in the early-20th century by German pediatrician Albert Niemann, German clinician Ludwig Pick, and later Crocker and Farber (3,4). In this disease, abnormal lipid (sphingomyelin) storage is seen in reticuloendothelial macrophages. Its incidence is 0.5 per 100,000 births, and three subtypes have been identified to date: Type A, acute neurovisceral form; Type B, chronic visceral form; in Type A/B: chronic neurovisceral intermediate form and Type C, although it has the same name, cholesterol accumulation occurs in tissues as a result of defects in intracellular transport and processing of cholesterol, not sphingomyelin.

In Type B, diagnosis is usually made in infancy or childhood based on the detection of hepatosplenomegaly, and patients generally survive until adulthood, when pulmonary involvement becomes common. Other common clinical signs include liver dysfunction, heart disease, hematological abnormalities, skeletal abnormalities and growth delays (5). Diagnosis is based on the measurement of sphingomyelinase activity in leukocytes, liver and bone marrow biopsies, and observations of foamy macrophages. We present here a 32-year-old female patient who did not receive a specific diagnosis for a long time who was followed up for interstitial lung disease, and who was diagnosed with NPD-B after bone marrow open lung biopsy was conducted in the light of the literature.

CASE
A 32-year-old female patient was admitted to our hospital for the first time in 2013 with complaints of cough and dyspnea. The patient was living in Istanbul and was employed as a plane cleaner. She was a non-smoker, and there was no additional disease. At the time of her first presentation in 2013, WBC: 5.06x10³/mm³, RBC: 4.87x10⁶/mm³, HGB: 12.2 g/dl, HCT: 37.7%, MCV: 77.5µ, PLT: 139x10³/mm³; respiratory function test; FEV1: 2.61 L (83%), FVC: 2.00 L (%65), %FEV1: 92.6% and DLCO 22.1 L (30%).

No specific diagnosis could be reached based on these results, but after consulting with the pathology unit, it was decided that the patient should be investigated for systemic diseases. In the meantime, splenomegaly and thrombocytopenia were detected in the internal medicine outpatient clinic where the patient applied for another reason, and a bone marrow biopsy was performed. The bone marrow biopsy pathology result was reported as mild hypocellular bone marrow showing histiocytic infiltration compatible with large patchy storage disease. Since a deficiency in sphingomyelinase enzyme activity was detected, the patient was diagnosed with Niemann-Pick disease Type B, and when lung preparations were re-consulted with pathology, the abundant histiocyte communities were stated to support storage disease involvement. The patient now has significant dyspnea and cough complaints, and although she has been using methylprednisolone 16 mg/day for a while, her symptoms are continuing.

DISCUSSION
In acid sphingomyelinase deficiency (ASMD), abnormal lipid (sphingomyelin) deposition is observed in reticuloendothelial macrophages. These cells are 50-90 µm in diameter and have a foamy appearance (6).

Since Niemann-Pick disease Type B, unlike Type A, has wide phenotypic heterogeneity and clinical findings of different severity, the presentation and disease progression of patients can differ. Patients are mostly diagnosed in adulthood, when lipid storage is slow and progressive and leads to deterioration in multiple organs, being most commonly deposited in the liver, spleen, lymph nodes, adrenal cortex and lungs. The most frequent findings at first presentation are splenomegaly (78%) and hepatomegaly (73%). With varying degrees of lung involvement, shortness of breath and recurrent pulmonary infections may also be presenting symptoms (42%) (7), and atherogenic lipid profile, hematological abnormalities, liver dys-
function, heart disease, skeletal abnormalities and growth delay may also be observed (5). Diagnosis is based on the measurement of sphingomyelinase activity in leukocytes, liver and bone marrow biopsies. The presence of foamy macrophages in the bone marrow and liver biopsies is also diagnostic. Our patient had pulmonary involvement, splenomegaly and thrombocytopenia, and was diagnosed with Niemann-Pick disease after observing foamy histiocytes in the bone marrow and lung biopsies. Since the patient had reached adulthood and no neurological involvement was detected, the subtype was determined as B. Pulmonary involvement in NPD Type B is seen at a rate of 90–98% (7,8) and the lower lobe is dominant. The clinical picture can range from mild symptoms to a more chronic form (9,10). The most commonly reported respiratory symptoms are dyspnea upon mild exertion and recurrent infections. Some studies have reported that lung disease is the clinical feature with the worst effect on the patient's clinic in NPD-B patients.

In a multi-center study in which 53 NPD-B patients (mean age 23.3 years) were examined prospectively, 47/53 (90%) and 51/53 (98%) were found to have interstitial lung disease based on chest radiography and CT, respectively (8), and the authors concluded that the lung is the most commonly affected organ in all age groups in patients with NPD-B. In another study, various degrees of ILD findings (ground glass, reticulonodular densities, pleural thickening and decreased lung volume) were found in almost all patients (90%; 53/59) (7). Although pulmonary involvement is common, it is a fact that pulmonologists do not consider storage diseases in the foreground in the differential diagnosis of ILD due to the different clinical spectrum. When our patient was re-evaluated retrospectively following diagnosis, the presence of splenomegaly in the upper abdominal sections of a lung tomography and low platelets in the hemogram were observed.

The radiological follow-up of patients diagnosed with NPD Type B is also recommended (8). Although it has been reported that interstitial pattern density and respiratory dysfunction are not correlated (8), it has been observed that patients with dyspnea in particular have lower FVC and DLCOs than those without (7). Furthermore, the annual pulmonary functional loss has been observed to be quite low in observational studies (11), which suggest that involvement is not in the form of progressive pulmonary fibrosis. In our patient, no significant decrease was noted in vital capacity during long-term follow-up, and despite prolonged radiological and functional stabilization, there was a marked progression of cough symptoms. Lipid-loaded macrophages can be observed in bronchoalveolar fluid, but are not specific for NPD. Especially in open lung biopsy, the appearance of lipid-loaded histiocytes stained dark blue with May-Grünwald-Giemsa supports a diagnosis of Niemann-Pick (sea blue histiocytes). Since the diagnosis of NPD was obtained later in life in our patient, an open lung biopsy was performed initially for the etiology of interstitial lung disease, and histiocytes with foamy cytoplasm were observed in the

Figure 1: Interlobular septal thickening and centriacinar nodules in all common zones (a,b,c)

Figure 2: Histiocytes with foamy cytoplasm filling the alveoli and interstitium on wedge biopsy (Hematoxylin Eosin, x40, x100)
alveolar area. The need for a lung biopsy in the presence of appropriate radiological findings in patients diagnosed with storage disease is controversial, as the risks associated with invasive interventions may be greater than the benefit, especially in patients without significant functional deterioration.

Although there is no effective treatment for Type B, limited success has been achieved in the small number of patients who underwent bone marrow and stem cell transplantation (12). Clinical studies have been conducted involving gene therapies and enzyme replacement therapy, and whole lung lavage has been reported in cases of lipid storage disease (13).

CONCLUSION

Due to the rarity of storage diseases and their wide heterogeneity, they may not be considered by the clinician dealing with interstitial lung disease in a differential diagnosis, although the systematic evaluation of patients is very important. As in our case, it is very important to evaluate patients with interstitial lung disease in a multidisciplinary manner in the presence of additional system findings.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - G.G., P.P., A.Y., E.Y.Ö.N., M.D.G., N.Ü., G.Ç.; Planning and Design - G.G., P.P., A.Y., E.Y.Ö.N., M.D.G., N.Ü., G.Ç.; Supervision - G.G., P.P., A.Y., E.Y.Ö.N., M.D.G., N.Ü., G.Ç.; Funding - G.G., P.P., A.Y., E.Y.Ö.N., M.D.G., N.Ü., G.Ç.; Materials - G.G., P.P., A.Y., E.Y.Ö.N., M.D.G., N.Ü., G.Ç.; Data Collection and/or Processing - G.G., P.P., A.Y., E.Y.Ö.N., M.D.G., N.Ü., G.Ç.; Analysis and/or Interpretation - G.G., P.P., A.Y., E.Y.Ö.N., M.D.G., N.Ü., G.Ç.; Literature Review - G.G., P.P., A.Y., E.Y.Ö.N., M.D.G., N.Ü., G.Ç.; Writing - G.G., P.P., A.Y., E.Y.Ö.N., M.D.G., N.Ü., G.Ç.; Critical Review - G.G., P.P., A.Y., E.Y.Ö.N., M.D.G., N.Ü., G.Ç.

REFERENCES

1. Schuchman EH, Desnick RJ. Niemann Pick Disease Types A and B: Acid sphingomyelinase deficiencies. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic & Molecular Bases of Inherited Disease. 8th ed. McGraw Hill; New York; 2001:3589-3610.

2. Spence M, Callahan J. Sphingomyelin-cholesterol lipidoses: The Niemann Pick group of diseases. McGraw-Hill; New York: 1989.

3. Swaiman KF, Ashwal S. Pediatric Neurology. 3rd ed. St Louis, Missouri: 1999;273:447-9.

4. Pentchev PG, Vanier MT, Suzuki K, Patterson MC. Niemann Pick type C: A cellular cholesterol lipodisosis. In: Charles RS, Arthur LB, William SS, David V eds. The metabolic and molecular bases of inherited disease. Vol 2, 1995:2625-29.

5. McGovern MM, Avetisyan R, Sanson BJ, Lidove O. Disease manifestations and burden of illness in patients with acid sphingomyelinase deficiency (ASMD). Orphanet J Rare Dis 2017;12:1-13. [CrossRef]

6. Watts RWE. Lysosomal storage disease. In: Weatherall DJ, Warrell DA, eds. Oxford textbook of medicine. 3rd ed. Oxford University Press;1996:1426-37.

7. McGovern MM, Wasserstein MP, Giugliani R, Bembi B, Vanier MT, Mengel E, et al. A prospective, cross-sectional survey study of the natural history of Niemann-Pick disease type B. Pediatrics 2008; 122:341-49. [CrossRef]

8. Mendelson DS, Wasserstein MP, Desnick RJ, Glass R, Simpson W, Skloot G, et al. Type B Niemann-Pick disease: findings at chest radiography, thin-section CT, and pulmonary function testing. Radiology 2006; 238:339-45. [CrossRef]

9. Minai OA, Sullivan EJ, Stoller JK. Pulmonary involvement in Niemann-Pick disease: case report and literature review. Respir Med 2000; 94:1241-51. [CrossRef]

10. von Ranke FM, Pereira Freitas HM, Mancano AD, Rodrigues RS, Hochhegger B, Escussato D, et al. Pulmonary involvement in Niemann-Pick disease: a state-of-the-art review. Lung 2016; 194:511-8. [CrossRef]
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11. Wasserstein MP, Desnick RJ, Schuchman EH, Hossain S, Wallenstein S, Lamm C, et al. The natural history of type B Niemann-Pick disease: results from a 10-year longitudinal study. Pediatrics 2004; 114:672-7. [CrossRef]

12. Bayever E, Kamani N, Ferreira P, Machin GA, Yudkoff M, Conard K, et al. Bone marrow transplantation for Niemann-Pick type 1A disease. J Inherit Metab Dis 1992; 15:919-28. [CrossRef]

13. Nicholson AG, Wells AU, Hooper J, Hansell DM, Kelleher A, Morgan C. Successful treatment of endogenous lipoid pneumonia due to Niemann-Pick type B disease with whole-lung lavage. Am J Respir Crit Care Med 2002; 165:128-31. [CrossRef]
Could BiPAP Cause Air in the Right Atrium?

BiPAP Sağ Atriyumdaki Havanan Nedeni Olabilir mi?

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Abstract

Air embolism refers to the entry of air into the venous or arterial system via direct conduction and pressure difference. The most common causes are iatrogenic, and are observed to be related to surgical and invasive procedures. The consequences of air embolisms depend on the air volume and the velocity of air entry. The clinical presentations may vary from asymptomatic course to shock. Emergency treatments include the provision of hemodynamics, oxygen support and positioning, and hyperbaric oxygen therapy in selected cases. In the present study we investigate the cause of the development of a venous air embolism in a patient on bilevel positive airway pressure (BiPAP) ventilation at home due to chronic respiratory failure and resorption in the short term without hyperbaric oxygen therapy.

Key words: Air embolism, BiPAP, Iatrogenic, Hyperbaric oxygen therapy.

Özet

Hava embolisi, havanın, direkt ileti ve basınç farklı yoluyla venöz veya arteriyel sisteme girmesi olarak tanımlanmaktadır. En sık görülen nedenleri iyatrojenik olup yapılan cerrahi ve invazif işlemlere bağlı olduğu görülmüştür. Hava embolisinin sonucu hava hacmine ve havanın giriş hızına bağlıdır. Kliniği asptomatik seyirden şoka giden tabloda kadar değişkenlik gösterebilir. Acil tedavi yöntemi ise hemodinaminin sağlanması, oksijen desteği ve pozisyon vermedir ve seçili olgularda hiperbarik oksijen tedavisi. Bu olgu sunumunda kronik solunum yetmezliği nedeniyle evde bilevel pozitif hava yoluna (BiPAP) kullanılarak geliştirilen hava embolisinin nedenlerini ve hiperbarik oksijen tedavisini verilmeden kısa dönemde rezorbe olduğunu göstermeyi amaçladık.

Anahtar Sözcükler: Hava embolisi, BiPAP, İyatrojenik, Hiperbarik oksijen tedavisi.

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Air embolism is a potentially life-threatening event that may occur within the venous or arterial system depending on the entry site, and is a rare complication of invasive medical or surgical procedures (1,2). The consequences of air embolism depend on the amount of air entering the bloodstream, the rate at which it enters and which bloodstream (venous or arterial) it enters. Arterial air embolisms can occur as a complication of lung biopsy, arterial catheterization or cardiopulmonary bypass. Emergency management involves placing the patient in the high flow oxygen and right lateral decubitus position. A venous air embolism can occur during pressurized venous infusions or catheter manipulation, and emergency treatment involves placing the patient on high-flow oxygen and in the left lateral decubitus and/or Trendelenburg position.

CASE

An 86-year-old male patient was admitted to the emergency room with abdominal pain, dizziness, fainting and short-term vision loss. He had a known diagnosis of hypertension, diabetes mellitus and heart failure, and was using BiPAP at home due to chronic respiratory failure. Upon entry to the emergency room, his vital signs were blood pressure, arterial 90/60 mmhg, and his room air oxygen saturation, measured by pulse oximetry, was 92–93%. The arterial blood gas examined revealed below 2 l/min oxygen, pH: 7.5 PCO2: 46.7 mmHg PO2: 88 mmHg and Sp02: 98 %. Among the laboratory findings, the leukocyte count was high, at 11000, CRP: 17 mg/L (0-8) and Creatine 1.95 mg/dL. A computed tomography (CT) guided pulmonary angiography was planned for the pulmonary embolism, but when the calculated glomerular filtration rate of the patient was low, a non-contrast computed tomography was performed. In the resulting tomography, the left subclavian vein, the vena cava at the level of the thoracic inlet, the right atriunm and the pulmonary trunk were leveled, and the linear air spaces in the anterior neighborhood of the right main pulmonary artery and findings were suggestive of pulmonary fibrosis (Figure 1) Air volume was calculated as 7–8 mL, although no air spaces were observed in the left pulmonary artery, or in the pulmonary artery segment and the subsegment branches. Cardiology consultation was requested for the patient for the assessment of cardiac functions, and the ejection fraction was calculated as 50–55%. Abdominal and cranial tomographies were also performed on the patient with suspected air embolism, but no pathology was detected. The patient was taken to the internal intensive care unit for close follow-up. Inotropic treatment was started due to a hypotensive course. Oxygen was given through a mask, and the patient was placed in the left lateral decubitus position. A control thoracic CT taken three days later revealed the air areas to have markedly resorbed (Figure 2). During follow-up, inotropic treatment was terminated after the patient progressed to normotensive.

DISCUSSION

Air embolism can develop on the venous or arterial side of the circulatory system. Generally, venous air embolism can be well tolerated. In humans, 200–500 mL of air given at 100 mL/sec has been defined as acutely fatal (~3–5 mL/kg) (3). Which pathway arises depends largely on the volume of gas deposited in the right ventricle. If the embolism is large (about 5 mL/kg), there may be a complete outlet obstruction due to the inability to des- tension the ventricular wall from the right ventricle. This can lead rapidly to right-sided heart failure and sudden cardiovascular collapse. Less volume venous air embolism, on the other hand, may lead to a decrease in cardiac output, hypotension, myocardial and cerebral ischemia, and even death. The entry of air into pulmonary circulation may cause pulmonary vasoconstriction, the release of inflammatory mediators, bronchoconstriction, and an increase in ventilation/perfusion mismatch. (2) The measured air embolism in our case was calculated as 7–8 mL. The adverse effects of air embolism depend heavily on the volume of the embolism and its delivery rate, with small acute volumes being generally well tolerated, while larger volumes have significant effects on the cardiovascular, pulmonary and cerebral systems. Upon admission, the patient presented here complained of dizziness, abdominal pain and short-term vision loss. No neurological pathology was identified upon examination. In previous studies air embolism is most often attributed to sitting position operations, neurosurgical interventions, varicose surgery, gynecological interventions, central venous catheter insertion or air in fluid sets, hemodialysis or high-pressure mechanical ventilation applications (2).

Figure 1: Air spaces leveled in the pulmonary trunk and right atrium
When the current case was questioned, no history of intervention was ascertained. Although there are cases with air embolism after high-pressure mechanical ventilation applications, a case of cerebral embolism after BiPAP use has been detected in the literature. (4-7) Previous studies have reported the application of positive end-expiratory pressure (PEEP) for the prevention of air embolisms (2,8). Since the patient in the present study was not detected with subcutaneous emphysema or pneumomediastinum, the air embolism was not attributed to the use of BiPAP. Following an evaluation, it was thought that the air may have developed iatrogenically during the routine vascular access upon entry to the first emergency room, and since the embolism amount was not too much and the clinical course did not worsen, the patient was followed up with mask oxygen, and the embolism was subsequently resorbed after 3 days.

CONCLUSION

Air embolisms are mostly attributable to iatrogenic reasons, and are a clinical condition that can change their clinical course depending on the duration of entry and the quantity of air. Air embolisms should be considered in cases of unexplained dyspnea, hypotension and neurological symptoms, and the necessary examinations and treatments should be planned accordingly.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - B.A., M.Ç., A.Ö.; Planning and Design - B.A., M.Ç., A.Ö.; Supervision - B.A., M.Ç., A.Ö.; Funding - M.Ç.; Materials - M.Ç., A.Ö., U.K., A.I.; Data Collection and/or Processing - B.A.; Analysis and/or Interpretation - B.A.; Literature Review - B.A., M.Ç.; Writing - B.A.; Critical Review - B.A., M.Ç.

REFERENCES

1. Muth CM, Shank ES. Gas embolism. N Engl J Med 2000; 342:476-82. [CrossRef]
2. Mirski MA, Lele AV, Fitzsimmons L, Toung TJ. Diagnosis and treatment of vascular air embolism. Anesthesiology 2007; 106:164-77. [CrossRef]
3. Feil M. Preventing central line air embolism. Am J Nurs 2015; 115:64-9. [CrossRef]
4. Huang HJ, Lei S, Yang L, Jin LM. Systemic air embolism in a fungal pneumonia patient with lung cavities formation and review of literature. Chin J Traumatol 2019 Oct; 22:308-310. [CrossRef]
5. Gursoy S, Duger C, Kaygusuz K, Ozdemir Kol I, Gurelik B, Mimaroglu C. Cerebral arterial air embolism associated with mechanical ventilation and deep tracheal aspiration. Case Rep Pulmonol 2012; 2012:416360. [CrossRef]
6. Weaver LK, Morris A. Venous and arterial gas embolism associated with positive pressure ventilation. Chest 1998; 113:1132-4. [CrossRef]
7. Rivara CB, Chevrolet JC, Gasche Y, Charbonney E. Fatal brain gas embolism during non-invasive positive pressure ventilation. BMJ Case Rep 2008; 2008:br0620080163. [CrossRef]
8. Perkins NA, Bedford RF. Hemodynamic consequences of PEEP in seated neurological patients—implications for paradoxical air embolism. Anesth Analg 1984; 63:429-32. [CrossRef]
Methemoglobinemia due to Dapson Use: A Case Report

Dapson Kullanımına Bağlı Gelişen Methemoglobinemi: Olgu Sunumu

Recai Ergün, Serap Atik, Dilek Ergün, Fikret Kanat

Abstract

Dapson, although generally well tolerated, can lead to hematological side effects. Although methemoglobinemia is a rare clinical condition, it can culminate in death if not treated in a timely and appropriate manner. A 21-year-old male patient presented to our outpatient clinic with shortness of breath, with oxygen saturation in ambient air measured by pulse oximetry at 88%. His initial medical history and physical examination were unremarkable for possible causes of dyspnea, while arterial blood gas measurements revealed methemoglobin elevation (Fmethb: 10.6). Detailed history revealed that dyspnea with subsequent hypoxia had started after dapsone treatment due to IgA dermatitis. We present this case report to highlight the possible role of dapsone as a rare cause of hypoxemia and methemoglobinemia, as exemplified in this young patient undergoing dapsone treatment for IgA dermatitis in which dyspnea was the initial symptom.

Key words: Methemoglobinemia, dapson, hypoxemia.

Özet

Dapson genellikle iyi tolere edilmesine rağmen hematolojik yan etkiler gösterebilir. Methemoglobinemi ender bir klinik durum olmasına karşın, zamanında ve uygun tedavi edilmemiş takdirde ölüme neden olabilir. Bir erkeğin 21 yaşında nefes darlığı nedeniyle poliklinikimize başvurusu üzerine; oda havasındak wurde %88 idi. Öykü, fizik muayene ve tetkiklerinde nefes darlığı açıklayacak bulgu yoktu. Arter kan gazında methemoglobin düzeyi yüksek (Fmethb: 10,6) olarak saptandı. Dispne ve hipoksi bulguları olan hastada dermatolojik anamnezde IG A Dermatitine bağlı dapson kullanımını öğrenildi. IG A dermatiti nedeniyle dapsone değer katmak ve dispne ile başvuran genç hastada hipoksemi ve methemoglobineminin nadir nedenlerinden olan dapson kullanımını akla getirmek adına bu olgu sunuyoruz.

Anahtar Sözcükler: Methemoglobinemi, dapson, hipoksemi.

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Hemoglobin (Hb) is an iron-containing molecule (iron in its ferrous form, i.e. Fe+2) that is found in erythrocytes and is responsible for carrying oxygen to tissues. Methemoglobinemia results from the oxidation of iron in hemoglobin into its ferric (Fe +3) form due to oxidative stress. The resultant methemoglobin is reduced by the cytochrome b5 reductase enzyme found in erythrocytes, and the inhibition of this enzyme causes methemoglobinemia. Dapson (4,4-Diaminodiphenylsulphone) is a sulfone antibiotic that inhibits the synthesis of folate and has potent anti-inflammatory effects (1), and is used for the treatment of leprosy, malaria, Pneumocystis jirovecii pneumonia and some other dermatological disorders (2).

We present this case report to remind clinicians of the potential of dapson to cause methemoglobinemia, exemplified here by a young male patient receiving dapson for the past 2.5 years due to IgA dermatitis.

CASE

A consultation was requested from the dermatology unit for a 21-year-old male patient with dyspnea with no symptoms other than shortness of breath, no reported tachycardia, tachypnea or headache, and no neurological complaints. The patient’s medical history revealed a diagnosis of IgA dermatitis dating back 5 years, treated with dapson (50 mg, q.i.d.) and methylprednisolone (16 mg o.m.) for the past 2.5 years, but no other disease or drug use history. A physical examination revealed blood pressure: 124/80 mmHg, pulse: 88 beats/minute, respiratory rate: 19/minute, saturation with pulse oximeter: 88% and fever: 36.5 °C. There was no cyanosis, and chest sounds were normal. The patient was conscious, oriented and cooperative, there was no cyanosis on the skin, or any significant pathological findings in other system examinations, and no significant pathological finding on electrocardiography except sinus tachycardia. Complete blood count, biochemistry panel, D-dimer and collagen disease markers were also normal. A chest x-ray revealed no pathological findings (figure 1), and arterial gas analysis results were as follows: pH 7.38, PaCO₂ 46.6 mmHg, PaO₂ 67.3 mmHg, arterial oxygen saturation 88%, lactate 1.6 mmol/l and methemoglobin (Fmethb) 10.6%.

Furthermore, no clinical or radiological signs suggestive of pulmonary embolisms were detected, and echocardiography, peripheral blood smear and hemoglobin electrophoresis were normal. The family history was negative for hereditary methemoglobinopathy. Due to the lack of other potential causes of methemoglobinemia and high Fmethb, a diagnosis of drug-related methemoglobinemia was suspected. His ongoing treatment with dapson was discontinued was monitored, and oxygen inhalation and high dose intravenous ascorbic acid (2 g infusion for 3 days) were administered, after which the patient's shortness of breath resolved. Blood pressure was 120/86 mmHg, pulse: 82/min, respiratory rate: 16/min and saturation measured with pulse oximeter: 96%. The blood gas analysis was as follows: pH 7.41, PaCO₂ 40.5 mmHg, PaO₂ 95.4 mmHg, arterial oxygen saturation 97%, lactate 1.6 mmol/l and methemoglobin (Fmethb) 1.2%. The patient responded to treatment with a reduction of methemoglobin, and was subsequently discharged.

DISCUSSION

Dapson is an aniline derivative belonging to the class of synthetic sulfones with both anti-bacterial and anti-inflammatory activities (2). Although the exact mechanism of action of dapson in inflammatory disorders is unknown, it has been proposed to inhibit neutrophil chemotaxis and lysosomal enzymes in addition to reducing free oxygen radicals as a result of its antioxidant properties (3). Dapson is metabolized by the hepatic cytochrome P450 enzymes. The hematological side effects of dapson, such as hemolytic anemia and methemoglobinemia, have been largely attributed to the potent oxidative effects of its metabolites (3,4). Methemoglobinemia emerges as a result of decreased activity in the enzyme cytochrome b reductase found in erythrocytes (5).
Methemoglobin is formed through the oxidation of ferrous iron (Fe²⁺) to its ferric form (Fe³⁺) in the hemoglobin molecule, leading to structural changes, reduced O₂ carrying capacity and the prevention of O₂ supply to tissues. Consequently, a shift in oxygen concentration is observed, and functional anemia develops (6). Methemoglobinemia may be acquired or hereditary, the former being more common (7). Most cases of acquired methemoglobinemia result from increased methemoglobin production induced by exogenous substances. To date, various chemical molecules and drugs have been reported to be associated with acquired methemoglobinemia, including nitrites, nitrates, chlorates, quinines, aminobenzenes, nitrobenzenes, nitrotoluenes, phenacetine, chloroquine, dapsone, phenytoin, sulfonamides and local anesthetics (2), among which dapsone and local anesthetic agents (benzocaine, lidocaine, prilocaine) represent the most frequent cause of methemoglobinemia. Heroin, cocaine and other illicit drugs may cause otherwise unexplained acquired methemoglobinemia (8,9), and nitrates and nitrates, root vegetables such as beetroot and carrots, turnip juice, mushroom poisoning and certain types of frozen foods containing nitrite as a preservative may be potential culprits. Dapsone, however, is the most frequent cause of methemoglobinemia, representing almost 42% of all cases in a reported series of 138 patients (10).

Methemoglobinemia should be suspected in patients with cyanosis and hypoxia that are unresponsive to oxygen replacement. The optimum first-line test in suspected cases is a simple blood gas analysis including quantification of methemoglobin levels. Pulse oximetry cannot detect methemoglobinemia and may present falsely normal oxygen levels. Symptoms may range from mild cyanosis, dyspnea or non-specific manifestations (headache, dizziness, fatigue, nervousness, drowsiness) to shock, severe respiratory depression, or sometimes fatal neurologic impairment (coma, seizures) resulting from tissue hypoxia (7).

Under normal conditions, methemoglobin comprises less than 1% of the total body hemoglobin (Hb), and when its levels rise, the oxyhemoglobin curve shifts to the left, leading to hypoxia, lactic acidosis and even death in severe cases. Methemoglobinemia is diagnosed when methemoglobin levels exceed 5% with the emergence of symptoms at levels greater than 10%. A methemoglobin percentage of >30% to 40% leads to severe symptoms, and is considered a life-threatening condition. A methemoglobin level of >10% is associated with cyanosis and skin discoloration, while tachycardia, fatigue, vomiting, nausea and respiratory stress become more marked at levels >30%. Lethargy, stupor and syncope may be observed at levels of >55%, and cardiovascular collapse and even death at levels of ≥70% (11,12).

A critical initial step in the management of methemoglobinemia is the elimination or discontinuation of the insulting agent. The need for treatment is dependent on the patient’s clinical condition and the level of methemoglobin. Appropriate supportive treatments should be given, such as opening an intravenous access route, fluid or vasopressor therapy for hypotension, intubation and mechanical ventilation for respiratory failure, and antiepileptic drugs for seizure. Active treatment is required in individuals with neurological signs or methemoglobin levels of >30% using methylene blue, ascorbic acid and riboflavin. Treatment may not be necessary in asymptomatic cases or in those with mild symptoms and methemoglobin levels of <20% (5, 12-14).

In the presented case, not requesting tests for hereditary methemoglobinemia can be considered a deficiency of the case report.

CONCLUSION
This case report highlights a potentially serious complication of dapsone treatment. In patients presenting with unexplained dyspnea, the potential for methemoglobinemia and dapsone as a triggering agent should be kept in mind. The first-line treatment should consist of methylene blue, and if this option is unavailable, high dose ascorbic acid should be considered.

CONFLICTS OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
Concept - R.E., S.A., D.E., F.K.; Planning and Design - R.E., S.A., D.E., F.K.; Supervision - R.E., S.A., D.E., F.K.; Funding - R.E., S.A., D.E., F.K.; Materials - F.K., S.A., U.K., A.I.; Data Collection and/or Processing - S.A., R.E., D.E.; Analysis and/or Interpretation - R.E., D.E., S.A.; Literature Review - R.E., S.A., D.E.; Writing - R.E., S.A., D.E., F.K.; Critical Review - F.K., R.E.

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REFERENCES

1. Ashurst JV, Wasson MN, Hauger W, Fritz WT. Pathophysiologic mechanisms, diagnosis, and management of dapsone-induced methemoglobinemia. J Am Osteopath Assoc 2010; 110:16-20.

2. Sago J, Hall III RP. Dapsone. Dermatol Ther 2002; 15:340-51. [CrossRef]

3. Wolf R, Matz H, Orion E, Tuzun B, Tuzun Y. Dapsone. Dermatol Online J 2002; 8:2. [CrossRef]

4. Cucinell SA, Israeli ZH, Dayton PG. Microsomal N-oxidation of dapsone as a cause of methemoglobin formation in human red cells. Am J Trop Med Hyg 1972; 21:322-31. [CrossRef]

5. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. Ann Emerg Med 1999; 34:646-56. [CrossRef]

6. Vieira JL, Riveira JG, Martins Ade N, Silva JP, Salgado CG. Methemoglobinemia and dapsone levels in patients with leprosy. Braz J Infect Dis 2010; 14:319-21. [CrossRef]

7. Cortazzo JA, Lichtman AD. Methemoglobinemia: a review and recommendations for management. J Cardiothorac Vasc Anesth 2014; 28:1043-7. [CrossRef]

8. Falkenhahn M, Kannan S, O’Kane M. Unexplained acute severe methaemoglobinemia in a young adult. Br J Anaesth 2001; 86:278-80. [CrossRef]

9. McKinney CD, Postiglione KF, Herold DA. Benzocaine-adultered street cocaine in association with methemoglobinemia. Clin Chem 1992; 38:596-7. [CrossRef]

10. Ash-Bernal R, Wise R, Wright SM. Acquired methemoglobinemia: a retrospective series of 138 cases at 2 teaching hospitals. Medicine (Baltimore) 2004; 83:265-273. [CrossRef]

11. Mansouri A. Methemoglobinemia. Am J Med Sci 1985; 289:200-9. [CrossRef]

12. Coleman MD, Coleman NA. Drug-induced methaemoglobinemia. Treatment issues. Drug Saf 1996; 14:394-405. [CrossRef]

13. Dötsch J, Demirkça S, Kratz M, Repp R, Knerr I, Rascher W. Comparison of methylene blue, riboflavin, and N-acetylcysteine for the reduction of nitric oxide-induced methemoglobinemia. Crit Care Med 2000; 28:958-61. [CrossRef]

14. Park SY, Lee KW, Kang TS. High-dose vitamin C management in dapsone-induced methemoglobinemia. Am J Emerg Med 2014; 32:684.e1-3. [CrossRef]

15. Mansouri A. Methemoglobinemia. Am J Med Sci 1985; 289:200-9. [CrossRef]
Spontaneous Pneumomediastinum without Pneumothorax in Non-ventilated COVID-19 Pneumonia: A Case Report

İnvazif-Non-İnvazif Ventilasyon Uygulanmayan COVID-19 Pnömonisinde Pnömotoraks Olmadan Spontan Pnömomediastinum: Olgu Sunumu

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Abstract

Spontaneous pneumomediastinum (SPM) is among the rare complications of Coronavirus Disease-19 (COVID-19) and usually involves patients with a severe form of disease who are undergoing treatment with invasive/non-invasive ventilation or high-flow oxygen therapy. A very low percentage of SPM cases are detected in non-ventilated COVID-patients, the underlying causes of which are still to be understood. We report here on the case of a 65-year-old patient with no clinical history of cardiovascular or pulmonary disease who developed SPM within a few days following hospital admission. SPM was detected on chest CT-angiography, and was unrelated to high-flow oxygen treatment.

Key words: COVID-19, Spontaneous pneumomediastinum, SARS-CoV-2.

Özet

Spontan pnömomediastinun (SPM) korona virüs (COVID-19) hastalığının nadir komplikasyonları arasında bulunmaktadır. Genellikle invazif / non-invazif ventilasyon veya yüksek akımlı oksijen tedavisi olan ve hastalığı ağır şekilde geçirmekte olan hastalarla görülür. Ventilasyon kullanılmayan COVID-19 hastalarında çok düşük oranda SPM tespit edilmektedir. Ancak SPM gelişmesinin altında yatan nedenler hala tam olarak anlaşılamamıştır. Bu makalede 65 yaşındaki, klinik olarak kardiyovasiküler veya pulmoner hastalıktan olmayan, hastaneye yatıştan sonraki birkaç gün içinde SPM gelişen bir olgu sunulmuştur. Toraks BT-anjiyografisinde SPM tespit edilmiş olup yüksek akımlı oksijen tedavisi kullanılmamıştır.

Anahtar Sözcükler: COVID-19, spontan pnömomediastinum, SARS-CoV-2.

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As of May 2021, more than 133 million confirmed coronavirus cases have been reported in 220 countries around the world, along with more than 3 million deaths. Coronavirus Disease-19 (COVID-19), the clinical manifestation of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection(1), is known to present with a wide range of symptoms and signs, such as fever, cough, dyspnoea, myalgias and asthenia, as well as digestive symptoms, although in most cases the course of infection is asymptomatic.

ARDS (Acute Respiratory Distress Syndrome) is the main cause of death, usually following a hyperinflammatory state, and develops rapidly in 5% of patients with coronavirus infection (2,3). The RT-PCR (reverse transcription-polymerase chain reaction) detection of SARS-CoV-2 mRNA is the standard approach for in-hospital and outpatient diagnosis, although in recent months CT scans have been used as a fundamental tool not only for diagnosis, but also for measuring the extent of the compromised parenchyma in COVID patients (4,5). Chest CT scans, together with laboratory inflammatory markers, can help clinicians decide upon an appropriate therapy, and CT examinations, in particular, may be useful for revealing some atypical signs that would not otherwise be detectable from a physical examination. Up to 1% of COVID patients have been stated to develop spontaneous pneumothorax (6), while spontaneous pneumomediastinum (SPM) is a rarer complication, remaining anecdotal, and has been described in only a few reports (7,8). SPM, defined as an air-flap in the mediastinum that is not associated with trauma, is a well-known complication in many infections of the lung (9-11), and is often associated with pneumothorax and/or subcutaneous emphysema, resulting from alveolar rupture, and often occurs secondary to acute increases in intrathoracic pressure.

Common causes include exercise, drugs, asthma, vomiting or Valsalva maneuvers. It is rarely benign and self-limited, and is more prevalent in young males. Typical symptoms include the triad of pneumomediastinum, being thoracic pain, dyspnea and subcutaneous emphysema. Harman’s sign, being crepitus heard on auscultation of the heart, is a common finding, and may be the only abnormal physical finding (12). A physical examination is often insufficient for a diagnosis of SPM, with a need for CT scans for confirmation. Released alveolar air dissects centripetally through the pulmonary interstitium along the bronchovascular sheaths, toward the pulmonary hila and into the mediastinum, which is a pathophysiological mechanism that was described by Macklin et al. in 1944, and is known as the Macklin effect (13).

High-flow oxygen therapy, when supplied, increases the risk of complications, such as those cited above; while CPAP, NIV and HFNC increase intra-alveolar pressure, and considering that acute lung deterioration with rapid desaturation is per se a reason favouring alveolar rupturing, it is easy to understand how severe forms of pneumonia treated with high-flow oxygen therapy can result in poor outcomes. We report here on the case of a 65-year-old male who developed SPM after being hospitalized for COVID-19, even without receiving high-flow or high-pressure oxygen therapy.

**CASE**

In April 2021, a 65-year-old male presented to the emergency ward of M. Bufalini Hospital in Cesena, Italy, with a 10-day history of fever, dry cough and diarrhoea, and was subsequently diagnosed with SARS-CoV-2 infection after a RT-PCR detection of viral mRNA on a nasopharyngeal swab.

He was a non-smoker with a history only of celiac disease, and had been on no drug-therapy prior to hospital admission. Upon arrival, he was awake, alert and oriented, with a body temperature of 36°C, respiratory rate of 30 breaths per minute, blood pressure 125/70 mmHg, pulse 92 beats per minute and arterial oxygen saturation (SpO2) 90% at rest. The Modified Early Warning Score (MEWS), calculated at the time of admission, was 3, while the National Early Warning Score (NEWS) score was 6. Both scores were calculated to assess the patient’s clinical stability (14).

The patient was placed on low-flow oxygen therapy through a non-rebreather mask, despite no signs of respiratory fatigue being reported. An arterial blood sample examination and routine blood tests were performed, the former of which revealed respiratory insufficiency with a PaO₂/φO₂ ratio of 296, while the latter showed increased serum LDH (384 U/L) and CPK (479 U/L), neutrophilic leukocytosis (WBC 12500/mmc, N 11500/mmc) with lymphopenia (L 600/mmc) and high serum CRP (15.7 mg/dl). Urinary antigen testing for L. pneumophila and S. pneumoniae was negative, as were the blood cultures. Table 1 presents a summary of the blood test results during the patient’s hospital stay.

| Table 1: Laboratory exams of patient during hospitalization |
|-------------------------------------------------------------|
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|                         | Day 1       | Day 2       | Day 7       | Day 11      | Day 13      | Range        |
|-------------------------|-------------|-------------|-------------|-------------|-------------|--------------|
| WBC (n/mmc)             | 12510       | 11620       | 13340       | 9370        |             | 4000-10000   |
| RBC (n*10^6/mmc)        | 4.62        | 5.12        | 5.19        | 4.83        | 4.50-5.70   |
| Hb (g/dl)               | 15.1        | 16.5        | 17.1        | 15.8        | 13.50-17.00 |
| Hct (%)                 | 44          | 50          | 48          | 45          | 40-52       |
| MCV (fl)                | 94          | 97          | 92          | 92          | 80-95       |
| MCHC (%)                | 34.6        | 33.3        | 36          | 35          | 32-36       |
| Neutrophils (n/mmcf)    | 11510       | 8200        | 10770       | 6490        | 2000-8000   |
| Lymphocytes (n/mmcf)    | 600         | 2540        | 1470        | 1960        | 1000-4000   |
| Monocytes (n/mmcf)      | 370         | 810         | 790         | 860         | 200-1000    |
| Eosinophils (n/mmcf)    | 0           | 10          | 290         | 50          | 0-500       |
| Basophils (n/mmcf)      | 200         | 60          | 20          | 10          | 0-20        |
| Platelets (n/mmcf)      | 207000      | 464000      | 354000      | 214000      | 150000-45000 |
| Creatinine (mg/dl)      | 0.88        | 0.83        | 0.68        | 0.75        | 0.70-1.20   |
| eGFR (ml/min)           | 90          | 92          | 100         | 96          | >90         |
| Azote (mg/dl)           | 24          |             |             |             | <71         |
| Tot bilirubin (mg/dl)   | 0.36        | 0.6         |             |             | <1.20       |
| Direct bilirubin (mg/dl)| 0.2         | 0.2         |             |             | <0.30       |
| Sodium (mmol/l)         | 132         | 138         | 138         | 135         | 136-145     |
| Potassium (mmol/l)      | 3.8         | 4.8         | 4.5         | 4.3         | 3.5-5.1     |
| Chlorine (mmol/l)       | 95          |             |             |             | 98-107      |
| Calcium (mg/dl)         |             |             |             |             | 9.5         |
| AST (U/L)               | 43          |             |             |             | <40         |
| ALT (U/L)               | 25          | 88          |             |             | <41         |
| GGTT (U/L)              | 33          |             |             |             | 8-61        |
| CPK (U/L)               | 479         |             |             |             | 30-240      |
| LDH (U/L)               | 384         |             |             |             | 135-225     |
| Troponin T (ng/ml)      | 9           |             |             |             | <15         |
| C-Reactive Protein (mg/dl)| 15.7      | 20.5        | 1.6         |             | <0.5        |
| PT (INR) (ratio)        | 1.1         |             |             |             | 0.80-1.20   |
| aPTT (ratio)            | 0.93        |             |             |             | 0.80-1.20   |
| D-dimer (ng/ml)         | 440         |             |             |             | <500        |
| Quantiferon             | Negative    |             |             |             | Negative    |
| IL-6 (pg/ml)            | 116         |             |             |             | <5.9        |
| Ferritin (mg/dl)        | 1390        |             |             |             | 30-400      |
| Procalcitonin (ng/ml)   | 0.24        |             |             |             | <0.5        |

WBC= White Blood Cells; RBC= Red Blood Cells; Hb= Haemoglobin; Hct= Hematocrit; MCV= Medium Corpuscular Volume; MCHC= Mean Corpuscular Haemoglobin Concentration; eGFR= estimated Glomerular Filtration Rate; AST= Aspartate Transferase; ALT= Alanine Transferase; GGTT= Gamma Glutamyl Transpeptidase; CPK= Creatine Phosphokinase; LDH= Lactic Dehydrogenase; PT= Prothrombin Time; aPTT= activated Partial Thromboplastin Time; IL-6= Interleukin-6
On day 8 following admission, we decided to increase the oxygen supply and to perform an arterial blood examination with 10 LPM and non-rebreather mask due to an increase in respiratory fatigue and lower SpO2 levels (92% with an oxygen flow of 6 litres per minute, LPM, fiO2 40%), leading to a mild worsening of pulmonary gas exchange (PaO2/fiO2 133 with fiO2 45%).

A chest CT-angiography was performed to allow a better assessment of parenchymal involvement in the lungs and to exclude signs of pulmonary embolism, revealing bilateral extended areas of parenchymal “ground glass” involvement in both the upper and lower lobes of the lungs, in addition to some areoles with a greater density that were suggestive of interstitial and alveolar pneumonia.

In contrast, a thorax study highlighted the presence of air within the adipose tissue of the anterior mediastinum with a 2 cm thick and 6 cm long air leak. Figure 2 shows the pneumomediastinal leak in the axial and coronal scanning planes (a and b, respectively).

We consulted hospital intensivists to decide upon the best course of treatment for our patient, who recommended only a conservative approach. For the better definition of the patient’s healthcare pathway, we transferred him to our dedicated rooms with parameter monitoring systems where he again underwent a chest X-ray, revealing a slight extension of the interstitial involvement already described in the lower-left pulmonary field (Figure 1b). As a result of a progressive improvement in the patient’s clinical condition, we were able to reduce oxygen support until complete weaning, and the patient was discharged from hospital on day 20.

DISCUSSION

SPM has already been associated with severe acute respiratory syndrome (SARS) with a prevalence of 11.6% in a Chinese study in 2004 (16). A group of researchers from Mexico recently published a report on the frequency of SPM and the related risk factors in a healthcare facility dedicated to COVID inpatients (17). Within a cohort of 271 patients, nine developed SPM (3.3%), while four developed spontaneous pneumothorax (1.47%). None of the patients received mechanical ventilation at the time of admission, although the authors did not clarify whether or not continuous positive airway pressure (CPAP) or high flow nasal cannulas (HFNC) were administered during hospitalization. The authors confirmed that SPM is not related exclusively to the mechanical ventilation of COVID-19 patients, and can involve subjects with risk factors such as young age, tobacco use, obesity, and an underlying chronic pulmonary disease. On the other hand, when pressure-controlled ventilation is needed, the use of a low-pressure setting and low tidal volume is important.

A chest X-ray revealed parenchymal thickening in the right middle lung field and accentuated broncho-vascular markings (signs compatible with interstitial pneumonia) (Figure 1a), and the patient was subsequently admitted to our Internal Medicine department dedicated to COVID inpatients.

Steroid therapy with dexamethasone was administered starting on the first day at a dose of 6 mg/day together with low molecular weight heparin (LMWH) at a prophylactic dosage; empiric oral treatment for the persistent dry cough with dihydrocodeine was also administered, together with acetylcysteine and PPI. In line with regional and local guidelines criteria, we decided to treat the patient with Tocilizumab, an immunosuppressive drug that is used mainly for the treatment of rheumatoid arthritis to reduce the hyperinflammatory response to SARS-CoV-2 (15).

The patient was placed on low-flow oxygen therapy with simple face mask until day 7. SpO2 was within the 94-96% range for the duration of observation. The patient remained afebrile, and was advised to sleep in the prone position at night. Other vital parameters (blood pressure, respiratory rate and heart rate) also remained within the normal ranges. An arterial blood examination was repeated on the 3rd and 7th days with similar PaO2/fiO2 ratios (196 with fiO2 33%, and 173 with fiO2 37%, respectively).

On day 8 following admission, we decided to increase the oxygen supply and to perform an arterial blood examination with 10 LPM and non-rebreather mask due to an increase in respiratory fatigue and lower SpO2 levels (92% with an oxygen flow of 6 litres per minute, LPM, fiO2 40%), leading to a mild worsening of pulmonary gas exchange (PaO2/fiO2 133 with fiO2 45%).

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smoking, asthma and/or pulmonary emphysema, and the male gender. Similarly, Jones et al., in their study of 83 critically ill COVID inpatients, found that seven patients developed pneumomediastinum, with a prevalence of 8.4%, and all were reported to develop pneumomediastinum after CPAP or non-invasive ventilation (NIV) therapy were administered.

Pneumomediastinum can also occur independently of assisted ventilation, and although it is rarely reported among non-ventilated COVID inpatients, previous studies have described it as a possible complication in patients with Severe Acute Respiratory Syndrome (SARS), leading to poor outcomes.

In general, SPM has a reported incidence in non-COVID patients of 1 in 25,000, and is more common in males and children (7). The exact prevalence of SPM in COVID patients is not known, and literature contains only a few case reports. Consequently, it is necessary to identify the precise cause of cases occurring independently of mechanical invasive ventilation or non-invasive ventilation. In our case, the patient was treated only with low-flow oxygen, aside from in the few hours preceding the chest CT-angiography, when he was treated with 10 LPM via a reservoir mask. The patient was not placed on high-flow oxygen therapy, nor did he need non-invasive ventilation until complete oxygen weaning.

CONCLUSION

Spontaneous pneumomediastinum is still a rare complication in COVID-19 patients, and occurs with more frequency in patients on high-flow oxygen therapy or those being ventilated, even non-invasively. In other conditions, as happening for patients receiving low-flow oxygen therapy without being ventilated, only a few cases were described and often with poor outcomes, even if the underlying causes of the development of SPM are still unknown. As is the case for other complications related to COVID-19, further studies of the topic are needed.

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CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - S.G., E.G., G.L.C., N.G., P.S., M.T.M., G.M., A.L., E.M., R.D., E.P., L.M.; Planning and Design - S.G., E.G., G.L.C., N.G., P.S., M.T.M., G.M., A.L., E.M., R.D., E.P., L.M.; Supervision - S.G., E.G., G.L.C., N.G., P.S., M.T.M., G.M., A.L., E.M., R.D., E.P., L.M.; Funding - E.P., L.M.; Materials - S.G., M.T.M., G.M., E.P., L.M.; Data Collection and/or Processing - S.G., E.G., G.L.C., N.G., G.M., R.D.; Analysis and/or Interpretation - S.G., P.S., G.M., E.P., L.M.; Literature Review - S.G., P.S., E.P., L.M.; Writing - S.G., E.P., L.M.; Critical Review - P.S., E.P., L.M.

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REFERENCES

1. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. World Health Organization 2020.
2. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China. Clin Immunol 2020; 214:108393. [CrossRef]
3. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol 2017; 39:529-39. [CrossRef]
4. Li Y, Xia L. Coronavirus disease 2019 (COVID-19): Role of chest CT in diagnosis and management. Am J Roentgenol 2020; 214:1280-6. [CrossRef]
5. Tenda ED, Yulianti M, Asaf MM, Yunus RE, Septiyanti W, Wulani V, et al. The Importance of chest CT scan in COVID-19. Acta Med Indones 2020; 52:68-73.
6. Yang Q, Liu Q, Xu H, Lu H, Liu S, Li H. Imaging of coronavirus disease 2019: A Chinese expert consensus statement. Eur. J. Radiol. 2020; 127:109008. [CrossRef]

7. Kouritas VK, Papagiannopoulos K, Lazaridis G, Baka S, Karavasilis V, Lampaki S, et al. Pneumomediastinum. J Thorac Dis 2015; 7(Suppl.1):S44-9. [CrossRef]

8. Alavian N, Stephens JR, DeWalt DA. Spontaneous pneumomediastinum in a patient with COVID-19 pneumonia. J Gen Intern Med 2021; 1-2. [CrossRef]

9. Chekkoth SM, Supreeth RN, Valsala N, Kumar P, Raja RS. Spontaneous pneumomediastinum in H1N1 infection: uncommon complication of a common infection. J R Coll Physicians Edinb 2019; 49:298-300. [CrossRef]

10. Zhang X, Wang J, Zeng Q, Wu X, Jiang S, Shen J. Spontaneous pneumomediastinum and subcutaneous emphysema in avian influenza A (H5N6) human pneumonia. Clin Case Rep 2019; 7:2594-5. [CrossRef]

11. Tutor JD, Montgomery VL, Eid NS. A case of influenza virus bronchiolitis complicated by pneumomediastinum and subcutaneous emphysema. Pediatr Pulmonol 1995; 19:393-5. [CrossRef]

12. Graham CA, Ong YS. Hamman sign. Can J Emerg Med 2010; 12:63. [CrossRef]

13. Macklin MT, Macklin CC. Malignant interstitial emphysema of the lungs and mediastinum as an important oc-
Spontaneous Pneumomediastinum in an Asymptomatic COVID-19 Patient

Asemptomatik COVID 19 Hastasında Gelişen Spontan Pnömomediastinum

Mehmet Veysel Coşkun, Selma Karaahmetoğlu, Sinem Karaoğlu, Sema Nur Arasan, Merve Öztürk

Abstract

Spontaneous pneumomediastinum is a rare and life-threatening complication in patients with COVID-19. Although there are a few reports of spontaneous pneumomediastinum related to COVID-19 in literature, most involve patients who have been followed up in intensive care units (ICUs) or COVID-19 clinics for a period due to mild to severe COVID-19 disease. We present here a case of spontaneous pneumomediastinum that developed in an asymptomatic COVID-19 patient with no medical history.

Key words: Asymptomatic, COVID-19, pneumomediastinum.

Özet

Spontan pnömomediastinum, COVID-19 hastalarında nadir görülen ve hayatı tehdit eden komplikasyonlardan biridir. Literatürde az sayıda COVID-19’la bağlı spontan pnömomediastinum bildirimi bulunmakla birlikte, bu olgular daha çok orta ve şiddetli derecede COVID-19 hastalığı nedeni ile yoğun bakım ünitselerinde veya COVID-19 kliniklerinde bir süredir takip edilen hastalardır. Burada, bilinen dahili hastalığı olan asemptomatik bir COVID-19 hastasında gelişen spontan pnömomediastinum olgusunu sunduk.

Anahtar Sözcükler: Asemptomatik, COVID-19, pnömomediastinum.
COVID-19 is still an urgent health problem around the world, despite more than a year having passed since the World Health Organization (WHO) declared a global pandemic on March 11, 2020. Due to the many different clinical manifestations associated with COVID-19, updates to literature become significant, especially for rare complications of COVID-19, for the management of patients. Spontaneous pneumomediastinum is an uncommon and life-threatening complication of COVID-19, however there have been few reports to date on spontaneous pneumomediastinum due to COVID-19 presented by different clinics in different countries (1,2). While there have been studies published relating to COVID-19 patients with an absence of positive pressure ventilation, no underlying pulmonary disease and no smoking history, all have mild to severe COVID-19 infection, and have a history of ICU or COVID-19 clinic follow-up. In the present study we present a case of spontaneous pneumomediastinum due to asymptomatic COVID-19 infection in a young patient with no medical history.

CASE
A 26-year-old female non-smoker medical doctor with no medical history presented to the emergency clinic after developing sudden onset retrosternal chest pain during her COVID-19 night shift. She denied any trauma to the chest or abdomen in her medical history, and reported no tobacco or other substance use. She reported no other recent symptoms, including weakness, shortness of breath, fevers, chills, cough, abdominal or chest pain, nausea or vomiting, and had an insignificant family history. Around two weeks earlier she had taken a COVID-19 reverse transcriptase-polymerase chain reaction (RT-PCR) test (Bioeksen R&D Technologies Inc. COVID-19 RT-qPCR Detection Kit v2.0, Istanbul, Turkey) and an anti-COVID-19 antibody test (VIDAS Anti-SARS CoV-2 IgG and IgM (BioMérieux, Marcy-l’Etoile, France) as a control due to her active employment in a COVID-19 clinic and her cohabitation with her family, and both test results were negative. A physical examination revealed a forward-bent posture, reducing body movement and preventing deep inspiration. Mild emphysema was detected on the right side of the neck skin; chest auscultation was normal; and other systemic examination findings were unremarkable. Her vitals were: SpO2 97% in room air, body temperature 36 °C, respiratory rate 22 breaths/min, heart rate 81 beats/min and blood pressure 110/70 mmHg. Electrocardiography revealed normal sinus rhythm and there were no signs of myocardial ischemia. A thin radiolucent line was noted on right side of an antero-posterior chest X-ray (CXRs) with no pneumothorax findings (Figure 1). A chest computed tomography (CT) revealed diffuse air values in the mediastinum around the trachea and esophagus, extending to the hiluses. There was no infiltration of the lung parenchyma and no pleural or pericardial effusion was detected. No pneumothorax was observed, and other findings were normal (Figure 2). In order not to miss any acute cardiac pathology, a bedside echocardiography was performed, and left ventricular ejection fraction (LVEF), pulmonary artery pressures (PAP), in which all cardiac chamber sizes were found to be within the normal ranges, and no valve pathology was observed. Laboratory examinations revealed no abnormality in the routine biochemistry and complete blood count, and serum C-reactive protein, ferritin, procalcitonine, cardiac enzyme levels and coagulation test results were within the normal range. When the COVID-19 RT-PCR test and anti-COVID-19 IgG+IgM test were performed again, the COVID-19 RT-PCR test was negative but the anti-COVID-19 IgG+IgM was >10, reactive (Normal 0–0.99). The patient was hospitalized with oxygen therapy by nasal canule, and 3x1 gr cefazolin antibiotic therapy was initiated due to the risk of development of mediastinitis. The patient was monitored with a daily physical examination and antero-posterior CXRs. The chest pain and the emphysema detected on the neck skin dissipated on the fourth day of hospitalization. No pathology or any other symptoms were observed during follow-up. As the patient wanted to rest at home, she was discharged after receiving the recommendations of the thoracic surgery clinic. On the seventh day following discharge, the patient attended the post-COVID-19 outpatient clinic for control. She had no complaints, and no pathology was found during a physical examination and control antero-posterior CXRs (Figure 3).

DISCUSSION
WHO defines asymptomatic COVID-19 infection as a laboratory-confirmed infection with no overt symptoms (3). Asymptomatic COVID-19 infections are an significant aspect of COVID-19 due to the potential for the spread of infection, and those who come into contact with infected persons must be tested or followed up for COVID-19, regardless of the presence of symptoms. It is hard, however, to determine the true incidence of asymptomatic COVID-19 infections due to the need for close and widespread surveillance studies that must extend beyond the estimated average incubation period (4).
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Based on a systematic literature review, pneumomediastinum due to COVID-19 reports belonged to the hospitalized patients because of mild to severe COVID-19 infection. Even some of them had no etiological condition or positive pressure ventilation applications as a risk factor for spontaneous mediastinum (6). In the case presented here, the patient was non-hospitalized, had an asymptomatic COVID-19 infection and carried no risk factor for pneumomediastinum, and so is somewhat unique in literature. Based on the findings of this study, it can be emphasized that spontaneous pneumomediastinum should be kept in mind not only in mild to severe hospitalized COVID-19 cases, but also in asymptomatic non-hospitalized patients with sudden onset chest pain, and such cases should be evaluated with a physical examination and lung imaging.

CONFLICTS OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
Concept - M.V.C., S.Karaa., S.Karaa., S.N.A., M.Ö.; Planning and Design - M.V.C., S.Karaa., S.Karaa., S.N.A., M.Ö.; Supervision - M.V.C., S.Karaa., S.Karaa., S.N.A., M.Ö.; Funding -; Materials -; Data Collection and/or Processing - M.Ö., S.N.A.; Analysis and/or Interpretation - M.V.C., S.Karaa., S.Karaa.; Literature Review -; Writing - M.V.C., M.Ö., S.N.A.; Critical Review - M.V.C., S.Karaa.

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REFERENCES
1. Pooni R, Pandey G, Akbar S. Broadening the differential: pneumomediastinum and COVID-19 infection. BMJ Case Rep 2020; 13:e237938. [CrossRef]
2. Greenberg DJ, Nabors C, Chandy D, Dhand A. Pneumothorax and pneumomediastinum in patients hospitalized with coronavirus disease 2019 (COVID-19). Heart Lung 2021; 50):386-7. [CrossRef]
3. World Health Organization. Clinical management of COVID-19: interim guidance, 2020. https://www.who.int/publications/i/item/clinical-management-of-covid-19.

4. Nikolai LA, Meyer CG, Kremsner PG, Velavan TP. Asymptomatic SARS Coronavirus 2 infection: Invisible yet invincible. Int J Infect Dis 2020; 100:112-6. [CrossRef]

5. Lemmers DHL, Abu Hilal M, Bnà C, Prezioso C, Cavallo E, Nencini N, et al. Pneumomediastinum and subcutaneous emphysema in COVID-19: barotrauma or lung frailty? ERJ Open Res 2020; 6:00385-2020. [CrossRef]

6. Quincho-Lopez A, Quincho-Lopez DL, Hurtado-Medina FD. Case report: pneumothorax and pneumomediastinum as uncommon complications of COVID-19 pneumonia-literature review. Am J Trop Med Hyg 2020; 103:1170-6. [CrossRef]
Simultaneous Bilateral Spontaneous Pneumothorax with COVID-19 Pneumonia

COVID-19 Pnömonisi ile Birlikte Multatane Bilateral Spontan Pnömotoraks

Pelin Erdizci, Mustafa Akyıl, Serkan Bayram, Ozan Kaya, Serdar Evman, Volkan Baysungur

Abstract

The declared COVID-19 pandemic has come to affect the entire world. Ever since the first cases were detected, pneumothorax has been considered a rare but possible complication, and may develop in patients under mechanical ventilation due to high pressure. We present here a case of simultaneous bilateral spontaneous pneumothorax with COVID-19 pneumonia with no history of chronic lung disease and no mechanical ventilation.

Key words: Bilateral, COVID-19, pneumothorax, videothoracoscopy.

Özet

COVID-19, tüm dünyayı etkileyen bir salgın haline geldi. İlk olgular tespit edildiğinden beri, pnömotoraks nadir görülen bir olası komplikasyon olarak kabul edildi. Mekanik ventilasyon uygulanan hastalarda yüksek basınç nedeni ile pnömotoraks gelişme biliniyordur. Kronik akciğer hastalığı öyküsü olmayan ve mekanik ventilasyon uygulanmayan, COVID-19 pnömonisi ile birlikte simultane bilateral spontan pnömotoraks tespit ettigimiz olgumuzu sunuyoruz.

Anahtar Sözcükler: Bilateral, COVID-19, pnömotoraks, videotorakoskopi.

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On March 11, 2020, the rapid increase in the number of patients worldwide led the World Health Organization (WHO) to declare COVID-19 a pandemic. COVID-19 infections can be asymptomatic or have mild symptoms, but can also cause severe symptoms, with fever, cough and shortness of breath being the most common (1,2). Studies of the infection caused by SARS-CoV-2 have concluded that 1–2% of patients develop pneumothorax, having been reported as a rare possible complication since the initial COVID-19 outbreak (3,4). In Chen et al. (3), of the 99 cases with a confirmed diagnosis of COVID-19, only one patient developed pneumothorax, while Yang et al (4) identified a case with the same diagnosis in an autopsy series involving 92 cadavers. Patients with COVID-19 infections and respiratory failure are often treated with positive pressure ventilation, and this can lead to the development of pneumothorax and worsen the progression of the existing condition. As massive pneumothorax is a life-threatening condition, it must be diagnosed and treated as a matter of urgency. Simultaneous bilateral spontaneous pneumothorax, while extremely rare, carries a high risk of mortality due to sudden lung collapse and tension pneumothorax, and so requires urgent treatment (5-7).

CASE
Simultaneous bilateral pneumothorax was detected on chest radiography of a 17-year-old male patient who was admitted to our emergency department with a complaint of chest pain. The patient had a history of smoking one pack per day for 7 years, while there was no comorbidity history. This was the patient’s first pneumothorax attack. A tube thoracostomy with a wet suction-control closed-drainage system was applied to the right and left hemithorax (Figures 1a and b). A thoracic computed tomography (CT) taken the next day revealed bilateral ground-glass density that was more prominent on the right (Figure 2). The patient was referred to the department of infectious diseases and clinical microbiology with suspected COVID-19 pneumonia. A combined nose and throat swab test was taken from the patient, and prior to a positive result, 5-day azithromycin + hydroxychloroquine treatment was initiated due to the patient’s high fever in the evening and CT findings compatible with COVID-19 pneumonia. A control combined nose and throat swab test was taken on the 13th day of hospitalization of the patient, whose first PCR test result was positive. Upon the receipt of a negative PCR test result on the 15th day of hospitalization, planned videothoracic surgery was performed and subpleural blebs were detected in the right hemithorax resected with wedge resection and a pleural abrasion were performed. In a control examination two weeks after discharge, a left recurrent pneumothorax was detected and tube thoracostomy with a wet suction-control closed-drainage system was performed. A videothoracoscopic wedge resection and apical pleural abrasion was performed to the left hemithorax on the third day of hospitalization. The tube thoracostomy was terminated on the postoperative third day, and the patient was discharged on the fifth postoperative day.

DISCUSSION
Among the complications associated with severe coronavirus 2 (SARS-CoV-2), the most frequently mentioned are acute respiratory syndrome and respiratory failure. Pneumothorax, on the other hand, is a rare possible complication with a stated incidence of 1% in literature. Pneumothorax related to COVID-19 infection is thought to be caused by degeneration in the lung parenchyma, resulting from long-term inflammatory damage and the resulting air leaks. The process would appear to resemble the formation of pneumothoraces in SARS caused by another virus in the Coronaviridae family. The alveolar damage caused by SARS-CoV-2 can lead to the rupture of the alveoli, and thus air leakage into the pleural space. In addition to alveolar damage, the presence of enlarged pneumocytes, as multinucleated syncytial cells in the alveolar spaces, has also been demonstrated, and it has been reported that pneumocyte desquamation and hyaline membrane may also be seen. The mechanism is thought to involve the rupture of the alveolar wall due to the increased pressure difference between the alveoli and pulmonary interstitium as a result of the diffuse alveolar damage caused by SARS-CoV-2, although this has not been fully clarified (7,8).

Figure 1a and b: Simultaneous bilateral pneumothorax detected in chest radiography of a 17-year-old male patient. Tube thoracostomy with a wet suction control closed-drainage system was applied to the right and left hemithorax, respectively.
The lung diseases that cause pneumothorax include cystic fibrosis, emphysema, necrotizing pneumonia, idiopathic pulmonary fibrosis, eosinophilic granulomatous disease, sarcoidosis, tuberculosis and lung cancer, although pneumothorax may also develop in patients who are mechanically ventilated due to the damage resulting from high pressure on the lung parenchyma (9). In some COVID-19 patients with pneumothorax, the presence of such underlying risk factors as chronic obstructive pulmonary disease (COPD) or the use of mechanical ventilation may raise doubts about the source of the complication – pneumothorax being a known complication of intubation-related mechanical ventilation (6,10), but it seems that even without barotrauma, pneumothorax can coexist with COVID-19 (10,11).

The case presented here was not treated with mechanical ventilation, and while there was a history of smoking, there was no COPD or other lung disease. We thus concluded that an alternative explanation should be sought for the development of pneumothorax in COVID-19 pneumonia. Tension pneumothorax is a possible complication, but most cases are reported as spontaneous pneumothorax (12,13). Although tube thoracostomy provides satisfactory results in these patients, operative treatment should be considered as an option as long-term hospitalization may be required. The surgical approach to pneumothorax in COVID-19 patients has been determined as thoracoscopic bullectomy/blebectomy and pleurodesis (14).

It should be kept in mind that in patients with suspected COVID-19, pneumothorax may worsen the prognosis by causing acute respiratory decompensation. COVID-19 patients treated with mechanical ventilation are at risk of pneumothorax associated with ventilation, and so should be kept under constant observation (15). The management of pneumothoraces in COVID-19 patients is vital for the prevention of life-threatening tension pneumothoraces. Simultaneous bilateral primary spontaneous pneumothorax is rare, occurring in less than 2% of all pneumothoraces, and given the high risk of mortality, it should be treated as a matter of urgency (16,17).

Chronic obstructive pulmonary diseases (COPDs) are reported to be the most common pathological factor in the development of concurrent bilateral secondary pneumothorax, and simultaneous bilateral pneumothorax can be seen after cystic fibrosis, malignancy metastasis, tuberculosis, trauma or interventions. The absence of any of these conditions in the case presented here raises the suspicion that COVID-19 was a factor in the development of simultaneous bilateral spontaneous pneumothorax. (7,16,17).

CONCLUSION

Simultaneous bilateral spontaneous pneumothorax is an extremely rare but life-threatening condition that requires immediate diagnosis and treatment. Pneumothorax is a possible complication of COVID-19 pneumonia and should be considered in the differential diagnosis of COVID-19 patients who experience sudden respiratory decompensation.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - P.E., M.A., S.B., O.K., S.E., V.B.; Planning and Design - P.E., M.A., S.B., O.K., S.E., V.B.; Supervision - P.E., M.A., S.B., O.K., S.E., V.B.; Funding - R P.E., V.B., S.E.; Materials - V.B., S.E.; Data Collection and/or Processing - P.E., O.K., S.B.; Analysis and/or Interpretation - P.E., M.A.; Literature Review - P.E., O.K.; Writing - P.E., O.K., M.A.; Critical Review - V.B., S.E., S.B.

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REFERENCES

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323:1061-9. [CrossRef]
2. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med 2020; 383:2451-60. [CrossRef]
3. Chen N, Zhou M, Dong X, Qu J, Gong F, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395:507-13. [CrossRef]
4. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475-81. [CrossRef]
5. Jacobi A, Chung M, Bernheim A, Eber C. Portable chest X-ray in coronavirus disease-19 (COVID-19): a pictorial review. Clin Imaging 2020; 64: 35-42. [CrossRef]
6. Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X. Analysis of 92 deceased patients with Covid-19. J Med Virol 2020; 92:2511-5. [CrossRef]
7. Williams-Johnson J, Williams EW, Hart N, Maycock C, Bullock K, Ramphal P. Simultaneous spontaneous bilateral pneumothoraces in an asthmatic. West Indian Med J 2008; 57: 508-10.
8. López Vega JM, Parra Gordo ML, Diez Tascón A, Ossa-ba Vélez S. Pneumomediastinum and spontaneous pneumothorax as an extrapulmonary complication of COVID-19 disease. Emerg Radiol 2020; 27:727-30. [CrossRef]
9. McCool FD. Diseases of the diaphragm, chest wall, pleura and mediastinum. In: Goldman L, Schafer AI, eds. Goldman- Cecil medicine. 26th ed. Philadelphia: Elsevier; 2020. p.602-12.
10. Yao W, Wang T, Jiang B, Gao F, Wang L, Zheng H, et al. Emergency tracheal intubation in 202 patients with COVID-19 in Wuhan, China: lessons learnt and international expert recommendations. Br J Anaesth 2020; 125: e28-e37. [CrossRef]
11. Zhou C, Gao C, Xie Y, Xu M. COVID-19 with spontaneous pneumomediastinum. Lancet Infect Dis 2020; 20: 510. [CrossRef]
12. Spiro JE, Sisovic S, Ockert B, Böcker W, Siebenbürger G. Secondary tension pneumothorax in a COVID-19 pneumonia patient: a case report. Infection 2020; 48:941-4. [CrossRef]
13. Flower L, Carter JL, Rosales Lopez J, Henry AM. Tension pneumothorax in a patient with COVID-19. BMJ Case Rep 2020; 13: e235861. [CrossRef]
14. Aiolfi A, Biraghi T, Montisci A, Bonitta G, Micheletto G, Donatelli F, et al. Management of persistent pneumothorax with thoracoscopy and blebs resection in Covid-19 patients. Ann Thorac Surg 2020; 110:e413-e415. [CrossRef]
15. Quincho-Lopez A, Quincho-Lopez DL, Hurtado-Medina FD. Case Report: Pneumothorax and pneumomediastinum as uncommon complications of COVID-19 pneumonia-Literature review. Am J Trop Med Hyg 2020; 103:1170-6. [CrossRef]
16. Lee SC, Cheng YL, Huang CW, Tzao C, Hsu HH, Chang H. Simultaneous bilateral primary spontaneous pneumothorax. Respirology 2008; 13:145-8. [CrossRef]
17. Sayar A, Turna A, Metin M, Küçükyağcı N, Solak O, Gürses A. Simultaneous bilateral spontaneous pneumothorax report of 12 cases and review of the literature. Ac-ta Chir Belg 2004; 104: 572-6. [CrossRef]
Effect of High-Flow Nasal Oxygen Therapy on Tracheobronchial Mucosa in COVID-19 Cases

COVID-19 Olgularında Yüksek Akımlı Nazal Oksijen Tedavisinin Trakeobronşiyal Mukozaya Etkisi

Melahat Uzel Şener¹, Semih Aydemir², Ayperi Ozturk¹

Abstract
In the ongoing COVID-19 pandemic, several patients have experienced respiratory failure, for which high-flow nasal oxygen therapy (HFNO) is a frequently preferred treatment modality. In the present study, three COVID-19 patients being followed up with HFNO in the intensive care unit underwent fiberoptic bronchoscopy, and a burned/wounded mucosa with widespread hyperemia, hyperpigmentation and mucosal damage throughout the entire tracheobronchial system mucosa was detected in all cases, the long-term effects of which are unknown. Herein, we aim to draw attention to the possible development of mucosal damage after HFNO, which should be kept in mind during the provision of ventilation support to COVID-19 patients.

Key words: High-Flow Oxygen, COVID-19, Bronchoscopy, bronchial mucosa.

Özet
COVID-19 pandemisinde birçok hastada solunum yetmezliği gelir ve yüksek akımlı nasal oksijen tedavisinin (HFNO) sıklıkla tercih edilen bir tedavi yöntemidir. Yoğun bakım ünitesinde HFNO ile izlenen üç COVID-19 hastasına fiberoptik bronkoskopi uyguladık. Her iki hastada da, trakeobronşiyal sistem mukozasının tamamında yaygın hiperemi, hiperpigmentasyon ve mukozal hasar ile birlikte yanmış/hasarlı bir mukoza tespit edildi. Uzun vadeli etkilerin bilinmemektedir. Bu yazida HFNO sonrası gelişen mukozal hasara dikkat çekmek istiyoruz. COVID-19 hastalarında ventilasyon desteği verirken bu etkilerin dikkate alınması uygun olacaktır.

Anahtar Sözcükler: Yüksek-akım oksijen, COVID-19, bronkoskopi, bronşiyal mukoza.

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Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV2) disease, which first emerged in China and spread rapidly around the world, is mostly mild/asymptomatic, although critical symptoms develop in 5–15% of cases (1). This minority of critical patients has placed an unexpected burden on the healthcare systems of every country, and has led to a significant increase in the requirement for intensive care. Acute hypoxic respiratory failure generally develops in severe cases of COVID-19, often requiring advanced oxygen therapy procedures such as HFNO, and non-invasive/invasive mechanical ventilation, among which HFNO, which can provide high fractional oxygen concentrations, has become the first-choice approach for the avoidance of invasive procedures (2). It has been stated that with the HFNO method, the need for invasive mechanical ventilation and the risk of ventilator-associated pneumonia is reduced, lessening the burden on the healthcare system (3).

As HFNO is thought to cause the spread of infective particles in ambient air, it should be preferred in cases refractory to conventional oxygen therapy (COT). Therapeutic fiberoptic bronchoscopy (FOB) was performed in three patients who were intubated due to clinical deterioration, and who developed atelectasis and hypoxia after being followed up with HFNO in the intensive care unit of our hospital. We present these cases to draw attention to the mucosal findings that may develop after HFNO. Literature contains no reports on similar oxygen toxicities in patients undergoing HFNO.

**CASE**

**Case-1:** A 75-year-old female patient was started on HFNO treatment after suffering hypoxic respiratory failure 3 days after being diagnosed with COVID-19. The patient was followed with HFNO treatment for 6 days via inspired oxygen fraction (FiO2): 100% and flow rate 40 L/min. Left total atelectasis was detected on a chest X-ray investigating the increased secretions and dyspnea progression, thereupon, FOB was performed on the 11th day following the diagnosis of COVID-19 pneumonia. Mucosal burn, accompanied by widespread hyperemia, hyperpigmentation and mucosal damage from the distal of the vocal cords to the subsegments, and throughout the entire tracheobronchial system, was observed. None of the mucosa was undamaged (Figure 1). The left lung was ventilated again by bronchoscopy for the aspiration of the secretions that were obstructing the left main bronchus.

**Case-2:** An 85-year-old male patient was started on HFNO therapy due to hypoxic respiratory failure 2 days after being diagnosed with COVID-19 pneumonia. The patient was followed up with HFNO, reducing FiO2 gradually from 100% to 60% over 8 days, but the patient needed to be intubated on the 10th day of follow-up due to deepening hypoxia, and FOB was performed simultaneously with the intubation to collect culture specimens and to clear the secretions. Mucosal damage accompanied by diffuse mucosal hyperemia, hyperpigmentation and an atrophic appearance were identified in the area extending from the lower end of the endotracheal tube throughout the entire trachea, the main bronchi and the whole subsegment (Figure 2).

**Case-3:** A 41-year-old male patient being treated for COVID-19 pneumonia was started on HFNO treatment on the fourth day due to respiratory failure. After being followed with 100% FiO2 and 40 lt/min flow for 5 days, the patient was intubated due to deepening hypoxia. In the FOB performed for secretion cleaning after intubation, mucosal damage accompanied by "diffuse mucosal hyperemia, hyperpigmentation, and atrophic appearance" could be observed beginning from the lower end of the endotracheal tube along the entire segmental bronchial mucosa (Figure 3). It was observed one month after the procedure that the mucosa become more atrophic and erosive after FOB was performed for a second time due to post-intubation tracheal stenosis.

![Figure 1: Bilateral consolidation, ground-glass opacity (a,b), wounded mucosa, trachea (c,d)](image-url)
**DISCUSSION**

HFNO can deliver heated and humidified air-oxygen mixture inspired oxygen fraction (FiO₂) of between 21% and 100% and with a flow rate that can be increased up to 60 L/min. HFNO has important physiological effects in reducing the anatomical dead space and the positive end-expiratory pressure effect, and providing a constant fraction of inspired oxygen. HFNO is used in various conditions, such as hypoxemic respiratory failure, acute exacerbation of chronic obstructive pulmonary disease (COPD), post-intubation and pre-intubation, and for end-stage patients. The incidence of hypoxic respiratory failure in COVID-19 pneumonia is uncertain, although approximately 14% of patients require oxygen support, and 5% need intensive care and mechanical ventilation (1,4).

In a systematic review of three RCTs and 17 reviews, HFNO was found to reduce the need for intubation when compared to COT, while there was no difference in in-hospital or intensive care mortality. In the same review, treatment-related complications linked to HFNO, thoraco-cervical discomfort, heat-related discomfort and mild consciousness levels were frequently observed (3). In a study conducted before the pandemic period, serious complications, including cardiac dysrhythmia, septic multiple cardiorespiratory arrest and nosocomial pneumonia were reported more frequently than COT with HFNO (5).

A review of literature revealed no information about the macroscopic effect of HFNO on the tracheobronchial system. Following a diagnosis of COVID-19 pneumonia in the intensive care unit, three patients underwent an early-period FOB after developing atelectasis, and similar lesions were observed in all parts of the tracheobronchial system, including mucosal hyperemia, hyperpigmentation, mucosal damage and oxygen burn-like lesions, and the mucosal structure was completely lost. No mucosal biopsy was taken in these patients because the procedures were performed through the intubation tube and under anticoagulant treatment, with high risk. In the absence of a pathological diagnosis, we believe that the damage was attributable to the HFNO, based on a macroscopic view, although the damage may also have developed due to ventilator-associated infections, primarily the COVID-19 infection, or microvascular damage. There is also no information about how this mucosal damage will progress in the future. In the future, secondary infections due to bronchial hyperplasia, granulation formation, deterioration of the ciliary structure, hemoptysis (due to bleeding diathesis) and malignancy developing on the scar formation may increase. The later complications associated with COVID-19 pneumonia and its treatment will become more apparent in time.

Studies are needed to evaluate how the flow rate and duration of HFNO therapy affect these clinical situations, although the most important hurdle is bronchoscopy, as if it is not indicated for a life-threatening situation in COVID-19, it can be considered too risky both for the medical staff and the patient. In the cases presented here, we performed the procedures with full personal protective equipment, in line with the recommendations of the American Association for Bronchology and Interventional Pulmonology (AABIP), since adequate oxygenation could not be provided by mechanical ventilation, and newly-developed atelectasis was observed from chest X-rays (6).

In the editorial letter of Torrego et al. (7), it was stated that 93 patients under invasive mechanical ventilation in the intensive care unit during the COVID-19 period underwent bronchoscopy for many reasons, such as atelectasis, hemoptysis and for the obtaining of specimens, and ultimately localized mucosal hyperemia, white gelatinous secretions and crusts were observed. This article makes no mention of the widespread, damage to the mucosa seen in our patients, and there is also a lack of information on the use of HFNO prior to invasive mechanical ventilation in this patient group.
The main limitation of the present study is the absence of a pathological diagnosis of the damage. Although there may be different etiologies, the similarity of the lesions strongly suggests that the damage may be due to HFNO. These mucosal findings have not been previously discussed in literature. HFNO is in wide use worldwide in patients who develop respiratory failure in COVID-19, although the long-term effects of this treatment remain unknown. When applying HFNO therapy, it is necessary to plan the duration of the treatment and the transition to other treatments, given the expected mucosal damage in the respiratory system. Patients may develop chronic cough, or apply as COPD in the long term, and the treatment they received during the COVID-19 period should be questioned in this respect.

CONFLICTS OF INTEREST
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REFERENCES
1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA2020; 323:1239-42. [CrossRef]
2. Delclaux C, L’Her E, Alberti C, Mancebo J, Abroug F, Conti G, et al. Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: a randomized controlled trial. JAMA 2000; 284: 2352-60. [CrossRef]
3. Agarwal, A., Basmaji, J., Muttalib, F, Granot D, Chaudhuri D, Chetan D, et al. High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. Can J Anaesth 2020; 67, 1217-48. [CrossRef]
4. Alhazzani W, Maller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020; 46:854-87. [CrossRef]
5. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015; 372:2185-96. [CrossRef]
6. Wahidi MM, Lamb C, Murgu S, Musani A, Shojaee S, Sachdeva A, et al. American Association for Bronchology and Interventional Pulmonology (AABIP) Statement on the Use of Bronchoscopy and Respiratory Specimen Collection in Patients with Suspected or Confirmed COVID-19 Infection. J Bronchology Interv Pulmonol 2020; 27: e52-e54. [CrossRef]
7. Torrego A, Pajares V, Fernández-Arias C, Vera P, Mancebo J. Bronchoscopy in patients with COVID-19 with invasive mechanical ventilation: a single-center experience. Am J Respir Crit Care Med 2020; 202:284-7. [CrossRef]
A Case with Avascular Bone Necrosis Developing as a Complication of COVID-19 Treatment

COVID-19 tedavisi Komplikasyonu Olarak Avasküler Kemik Nekrozu Gelişen Olgu

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Abstract

As our knowledge and experience of COVID-19 increases, our treatment approaches may change. For patients with respiratory failure due to COVID-19 disease, the disease table can be better controlled with systemic glucocorticoids, and mortality rates and hospitalization periods can also be reduced. Steroid therapy can be applied for the long-term, especially in cases with organized pneumonia, and patients can be discharged from hospital with maintenance treatment. Complications have been noted in patients in the post-COVID period resulting from the use of glucocorticoids. While mostly bacterial and fungal lung infections are seen, another side-effect of glucocorticoids is their negative effect on bone metabolism. We present here a case in which avascular bone necrosis developed as a result of long-term steroid use for the treatment of COVID-19.

Key words: Covid-19, steroid therapy, avascular bone necrosis.

Özet

COVID-19 hastalığı ile ilgili bilgilerimiz ve deneyimlerimiz artışça tedavi yaklaşımlarımız da değişebilmektedir. COVID-19 hastalığına bağlı olarak solunum yetmezliği gelişmiş olan hastalarda sistemik glukokortikoidler ile hastalık tablosu daha iyi kontrol altında alınabilmekte ve mortalite oranları ile hastane yatış süreleri de azalmaktadır. Özellikle organizel pnomoni gelişmiş olgularda steroid tedavisi uzun süreli olabilmekte ve hastalar idame tedavisi ile taburcu olabilmektedirler. Bununla beraber, hastalarda glukokortikoid kullanımlına bağlı olarak postcovid dönemde komplikasyonlar da görebilmektediriz. Daha çok bakteriyel ve mantara bağlı akciğer enfeksiyonları görüürken, glukokortikoidlerin diğer bir yan etkisi de kemik metabolizmasının üzerinde olan olumşuz etkileridir. Burada, COVID-19 nedeni ile uzun süreli steroid kullanımı sonucu avasküler kemik nekrozu gelişen olguyu sunduk.

Anahtar Sözcükler: Covid-19, steroid tedavisi, avasküler kemik nekrozu.

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The world has been struggling since December 2019 with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), being a new-type coronavirus identified in pneumonia cases first in Wuhan (1). The vast majority of infected people (81%) do not develop symptoms or the disease is overcome with mild symptoms. Although the World Health Organization (WHO) and national guidelines have put forward some clinical classifications, such as mild, moderate, severe, ARDS and shock, for symptomatic patients, they do have made no clear recommendation regarding the treatment to be applied in the different phases of the disease (2).

At the beginning of the pandemic, WHO did not recommend the routine use of corticosteroids for viral pneumonia, and concerns were expressed that these would not have any survival benefit and may even lead to such issues as avascular necrosis, diabetes, psychosis and reduced viral clearance (3). It has been shown, however, that the use of corticosteroids has positive effects on critically ill patients in terms of hospitalization periods and mortality, with the complications in these patients being due to invasive mechanical ventilation rather than the side effects of corticosteroids (4).

In the RECOVERY treatment study it was reported that a significant reduction in 28-day mortality and hospitalization period was achieved with dexamethasone treatment at a dose of 6mg/day for 10 days. In patients not receiving oxygen therapy, however, no positive effect on either mortality or the hospitalization period was detected, and it was not recommended due to the possible side effects (5).

Avascular necrosis of the femoral head (ANFH) is the name given to osteonecrosis that develops in the femoral head as a result of the development of atherosclerosis or ischemia in the femoral head for different reasons. In this article, we present a case of avascular necrosis of the femoral head as a complication of COVID-19 treatment.

CASE

A 44-year-old female patient with congenital torticollis who is employed as a nurse was placed on Favipiravir for 5 days after testing positive in a COVID-19 PCR test by the filiation team, taken after her daughter recorded a positive COVID-19-PCR test. In post-treatment, the patient complained of shortness of breath and fever, and an image compatible with bilateral COVID-19 infection was observed on a Thorax Computed Tomography (CT) (Figure 1a). The patient was subsequently admitted to the pandemic clinic on November 25, 2020.

The results of laboratory tests were CRP: 72.6mg/l (0-5), D-dimer: 0.89mg/l (0-0.55), and hemogram, ferritin and fibrinogen levels within normal limits. The patient was hypoxic and so was placed on dexamethasone 6 mg/day (oral), levofloxacin 750 mg iv/day, enoxaparin sodium sc 1x1 iv and oxygen therapy. The favipiravir treatment was complemented to 10 days.

Upon a deterioration in respiratory distress and progression observed in a CT on the 5th day, the patient was transferred to the intensive care unit (ICU) and placed on high flow oxygen therapy in the prone position, and three doses of immune plasma were given. After 5 days, upon the stabilization of the vital indicators, the patient was returned to the pandemic service. Upon increased need for nasal oxygen and no regression was observed in radiology imaging dose of the dexamethasone was adjusted as 2x 8 mg iv (Figure 1b). The dexamethasone dose was reduced daily in accordance with the patient’s clinical condition. On the 35th day of the treatment, when the patient’s need for oxygen had ceased and radiological improvement was observed (Figure 2), 2 mg of dexamethasone and enoxaparin sodium treatment were recommended, and the patient was discharged.

The patient was examined 10 days later in the outpatient clinic, when her respiratory complaints were found to have regressed significantly, but knee joint and hip pain had developed, and so the patient was checked by the Physical Therapy and Orthopaedics clinic. A Magnetic Resonance Image (MRI) taken 2 months after discharge, avascular necrosis was detected in the bilateral femoral head, adjacent to the acetabular joint (Figure 3a, b).

Further examinations of the patient performed by all relevant clinics revealed no cause of avascular bone necrosis other than the glucocorticoids treatment. The heparin treatment of the patient was continued for 2 more months after discharge, and acetylsalicylic acid 100 mg was recommended. Hyperbaric oxygen therapy was planned for the patient for the treatment of avascular necrosis in the Orthopaedics clinic.

Figure 1: In the initial chest computed tomography examination of the patient (a), peripherally distributed ground-glass opacities were identified, and were more prominent in the lower lobes. A chest computed tomography 3 weeks later (b) revealed significant progression in infiltrations.
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DISCUSSION

Glucocorticoids are drugs that have immunosuppressive and anti-inflammatory effects in appropriate therapeutic doses, although there are many side effects encountered during glucocorticoid use (6). While osteoporosis is a recognized and common side effect affecting bone metabolism, avascular necrosis is a less frequent side effect (7,8).

ANFH is defined as the death or necrosis of regional bone tissue due to the loss of vascular support (9,10), and is divided into two groups, as primary (idiopathic) and secondary (traumatic-nontraumatic) based on the underlying aetiology (11). Secondary reasons include femoral neck fracture, hip dislocation, steroid and alcohol use, collagen tissue diseases, hypofibrinolytic and thrombophilia diseases, Caisson disease, transplantation and sickle cell anaemia (12).

Although corticosteroids were not recommended for treatment by WHO at the beginning of the pandemic, in subsequent studies the use of anti-inflammatory therapy in the hyperinflammation period in the clinical staging of COVID-19 was suggested to be effective (13).

In early September 2020, a WHO-mandated panel of experts published guidelines on the use of corticosteroids for the treatment of COVID-19. While this guideline was being prepared, two meta-analyses were reviewed, including eight randomized controlled trials, including the RECOVERY study that had been published by that time. As a result, while systemic (oral or intravenous 6 mg dexamethasone per day, or 50 mg hydrocortisone every 8 hours) corticosteroid therapy for 7–10 days in severe and critically ill COVID-19 patients was strongly recommended, as a conditional recommendation, corticosteroid therapy (14) was not advised for non-severe COVID-19 patients.

According to the guidelines published by the Ministry of Health of Republic of Turkey, 6mg/day dexamethasone or 0.5–1 mg/kg prednisolone, or an equivalent methylprednisolone, are recommended for 10 days in patients in need of oxygen therapy support due to respiratory distress. Despite this treatment, considering the risk conditions it has been stated that high-dose steroids (≥ 250mg/day methyl prednisolone, 3 days) can be given to patients with an increased oxygen need or acute phase reactants within 24 hours. After the application of high-dose steroids, it was recommended that treatment continue with 6 mg/day dexamethasone or 0.5-1mg/day prednisolone, or an equivalent methylprednisolone (15).

Cases of avascular bone necrosis as a complication of treatment during past viral pandemics have been reported in literature. During the SARS pandemic in 2003, corticosteroids were found to improve a patient’s condition in the early stages by lowering the fever, reducing lung inflammatory infiltration and improving oxygenation, although their long-term use (especially in high doses) was associated with potentially serious adverse incidents (16). In a follow-up study, 23.1% (18/78) of Chinese patients with SARS developed steroid-induced ANFH, due mainly to the use of high-dose glucocorticoids during SARS treatment (17).

In coronavirus literature, in a series of three cases by Agarwala SR et al., ANFH was reported in COVID-19 patients after a mean steroid (methylprednisolone) dosage of 758mg (min. 400mg, max. 200mg) and a mean 58 days after diagnosis (18).

In our patient, the need for intensive care emerged due to the onset of COVID-19 disease with a severe clinical manifestation, and the steroid dose was increased to 2 x 8 mg dexamethasone dose, the steroid dose was reduced and given for about 1 month. ANFH developed in our patient as a result of the long-term use of glucocorticoids.
In our clinical practice, infectious complications are mostly related to long-term glucocorticoid use in patients with COVID-19, while ANFH has been observed as a treatment complication in only one patient to date. In conclusion, the long-term use of glucocorticoids is possible in patients with severe COVID-19 requiring inpatient treatment. In the post-discharge follow-up of these patients, it is very important to look for the possible adverse effects of glucocorticoids on bone metabolism to ensure the early diagnosis and treatment of any complications.

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REFERENCES
1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382:727-33. [CrossRef]
2. WHO. Coronavirus disease (COVID-2019) situation reports. 2020.
3. WHO. Clinical management of COVID-19 interim guidance. 27 May 2020.
4. Chen R, Tang Y, Wang L, Xiao Y, Shen Y, Wang X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223):507-13. [CrossRef]
5. Zeng L, Liang W, Wang X, Song J, Wang Y, Wang Y, et al. The clinical characteristics of 130 critically ill patients with COVID-19 in Wuhan, China. Intensive Care Med 2020; 46(5):941-948. [CrossRef]
6. Fardet L, Kossar A, Cabane J, Flahault A. Corticosteroid-induced adverse events in adults: frequency, screening and prevention. Drug Saf 2007; 30:861-81. [CrossRef]
7. Canalis E, Mazzotti G, Guistina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporosis Int 2007; 18:1319-28. [CrossRef]
8. Devogelaer JP. Glucocorticoid-induced osteoporosis: mechanisms and therapeutic approach. Rheum Dis Clin North Am 2006; 32:733-57. [CrossRef]
9. McKee MD, Waddell JP, Kudo PA, Schemitsch EH, Richards AR. Osteonecrosis of the femoral head in men following short-course corticosteroid therapy: a report of 15 cases. CMAJ 2001; 164:205-6.
10. Jacobs JW, de Nijs RN, Lems WF, Geusens PP, Loan RF, Huisman AM, et al. Prevention of glucocorticoid induced osteoporosis with alendronate or alfacalcidol: relations of change in bone mineral density, bone markers, and calcium homeostasis. J Rheumatol 2007; 34:1051-7.
11. Kamal D, Traistaru R, Alexandru DO, Kamal CK, Pirici D, Pop OT, et al. Morphometric findings in avascular necrosis of the femoral head. Rom J Morphol Embryol 2012; 53(3 Suppl):763-7.
12. Özçakı Ş. Kalçanın avasküler nekrozu. Türk Fiz Tıp Rehab Derg 2009; 55:25-9.
13. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical—therapeutic staging proposal. J Heart Lung Transplant 2020; 39:405-7. [CrossRef]
14. WHO/2019-nCoV/Corticosteroids/2020.1.
15. T.C. Sağlık Bakanlığı COVID-19 (SARS-CoV-2 Enfeksiyonu) Ağır pnömoni, ARDS, sepsis ve septik şok yönetimi. 7 Kasım 2020.
16. Auyeung TW, Lee JSW, Lai WK, Choi CH, Lee HK, Lee JS, et al. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study. J Infect 2005; 51:98-102. [CrossRef]
17. Xie L, Liu Y, Fan B, Xiao Y, Tian Q, Chen L, et al. Dynamic changes of serum SARS-coronavirus IgG, pulmonary function and radiography in patients recovering from SARS after hospital discharge. Respir Res 2005; 6:5. [CrossRef]
18. Agarwala SR, Vijayvargiya M, Pandey P. Avascular necrosis as a part of ‘long COVID-19’. BMJ Case Rep 2021; 14:e242101. [CrossRef]
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