Multiple Lung and Mediastinal Hydatid Cysts Covering the Heart: A Case Report

Kalbi Çepeçevre Saran Multipl Akciğer ve Mediastinal Kist Hidatik: Olgu Sunumu

Nigar Alizade¹, Emrah Karci¹, Aydin Şanlı¹, Dündar Özalp Karabay²

Abstract

Hydatid cyst is a parasitic disease frequently seen in our country, mostly caused by Echinococcus granulosis. In this article, a 31-year-old female patient with multiple lung and mediastinal hydatid cysts invading all major vascular structures and completely filling the heart is discussed. In 2014, multiple cystic cavities were seen in the left ventricular wall, and it was excised by the cardiovascular surgery. In 2017, cysts that developed in the right lower lobe were excised. Cardiac cysts could not be excised due to advanced pericardial adhesion. In November 2022, widespread cystic formations were detected in all cavities of the heart and main vascular structures. The patient, who had extensive pericardial adhesions and cysts filling all the cavities of the heart and surrounding the heart, was considered inoperable by the cardiovascual and thoracic surgeons because the operation was extremely morbid. The patient has been followed up with outpatient clinic controls since 2014.

Keywords: Cardiac hydatid cyst, hydatid cyst, multipl cyst.

Oz


Anahtar Kelimeler: Kardiyak kist hidatik, hidatik kist, multipl kist.

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Hydatid cysts usually reside in the small intestine of carnivorous animals and are released into the environment through feces containing infective eggs. Larvae ingested by direct contact with the human body or with infected food enter the portal circulation and reach the liver, where most of them settle (60%), while the remainder pass into the microcirculation and settle in the lungs (30%). Cardiac echinococcal cysts are rare in cases with hydatid cysts, amounting to only 0.5–2% of the cases (1).

**CASE**

A 31-year-old female patient was operated on for a liver hydatid cyst in an external center in 2014, and was admitted to another center one week after the operation due to tachypnea and dyspnea, where pulmonary computed tomography (CT) angiography revealed mediastinal enlargement and pulmonary embolism. Transthoracic echocardiography (TTE) revealed multiple cystic appearances in the vicinity of the left ventricular wall, but no cystic appearance in the heart cavities. The case underwent evaluation with cardiovascular surgery (CDC) in our hospital, and the cysts adjacent to the left ventricular wall were removed by opening the pericardium. Postoperatively, the patient was started on albendazole (Andazol, Biyofarma Pharmaceutical Industry, Türkiye) treatment (15 mg/kg), but the patient used the treatment at irregular intervals due to deterioration in liver function tests (LFT). In 2017, cysts that had developed in the superior of the lower lobe of the right lung were excised by thoracotomy, and while the pericardium was opened in the same session, the cardiac cysts could not be excised due to the extent of adhesion. After the cyst content was aspirated, the patient was injected with 3% NaCl and the operation was terminated. Albendazole treatment was restarted, and the patient was followed up without medication after her LFT values deteriorated again. The patient applied to an external center with tachypnea and dyspnea in November 2022, when multiple mass lesions measuring approximately 18x12 mm in wide areas were identified on CT invading the pulmonary trunk in the mediastinum, embracing the main pulmonary arteries on both sides and extending to the right atrium, completely covering the heart and main vascular structures and showing heterogeneous contrast (Figures 1A and B), and multiple solid lesions measuring approximately 20 mm in the lower pole of the left lung. Contrast-enhanced thoracic magnetic resonance imaging (MRI) revealed multicystic lesions filling the entire mediastinum, up to approximately 17x15x13 cm in size, and cystic lesions surrounding all mediastinal main vascular structures. The right pulmonary artery was completely occluded, and no flow was observed (Figure 2A and B). The cystic structures extending into the pulmonary trunk, superior vena cava (VCS), right atrium and left ventricle obliterated the VCS. All heart structures were surrounded by the lesion except for the right ventricular free wall, and cystic lesions were seen invading the right and left atria and protruding into their cavities.

The case was evaluated by a multidisciplinary council of thoracic and cardiovascular surgeons, and was considered inoperable due to the potential for morbidity and even mortality with the excision of the cysts, which were common to all cavities of the heart. Furthermore, the cardiac cyst of the patient, whose pericardium was opened in the previous operation, could not be excised due to extensive adhesions, and the possibility of experiencing the same problem in a further operation was evaluated as strong. Close follow-up was continued with intermittent albendazole treatment based on LFT results. The patient's tachypnea and dyspnea continued during follow-up, and the albendazole treatment was discontinued and restarted intermittently based on LFT results, as a partial relief of symptoms was noted under albendazole therapy.

Figure 1a and b: Cystic lesion in the mediastinum on a contrast-enhanced thorax CT of the case, axial section (a). Cystic lesion in the mediastinum on a contrast-enhanced thorax CT of the case, coronal section (b)
NaCl intraoperatively can be beneficial. To prevent possible recurrences, the surgical area must be thoroughly washed with a hypertonic NaCl server during every operation. Albendazole is the primary medical treatment approach to the prevention of recurrence and spread after surgery and in non-surgical cases (5). In our case, it is thought that the irregular use of albendazole treatment due to LFT disorder led to continued recurrences and recurrences in common localizations. Although cardiac hydatid cysts are usually asymptomatic, complications such as angina, arrhythmia, valvular dysfunction, pericardial reaction, pulmonary and systemic embolisms, pulmonary hypertension and anaphylactic reaction can sometimes be seen. The most common complication is cyst rupture (24–60%) (4). In our case, the cardiac hydatid cyst caused a pulmonary embolism and the patient was admitted to hospital with complaints of tachypnea and dyspnea. Mediastinal echinococcosis cannot be distinguished from other mediastinal cystic lesions clinically or radiologically. TTE is the best method for the diagnosis of cardiac hydatid cysts, and the clinical picture is defined by the location, size and complications of the cyst. Thorax CT and Thorax MRI can help distinguish cystic lesions from solid masses and can reveal invasions into other mediastinal structures. Serological tests are often negative if the cyst is intact and uncomplicated. The study by Thameur H. et al. in 2000 reported the definitive treatment of cardiac hydatid cysts to be surgical excision. The standard approach involves the excision of the germinal membrane and pericyst (4). The surgical mortality rate due to cardiac hydatid cysts has been reported in the range of 0.29–0.6% (6). Clinical findings may vary depending on the localization, diameter and complications associated with the cyst. The standard approach involves the excision of the germinal membrane and pericyst. In our case, however, the patient was considered inoperable due to the widespread nature of the cysts in all major vascular and cardiac structures.

CONCLUSION
Although cardiac hydatid cyst is a rare condition, it should not be ignored in the differential diagnosis of mediastinal lesions. The optimum treatment approach to hydatid cysts is surgery. Careful intraoperative dissection and neutralization with a hypertonic solution are important in reducing recurrence.

CONFLICTS OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
REFERENCES


Diffuse Alveolar Hemorrhage in Orthopaedic Surgery: Think Beyond Embolism - A Case Report

Ortopedik Cerrahide Diffüz Alveoler Kanama: Embolizmin Ötesini Düşünün - Olgu Sunumu

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Abstract

Diffuse alveolar hemorrhage (DAH) is a dreaded and life-threatening complication. Although it is rarely reported in postoperative orthopaedic patients but few cases of fat embolism-associated DAH had been reported in the literature. We report a postoperative intramedullary femur patient with underlying undiagnosed vasculitis presenting as diffuse alveolar hemorrhage. A 56-year-old gentleman suffered a right femur fracture, managed with an interlocking nail. On postoperative day 4, the patient presented with hemoptysis, dyspnea, and a sudden fall in hematocrit suspecting diffuse alveolar hemorrhage (DAH). Pulmonary angiography and other investigations were not suggestive of pulmonary tromboembolism or fat embolism. Vasculitis was then suspected and cANCA(PR3) antibodies were positive. The patient was managed with corticosteroids, methotrexate, and oxygen supplementation. At 1 year follow-up, the femur fracture had united with no respiratory problem. As a conclusion, vasculitis, though a rare cause of DAH in postoperative orthopaedic surgery patients should be kept in mind.

Keywords: Diffuse alveolar hemorrhage, orthopaedic surgery, respiratory distress, vasculitis, bronchoaveolar lavage, respiratory distress.

Öz


Anahtar Kelimeler: Diffüz alveolar kanama, Ortopedik cerrahi, solunum zorluğu, vaskülit, bronkoaveolar lavaj, solunum zorluğu.

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Many postoperative orthopedic complications can lead to serious morbidity and mortality, and specific complications common to femoral intramedullary nailing include pulmonary embolism and fat embolism (1). Diffuse alveolar hemorrhage (DAH) is a life-threatening condition that can be associated with postoperative fat or pulmonary embolism (2,3), while a rarer cause can be an underlying undiagnosed immune disorder like vasculitis. Despite various radiological and laboratory investigations, the etiology of DAH has yet to be ascertained, and in such cases, immune disorders such as vasculitis should be considered. In this first-case presentation, we report on a patient with vasculitis (granulomatosis with polyangiitis) as the causative factor for the development of DAH post-intramedullary femoral nailing.

CASE
A 56-year-old male suffered an injury to his right thigh in a road traffic accident. Upon presentation in the emergency room the patient was conscious and oriented with stable vital parameters and no other visceral injuries. Radiographs revealed a fracture of the femur shaft with no other bone injuries. Laboratory investigations revealed hemoglobin (Hb): 14.2 g/dL, platelet 3.2 * 10^5/dL, total leukocyte count (TLC): 11300/mm³, urea: 34 mg/dL, serum creatinine: 0.9 mg/dL, total bilirubin: 0.8 mg/dL, alanine transaminase/aspartate transaminase (ALT/AST): 38/42 U/L, prothrombin time (PT): 14 seconds and international normalized ratio (INR): 1.1, while a chest radiograph and electrocardiography were both normal. The limb was splinted and fluid resuscitation was performed for the next 48 hours. The Hb was 13.6 g/dL with rest normal parameter the day before surgery. On the 3rd day following admission, the fracture was repaired with an interlocking femur nail while the patient was under spinal anesthesia with bupivacaine hydrochloride 0.5% w/v (heavy). The duration of surgery was around 1 hour and 10 minutes, during which no intraoperative complications were encountered, and the postoperative period was also uneventful. The patient was well hydrated with normal saline (0.9%) in the postoperative period with no requirement of supplemental oxygen for the next 48 hours. The patient was mobilized on post-op day 1 with the help of a walker. The day after surgery, the patient’s Hb was 12.4 g/dL and aspirin (acetylsalicylic acid) 75 mg/day was started. The mobility of the patient continued on the following 2 days (until postoperative day 3).

In the evening of post-op day 4 the patient had an episode of hemoptysis and coughing, and streaks of bright red blood were noted in every cough thereafter. Over 15 minutes, the patient was dyspneic with fingertip oxygen saturation of 80–83% in room air. The patient was admitted to the ICU and given supplemental oxygen by reservoir mask at a rate of 8 L/min. The vital parameters of the patient were stable with a radial pulse rate of 132/min, and fingertip oxygen saturation (SpO₂) with supplemental oxygen after 15–20 mins was 92–95%. Fluid resuscitation was continued, and the patient was kept under observation. The frequency of hemoptysis episodes increased over the next 12 hours. The patient was hemodynamically stable, but his respiratory rate increased to 28–30/min. The labored breathing increased, and the patient was given BIPAP ventilation with an inspiratory positive airway pressure of 12 mm Hg, expiratory positive airway pressure of 6 mm Hg and oxygen flow rate of 10 L/min. A chest radiograph revealed diffuse alveolar infiltrates in bilateral lung fields (Figure 1a). Laboratory investigations showed Hb: 7.6 g/dL, platelet: 1.4 * 10^5/dL, TLC: 12400/mm³, D-Dimer: 1240 ng/mL, procalcitonin level: 2.6 ng/mL, PT/INR: 15 seconds/1.22, erythrocyte sedimentation rate (ESR): 60 mm/h and C reactive protein: 42 mg/L. The patient remained stable under this ventilation mode for the next 24 hours with a fluctuating radial pulse rate of 92–144/min and a respiratory rate of 24–33/min. Based on this clinical presentation, fat embolism and pulmonary embolism were considered possible diagnoses. There was no axillary/ subconjunctival petechiae, no fat globules in the urine, and a venous Doppler ultrasound of the bilateral calf was negative for deep vein thrombosis. On a postoperative day 5, total bilirubin was 3.2 mg/dL, unconjugated bilirubin: 2.0 mg/dL, and ALT/AST: 79/84 U/L on a normal renal function test. The ESR of the patient was 54 mm/h along with raised serum lactate dehydrogenase (LDH) levels: 340 IU/L, while a peripheral smear revealed no toxic granules. No pulmonary thrombus was identified on CT, while bilateral diffuse ground glass opacity in the lungs, patchy consolidations and nodular septal thickening suggestive of acute respiratory distress syndrome (ARDS) were identified (Figure 1b). The PCR COVID test was negative. Two units of packed red cells were transfused and a computer tomography (CT) of the chest along with an angiography were performed (Figure 2a). The patient deteriorated over the next 24 hours (postoperative day 6) with an Hb of 7.8 g/dL (after 2 units of packed cell transfusion), platelet: 1.8 * 10^5/dL, TLC: 16600/mm³, total bilirubin: 7.8 mg/dL, unconjugated bilirubin: 4.8 mg/dL, ALT/AST: 118/142 U/L, LDH: 480 IU/L and PT/INR: 16 sec/1.42. A routine urine examination revealed proteinuria and hematuria. Serial bronchoscopy and lavage (BAL) were performed and revealed bloody aliquots. The bronchoalveolar lavage (BAL) culture was sterile for bacteria and fungus and depicted blood clots, but few lipid-laden macrophages. After ruling out the possibility of embolism, vasculitis was considered as the causative factor. A careful elucidation of the patient’s past surgical history revealed similar episodes of postoperative hemoptysis 8 years earlier (fore-
arm plating surgery) that resolved without any specific intervention. The patient had a palpable purpuric lesion measuring 7*12 cm on his back that had been there for 20 years. Treatment was initiated with an injection of methylprednisolone (80mg twice daily for 3 days and then tapering over the next 10 days to a 10mg daily dose) and an injection of tranexamic acid 500mg three times a day, and BIPAP ventilation was continued. The frequency of hemoptysis attacks and cough decreased, and the infiltrations also improved over the next 10 days, as shown on chest radiography (Figure 2b). The patient was hemodynamically stable with a respiratory rate of 18–20/min with SpO₂ 92-96% on room air. Hb had increased to 10.4 g/dL, TLC: 8900/mm³, platelet: 1.6 lac/dL, total bilirubin: 2.1mg/dL and PT/INR: 14 seconds/1.1. The Anti-GBM antibodies were negative but cANCA (PR3) positive with CRP: 20mg/L and ESR: 36 mm/h (on postoperative day 10). A provisional diagnosis of granulomatosis with polyangiitis was made and the patient was managed accordingly. The patient was gradually weaned off BIPAP support and was stable in room air. On postoperative day 16 the sutures were removed with no wound complications and the patient was discharged with a prescription of corticosteroid 10 mg daily, methotrexate 15mg once weekly, and nebulization in consultation with a rheumatologist.

At 2 2-month follow-up, the patient had no complaint of cough, dyspnea, hemoptysis or hematuria, and was mobile with the help of a stick.

**DISCUSSION**

DAH is a life-threatening condition triggered by various disorders in which the primary pathology involves disturbances in pulmonary microcirculation and alveolar capillaries, leading to an accumulation of red blood cells in alveoli (2-5). There is a lack of consensus on the diagnostic criteria of DAH, although it is characterized by hemoptysis, dyspnea, hypoxemia, sudden falling hematocrit and bronchoalveolar lavage findings, as well as chest radiograph and CT correlation (2,4). There is a high incidence of mortality and morbidity associated with DAH, which is further increased by delayed diagnosis. There are various etiologies of DAH, including fat embolism, pulmonary embolism, vasculitis-like Goodpasture syndrome, Wegner granulomatosis, systemic lupus, infection, hemosiderosis, drug-induced, etc. (4-7). DAH can mimic other morbid conditions, such as pulmonary embolism, fat embolism, etc. There have been a few studies to date reporting DAH to occur post-operatively in orthopedic surgeries, most of which report fat embolism associated with DAH (3,8). Orthopedic surgeries, especially intramedullary nailing, have been associated with a high chance of fat embolism.

The presentation of DAH is similar to other life-threatening disorders, and so identifying the etiology is vital for optimum management. The clinical signs of sudden decreased SpO₂ and blood pressure are common in fat and pulmonary embolisms, and similarly, ARDS-like changes can be noted on radiographs (9). The suggestive changes, although not specific to pulmonary embolism, were not evident in our case, however, a pulmonary embolism was ruled out based on the lack of evidence of a pulmonary thromboembolism on chest CT angiography. Diagnoses of fat embolism can be supported by various criteria (10–12), but the presented case did not meet any of these. The event occurred on postoperative day 4, which is outside the window determined for fat embolism (2-3 days), although fat embolisms have been reported to occur as late as 2 weeks postoperatively (8).
Vasculitis-like granulomatosis with polyangiitis, Goodpasture syndrome, etc. inherently cause inflammation of the pulmonary vasculature in the patient, and is accentuated due to trigger-like surgery, leading to altered capillary permeability and an intra-alveolar accumulation of blood. Such vasculitis disorders can exist in patients for years without their knowledge before symptoms arise due to an inciting factor. In our case, surgery was the triggering factor leading to DAH. A similar event in a past postoperative period in the patient led us to look for immune causes of DAH. Our investigations in this direction revealed anti-GBM antibodies to be negative but cANCA (PR3) to be positive, raising the suspicion of granulomatosis with polyangiitis. To the best of our knowledge, this is the first case report of a case of DAH in granulomatosis with polyangiitis in a postoperative patient. Flexible bronchoscopy can help in the diagnosis and management of DAH. Serial BAL lavage specimens in fat embolism-associated DAH can reveal increased hemorrhage, hemosiderin-laden macrophages and lipid-laden macrophages (4-6), although BAL should not be considered diagnostic for any specific disorder leading to DAH. BAL also helps to remove intra-alveolar red blood cells and improve ventilation. Our patient was not on any anticoagulant medication, and had no sign of infection, skin rash, or any cardiac or renal disorders. The management of such conditions should be initiated as soon as possible to ensure an optimum outcome, as the mortality rate of DAH has been reported in the range of 20-100%. Identifying etiology can support directed management and better clinical outcomes. Although management approaches are generally supportive of DAH, there are a few critical points that should be noted. The treatment of pulmonary embolisms involves the use of an anti-coagulant like heparin, which can accentuate DAH due to vasculitis (13,14), and so the use of heparin or anti-coagulant medications can be detrimental and even life-threatening in cases of DAH. It is thus important to rule out vasculitis before proceeding with management in cases of DAH. Early diagnosis and prompt treatment are the keys to better clinical outcomes. Oxygen supplementation and steroids are the mainstays of treatment, although high doses of steroids may be required in vasculitis patients. The patient responds well if treatment is initiated early following diagnosis.

CONCLUSION
DAH is a much feared but rare complication seen in orthopedic surgery. The surgeon and intensivist should be aware of the etiologies and management of the condition, as early diagnosis and treatment are the keys to a better outcome. Cases in which DAH results from vasculitis are rare, but should be investigated and managed appropriately. Patients should be investigated for vasculitis if there is any suspicion of the condition to prevent the development of life-threatening complications. The careful elucidation of subtle clues is necessary if the disorder is to be identified in asymptomatic patients.

CONFLICTS OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
Concept - B.H., S.A., L.G.; Planning and Design - B.H., S.A., L.G.; Supervision - B.H., S.A., L.G.; Funding - ; Materials - ; Data Collection and/or Processing - B.H., S.A.; Analysis and/or Interpretation - ; Literature Review - ; Writing - ; Critical Review - L.G.

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A Rare Condition Mimicking a Mediastinal Tumor: Gossypiboma

Öz


Anahtar Sözcükler: Yabancı cisim, komplikasyonlar, toraks, mediasten.

Osman Emre Ersin, Fazlı Yanık, Yekta Altemur Karamustafaoglu, Yener Yoruk

Abstract

The mediastinum is the region within the thoracic cavity that contains the heart, great vessels, esophagus, trachea, thymus, lymph nodes and neural structures. The mediastinum is divided into three sections: anterior, middle and posterior. The presence of so many different tissues in this area makes it prone to the development of many different types and numbers of malignant/benign tumors. Materials left behind during surgical operations can mimic mediastinal tumors in all three compartments of the mediastinum. Gossypiboma or textileoma are the terms used for granulomatous inflammations caused by surgical gas packs or foreign bodies left in the body after surgery. The present study relates to a case of gossypiboma originating from the paravertebral sulci and extending into the visceral mediastinum, mimicking a mediastinal tumor, in the light of current literature.

Keywords: Foreign body, complications, thorax, mediastinum.
The mediastinum is the region within the thoracic cavity that is bordered by the sternum anteriorly, the vertebral column posteriorly and the lungs on either side, and contains the heart, great vessels, esophagus, trachea, thymus, mediastinal lymph nodes and neural structures. The mediastinum is divided into three sections: anterior, visceral (middle) and paravertebral sulci bilaterally. Benign or malignant tumors can be detected in these three compartments, depending on the characteristics of the anatomical structures (1,2). Materials left in the cavity after surgical operations can mimic mediastinal tumors in all three compartments of the mediastinum.

The term gossypiboma (and textileoma) refers to granulomatous inflammations that develop as a result of surgical gas packs or foreign bodies being left in the body after surgery, which can occur even with the close attention of the surgical teams. The term derives from the Latin gossypium (cotton) and the Swahili boma (hide place) (3). Gossypiboma (GB) is a rare and preventable complication that may lead to medicolegal problems, and while it is usually seen after abdominal surgery, it can less frequently be seen after thoracic surgery. GB should be considered in the differential diagnosis when an intrathoracic mass is detected in patients who have previously undergone thoracotomy for any reason (4). It is clinically evaluated as a mass in cases where gauze without radiopaque labeling is forgotten. This study reports retrospectively on a case of gossypiboma that mimicked a paravertebral sulci tumor after coronary bypass surgery in the light of current literature.

CASE
A 63-year-old male patient treated for respiratory failure in the intensive care unit was directed to the thoracic surgery clinic after a mass was observed on chest X-ray. It was learned from his history that he had undergone coronary bypass surgery with a median sternotomy incision 8 years earlier and had undergone various medical treatments for chest pain, arrhythmia and heart failure. A paracardial localized mass opacity was identified in the lower zone of the left hemithorax on PA radiograph (Figure 1), while Thorax Computed Tomography (CT) revealed a 6x8 cm giant mass lesion originating from the paravertebral sulci and extending to the visceral mediastinum, containing calcifications and cystic areas, and causing compression on the heart in the left hemithorax lower zone (Figure 2). A Positron Emission Tomography (PET) requested for systemic screening revealed no pathological findings other than involvement of the mediastinal lesion with a SUVmax of 1.7. The patient was subsequently scheduled for explorative thoracotomy.

A muscle-sparing left lateral thoracotomy incision was made to allow entry to the thorax through the sixth intercostal space. A giant mass lesion was encountered as soon as the thoracic cavity was entered that seemed to have invaded the surrounding soft tissues and pericardium. The lungs and diaphragm were preserved. While attempting to separate the lesion with blunt and sharp dissections, purulent drainage was observed inside the lesion and an abdominal gas pack was detected in the lesion while it was being aspirated and removed (Figure 3). After irrigation of the thorax with povidone iodide, a thoracic drain was placed, and the operation was terminated.

The drain was terminated on the second postoperative day as no postoperative complications developed and no drainage or leakage. Since there was no growth in the microbiology culture, the patient was discharged on the third postoperative day with a prescription of broad-spectrum antibiotics.
**DISCUSSION**

In mediastinal pathologies, the mediastinum is generally divided into three parts, namely the anterior (superior + anterior mediastinum), visceral (middle) and paravertebral sulci. The anterior compartment is bounded anteriorly by the undersurface of the sternum, inferior to the innominate vessels and posteriorly by an imaginary line formed by the anterior surfaces of the great vessels and pericardium. The visceral compartment (referred to also as the postvascular space, the middle mediastinum or the central space) extends from the posterior surface of the superior portion of the sternum above the innominate vessels, and from the posterior limit of the anterior compartment below these vessels to the ventral surface of the vertebral column. The paravertebral sulci (costovertebral regions) as noted, are not truly mediastinal in location but are rather potential spaces along each side of the vertebral column and adjacent proximal portions of the ribs. The anterior mediastinum contains the thymus, lymph nodes and fatty tissue, while the visceral mediastinum contains the heart and great vessels, trachea, main bronchi, esophagus, vagus and phrenic nerves, the thoracic duct and lymph nodes. Finally, the paravertebral sulci contains the sympathetic chain, intercostal nerves and spinal nerve roots (1).

Mediastinal tumors generally originate from their own tissue; anterior mediastinal tumors commonly differentiate from thymus, germ cells, thyroid, parathyroid and lymphatic tissue; visceral mediastinal tumors differentiate from lymph nodes, esophagus and cysts; and paravertebral sulci tumors most commonly originate from neurological tissues. Mediastinal diseases are summarized in table 1 (1).

GB is the general name given to foreign bodies that are left behind after surgery in any part of the body that leads to the appearance of masses, with the most common culprit being surgical pads. Although GB is frequently reported in abdominal cavities in literature, it has also been reported in the nose, breast, pancreas, pararenal region, tracheobronchial tree, vagina, spine, femur, neck and prostate. In a recently reported case in national literature, GB developed after a paravertebral abscess operation (4-6).

The patient had undergone coronary bypass surgery 8 years earlier and his chronic complaints did not regress despite various medical treatments. Upon the detection of a lesion in the lower left region during radiological imaging in the intensive care unit in which the patient was hospitalized, different possible pre-diagnosis began to be considered.

Paravertebral sulci tumors can be divided into four groups: neurogenic tumors; tumors originating from spinal nerves; cysts; and others. Paravertebral sulci tumors account for 20% of all mediastinal tumors, and 75% of paravertebral sulci tumors are neurogenic, most commonly originating in the intercostal nerves or in the sympathetic chain regions. They are usually asymptomatic and may present with nonspecific weight loss, weakness and back pain (1). In our case, the patient’s advanced age and arrhythmia were not an expected situation.

In the differential diagnosis, mature teratoma was first considered due to the presence of calcification identified on PET/CT and CT images and its mediastinal origin, however the advanced age of the patient and the low SUVmax value on PET/CT excluded the possibility of teratoma.

Thorax CT and FDG PET/CT imaging methods can be used in differential diagnosis, and FDG PET/CT positivity in particular can be useful in confirming the possibility of malignancy. Diagnostic procedures such as transthoracic needle aspiration biopsy, thoracentesis and pericardiocentesis can be performed under the guidance of fiberoptic bronchoscopy or ultrasonography. Sonographically, masses with an echogenic center and a hypoechoic margin have been defined as a typical finding for GB (7,8). Many differential diagnoses can come to mind in a patient with a history of coronary bypass surgery who presents with dyspnea and chest pain, as such symptoms can be associated with angina pectoris, phrenic nerve palsy, pleural-pericardial effusion and heart failure. The presence of a lesion in the lower left region of the chest X-ray, however, points rather to a lung tumor, mediastinal tumor, lung abscess, lobar pneumonia, solitary fibrous tumor or pulmonary hydatid cyst. In cases of malignancy, additional symptoms such as weight loss, hemoptysis, cough and anorexia may accompany, while in cases where infection is suspected, fever, leukocytosis and other septic findings may be added to the picture. A much rarer cause of chest pain and shortness of breath is foreign bodies forgotten in the thoracic cavity during previous operations. Aside from all the mentioned differential diagnoses, further radiological and laboratory investigations may be required to reach a definitive diagnosis.

Tumor markers released as a result of the biological activity of masses are molecules in the blood or tissue that provide information pointing to the diagnosis or course of the mass. These may take the form of hormones, enzymes, intracellular proteins or cell membrane antigens, and can be detected in serum, plasma, urine or other body fluids. Tumor markers have various characteristics that can aid in the distinction of malignant tissue from normal tissue or one malignancy from another, that can determine response to treatment, or that can show different behavioral patterns within a tumor type. They may, however, not be sufficient to make a diagnosis in every case (9-11).
Table 1: Tumor localizations by mediastinal segments

<table>
<thead>
<tr>
<th>Localization</th>
<th>Origin</th>
<th>Disease</th>
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<tr>
<td><strong>Anterior mediastinum</strong></td>
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<td>Thymus</td>
<td>Thymoma, thymic carcinoma, thymic carcinoid, thymolipoma, thymic cyst, thymic hyperplasia</td>
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<tr>
<td>Lymph</td>
<td>Hodgkin lymphoma, Non-Hodgkin lymphoma</td>
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<td>Germ cell</td>
<td>Teratoma, seminoma, nonseminomatous GCT</td>
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<td>Pericard</td>
<td>Pericardial cyst</td>
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<tr>
<td>Others</td>
<td>Mesenchymal tumors (lipoma, liposarcoma, angiosarcoma, leiomyoma), cystic hygroma</td>
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<td><strong>Middle mediastinum</strong></td>
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<td>Lymph node enlargement</td>
<td>Lymphoma, benign lap, infectious and non-infectious granulomatous diseases, Castleman disease, amyloidosis, metastatic lap, lung, renal cell, gastrointestinal cancer and breast tumors and malignant melanoma</td>
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<tr>
<td>Cysts</td>
<td>Bronchogenic cyst, enteric cysts</td>
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<tr>
<td>Esophageal diseases</td>
<td>Achalasia, diverticulum, benign and malignant esophageal tumors</td>
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<td>Vascular lesions</td>
<td>Aneurysms, hemangioma</td>
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<td>Others</td>
<td>Morgagni hernia</td>
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<td>Tuberculous pleural effusion</td>
<td>Lymphoma, benign lap, infectious and non-infectious granulomatous diseases, Castleman disease, amyloidosis, metastatic lap, lung, renal cell, gastrointestinal cancer and breast tumors and malignant melanoma</td>
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<tr>
<td><strong>Posterior mediastinum</strong></td>
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<tr>
<td>Neurogenic tumors</td>
<td>Schwannoma, neurofibroma, malignant peripheral nerve tumor, ganglioneuroma, ganglioneuroblastoma, neuroblastoma, pheochromocytoma, paraganglioma</td>
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<tr>
<td>Spinal</td>
<td>Meningoceles, paraspinous abscess (pott’s abscess)</td>
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<tr>
<td>Cysts</td>
<td>Enteric cysts</td>
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<tr>
<td>Others</td>
<td>Extramedullary hematopoiesis, ductus thoracic cysts, hiatus hernia</td>
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Increases in AFP and B-HCG are important especially in anterior mediastinal tumors, and it should be kept in mind that an increase in B-HCG in male patients is a pathological condition. An increase in chromogranin and NSE can be expected in paravertebral sulci tumors, while increased urinary catecholamines may be found in paravertebral sulci tumors (10-12). In the presented case, B-HCG and AFP were reported as negative.

In cases of acute inflammation, increased leukocytes, sedimentation and CRP may be observed, although in our case the inflammatory mediators were also reported as negative. When evaluated together with tomography findings, a lesion may have the appearance of a mature cystic teratoma, a mediastinal tumor such as a neurogenic mediastinal tumor, a solitary fibrous tumor or a complicated hydatid cyst. The origin of the lesion in the mediastinum, the calcified areas and the semi-solid-cystic density made the diagnosis different from lung tumor. FDG PET/CT was not considered due to the low malignant potential of the lesion. Explorative surgical procedures can be considered a good alternative approach to the establishment of diagnosis from among all the aforementioned preliminary diagnoses and to steer surgical curative treatment. A surgical approach can be considered with a classic posterolateral thoracotomy, or alternatively, a median sternotomy or Video Assisted Thoracic Surgery (VATS) can be performed. However, considering the size of the lesion and the difficulty of manipulation, open procedures were found to be more appropriate for the present case, and exploration with a muscle-sparing left lateral thoracotomy incision was preferred.

Figure 3: Perioperative view of the case. GB coming out of the mass appears
CONCLUSION
Gossypiboma can be detected in all compartments of the mediastinum, and can mimic a mediastinal tumor. A differential diagnosis between mediastinal lesions and GB can be made with the help of various clinical, radiological and laboratory tests. This rare condition should be kept in mind when evaluating lesions originating in the mediastinum.

CONFLICTS OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS

REFERENCES
Rare Complication of Difficult Intubation Using a Double-lumen Tube: Thoracic Esophageal Perforation

Zor Entübasyonda Çift Lümenli Tüp Kullanımının Nadir Bir Komplikasyonu: Torasik Özofagus Perforasyonu

Abstract

Double-lumen intubation is more difficult to achieve than conventional intubation due to the broader, lengthier and stiffer nature of the tube, leading to more frequent complications in execution. Thoracic esophageal perforation was observed following a difficult intubation in a patient who underwent a left lower lobectomy for lung cancer. In this case presentation we share our experiences of the diagnosis, monitoring and treatment of esophageal perforation. We believe that the utilization of auxiliary instruments such as fiberoptic bronchoscopy can aid in the prevention of major complications arising from difficult intubations.

Keywords: Esophageal Perforation, thoracic surgery, intubation.

Oz

Çift lümenli entübasyon, tüpün daha geniş, daha uzun ve sert olması nedeniyle konvansiyonel entübasyondan daha zordur. Bu sebeple tek lümenli tüp ile entübasyonlara göre daha sık komplikasyon görülmektedir. Akciğer kanseri nedeniyle sol alt lobektomi yapılan hastada zor entübasyona bağlı torasik özofagusda perforasyon görülmuştur. Olgumuzda perforasyonun tanı, takip ve tedavi sürecindeki deneyimlerimizi paylaşmak istedik. Zor entübasyon bağlı majör komplikasyonlar önlemek için, fiberoptik bronkoskopi gibi yardımcı enstrümanların kullanılmamasının faydaları olabileceğini düşünmektediyiz.

Anahtar Kelimeler: Özofagus perforasyonu, göğüs cerrahisi, entübasyon.

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For anesthesia ahead of thoracic surgical interventions, single-lung ventilation using a double-lumen intubation tube is often required, although double-lumen intubation can be more challenging than conventional intubation due to the wider diameter, longer length, and curved and rigid structure of the tube. The placement of double-lumen tubes is more challenging than single-lumen tubes even in patients with a normal airway, while in cases with a difficult airway, the difficulty is further amplified, leading to an increased likelihood of complications (1). In this case presentation we report on the early-stage primary repair of a thoracic esophageal perforation with a right thoracotomy in which the perforation resulted from difficult intubation with a double-lumen tube in a patient scheduled for left thoracotomy due to lung cancer, supported by a review of literature on this topic.

CASE

A 70-year-old male patient was admitted for a planned left lower lobectomy after being diagnosed with adenocarcinoma based on the biopsy results of a 3 cm mass located in the left lower lung lobe. The patient's medical history revealed coronary artery disease and current use of clopidogrel, with no other notable features. The patient was classified as ASA 3 (American Society of Anesthesiologists physical status classification system). In the preoperative anesthesia assessment, no abnormalities were detected in the laboratory values, while a physical examination revealed a Mallampati score of III, indicating a short and thick neck structure with a posteriorly positioned lower jaw. The patient was classified as difficult intubation as the procedure failed on the first attempt, while intubation with a double-lumen tube also failed in two subsequent attempts. Successful intubation was finally achieved using a single-lumen tube with the assistance of fiberoptic bronchoscopy. During the operation, which involved left thoracotomy for lower lobectomy and mediastinal lymph node dissection, low saturation (SpO₂: 85-90%) was experienced by the patient throughout the procedure, and was subsequently transferred to the postoperative intensive care unit. No issues were reported during extubation. A chest X-ray revealed total pneumothorax on the right side (Figure 1), upon which a chest tube was inserted and connected to a closed underwater drainage system. In the follow-up chest X-ray, both lungs were noted to have re-expanded (Figure 2). On the first postoperative day, in line with the standard procedure for all patients, the patient was monitored while under oral restriction. The patient was generally stable and had no complaints other than severe pain in the epigastric region and back. The patient, after achieving normal chest X-ray and laboratory values, was discharged from the intensive care unit on the first postoperative day and transferred to the ward for further monitoring. Following oral intake, the patient reported a change in drainage color accompanied by severe chest and back pain and an increased shortness of breath, leading to esophageal perforation being considered. The patient was thus administered oral methylene blue, after which methylene blue-stained drainage fluid from the chest tube was observed. Biochemical analysis of a pleural fluid sample revealed an amylase level of 374 U/L, and to confirm the suspected diagnosis and the level of esophageal perforation, the patient underwent Neck and Thorax Computed Tomography (CT) imaging after being administered an oral contrast material. The CT scan revealed extravasation of the contrast material from the lower portion of the thoracic esophagus into the right pleural cavity (Figure 3), and a subsequent laboratory blood analysis revealed leukocytes: 10.7x10³/uL, C-reactive protein (CRP): 235 mg/L, and hemoglobin: 11.3 gr/dL. The patient's oral intake was discontinued, and broad-spectrum antibiotic therapy was initiated. The patient underwent surgery at the 36th postoperative hour based on the diagnosis of esophageal perforation for which a right thoracotomy was performed on the patient to facilitate access to the perforation site of perforation. The thoracic cavity was irrigated with saline solution, and a 1 cm-sized esophageal perforation area adjacent to the subcarinal region was observed (Figure 4). The perforation was first debrided, after which the membranous and muscular layers were repaired separately using absorbable multifilament 2/0 polyglactin sutures for primary closure. Insufflating air through the nasogastric tube revealed no leakage from the suture line and no other perforation or laceration (Figure 5). The patient was closely monitored in the intensive care unit for the first postoperative day and was transferred to the general ward on the second day. No air or fluid drainage from the right chest tube was observed during follow-up, and the right chest tube was transitioned to a Heimlich valve system on the third postoperative day. Following confirmation with a follow-up chest X-ray, the left chest tube was clamped and removed after a 12-hour observation period. The oral restriction continued for 5 days, during which the patient was fed through total parenteral nutrition. A subsequent leak test involving the administration of approximately 200 cc of water stained with methylene blue resulted in no drainage from the chest tube and no complaints of chest pain, and so the nasogastric tube was removed and controlled oral fluid intake was allowed. No changes were observed in the color or amount of drainage following the resumption of oral intake, a follow-up chest X-ray revealed normal findings, and a decrease was noted in the leukocyte count to 9.7x10³/uL and CRP level to 122 mg/L. On the seventh postoperative day, the right chest tube was removed after a 12-hour period of clamping and confirmation with a follow-up chest X-ray,
and the patient was discharged on the eighth day. During outpatient follow-up in the second postoperative month, no issues were encountered with the patient. Based on the pathology results, the patient was classified as Stage 3A, and was referred to the oncology clinic for the planning of oncological treatment.

DISCUSSION
The use of double-lumen tubes is crucial for the anesthesia management of patients undergoing lung surgery. The separation and isolation of the lungs provide significant convenience to the surgeon during lung resections, although the placement of double-lumen tubes can be more challenging than single-lumen tubes, even in patients without airway pathologies due to the long length and large diameter of the tube, and its curved shape and rigid structure. Indeed, in the presence of a difficult airway, this situation can make the anesthetist’s job quite complex (2). We describe here our management of an esophageal perforation of a difficult airway, a rare but life-threatening complication, that occurred during intubation with a double lumen tube in a patient with a Mallampati score of 3 who was scheduled for elective lung cancer surgery.

Difficult airway intubations can be encountered in any healthcare setting, with a reported incidence of approximately 6% in anesthesia practice (3). Difficult airway during endotracheal general anesthesia can lead to various complications, ranging from trauma to the trachea or esophagus, to myocardial infarction, cardiopulmonary arrest, hypoxic injury and even death. Published guidelines and practices relating to the management of difficult airways have identified different intubation techniques and alternative airway devices aimed at reducing such complications and securing the airway (4). It is certain that having access to proper equipment and proficiency in the established techniques will help reduce the risk of complications. The use of a specially designed fiberoptic laryngoscope set for difficult intubations, along with a suitable diameter flexible fiberoptic bronchoscopy (FOB) set to assist in double-lumen tube intubation, is highly recommended for the safety of the procedure.

The correct placement of blindly inserted double-lumen endotracheal tubes can be confirmed by observing the movement of the chest wall and auscultating both lungs. It should be noted, however, that these assessments may not always detect incorrect placement of the tube. There are numerous publications reporting that more than 30% of blindly inserted double-lumen endotracheal tubes are misplaced, highlighting the need for the use of FOB in patients undergoing planned double-lumen intubation to ensure accurate tube placement. That said, there are also publications advocating against the routine use of FOB due to its cost, the longer procedure time and the need for specialized training for its application (5). The search is thus continuing for alternative devices or methods to FOB for the confirmation of the correct placement of double-lumen endotracheal tubes. The wireless video endoscope, designed specifically for challenging intubation cases, is a lightweight and user-friendly device that allows visualization through the tube and can be advanced up to a distance of 37-48 cm, and can also serve as a basic bronchoscope. Our clinic has access to a standard fiberoptic bronchoscope that is used occasionally as an adjunct instrument for single-lumen intubations, as the diameter of the double-lumen intubation tube is not suitable for the standard fiberoptic bronchoscope. Moreover, our hospital lacks a wireless video endoscope or a fiberoptic bronchoscope suitable for pediatric patients. All of these limitations increase the risk of complications associated with double-lumen intubations in cases with difficult airways, as exemplified in the presented case.
Esophageal perforation is a rare but life-threatening condition with a reported incidence of 3.1 cases per 1 million population (6). The overall mortality rate is 13.3%, but can range from 4–80% depending on the type of perforation and the time to diagnosis (7). Esophageal perforations most frequently have iatrogenic (46.5%), spontaneous (37.8%), foreign body (6.3%), corrosive (1.8%) and traumatic (<1%) causes (8). In general, 72.6% of esophageal perforations are thoracic, 15.2% are cervical and 12.5% are abdominal (9). Iatrogenic injuries related to esophageal intubation are likely underrecognized and underreported. The risk factors for perforation are similar to those for difficult intubations, and include inadequate visualization, macroglossia, trismus and short neck. Another potential cause of esophageal rupture is direct trauma resulting from the misplacement of a double-lumen endotracheal tube into the esophagus, which can be attributed to the characteristics of the tube.

The most common symptom of esophageal perforation is chest pain, and while patients may present with fever, dysphagia, subcutaneous emphysema, injury site swelling and foul-smelling discharge, they may also be asymptomatic. In our patient, the presence of severe chest pain and dyspnea, particularly after initiating oral intake, along with a change in drainage color, raised suspicion of esophageal perforation. Diagnosis is generally confirmed by esophageal contrast studies or Neck and Thorax CT scans with oral contrast administration, and adding esophagoscopy to these investigations not only helps determine the level of rupture, but also provides 100% specificity in ruling out injury. In our case, the clinical suspicion of esophageal perforation led to a direct radiograph being taken followed by the administration of oral methylene blue. After a methylene blue discharge was identified from the thoracic drain, information about the size and location of the perforation was sought through CT imaging with oral contrast. The images revealed a passage of contrast material from the esophagus into the subcarinal area and accumulation in the right hemithorax within the pleural space, confirming the presence of a perforation, and a decision was made to repair the perforation in the thoracic esophagus. The approach to the treatment of esophageal perforations may vary depending on the patient's clinical condition and the size of the defect. Options include fluid resuscitation, broad-spectrum antibiotics, endoscopic treatment with clips, and surgical repair with primary sutures or esophagotomy (10). Non-operative treatment is generally reserved for rare cases in which the patient is contraindicated for surgery due to associated comorbidities or meets the very narrow set of criteria modified by Cameron et al. (11). Another study by Vrouenraets et al. (12) reported that conservative treatment or surgical repair with primary sutures could yield good outcomes in cases where the defect is small, and the patient is asymptomatic. Following perforation, the leakage of gastric content and bacteria into the mediastinum can cause mediastinitis, which is one of the leading causes of mortality, and to prevent mediastinitis, adequate drainage should be ensured, and broad-spectrum antibiotic therapy should be initiated (9).
In our patient, who was scheduled for lobectomy due to lung cancer and developed the rare complication of esophageal perforation during difficult intubation with a double lumen tube, the prompt diagnosis and rapid surgical treatment without the development of mediastinitis contributed to treatment success. An ideal treatment for iatrogenic intrathoracic esophageal perforation should involve direct closure of the perforation to prevent further contamination of the mediastinum, prevention of gastric reflux at the perforation site, elimination of infection in the mediastinum and pleural spaces, preservation of gastrointestinal integrity, and, preferably, enteral or parenteral nutritional support.

CONCLUSION

Iatrogenic esophageal perforations can be diagnostically and therapeutically challenging, and any delay in treatment exceeding 24–48 hours significantly increase morbidity and mortality. In cases of esophageal perforation due to intubation injury, an early diagnosis and prompt intervention involving the primary repair of the esophagus within the first 48 hours can be considered an appropriate approach. In the presented case, the use of auxiliary instruments such as FOB could be considered necessary for the prevention of major complications during difficult intubation.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS


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Experience of a single referral center. J Trauma Acute Care Surg 2022; 92:108-16. [CrossRef]


Pulmonary Lymphangioleiomyomatosis: A Rare Diffuse Cystic Lung Disease

Pulmoner Lenfanjiyoleyomyomatozis: Nadir ve Diffüz Kistik Akciğer Hastalığı

Tuğçe Çelen¹, Pınar Mutlu¹, Hasan Öğuz Kapıcıbaşı², Arzu Mirici¹

Abstract

Pulmonary lymphangioleiomyomatosis is a rare disease that affects women of reproductive age, and causes progressive dyspnea on exertion. Patients may present with a clinical picture of recurrent pneumothorax, hemotherax, chylothorax and hemoptysis. We present here the case of a 42-year-old female patient who presented with dyspnea on exertion and non-productive cough. High-resolution computed tomography scans revealed multiple air cysts in all zones, affecting the central and peripheral parts of both lungs. The patient underwent VATS wedge resection, and a diagnosis of lymphangioleiomyomatosis was established based on a histopathological examination. We present this case to literature as a rare disease, the preliminary diagnosis of which was confirmed histopathologically.

Keywords: Lung cystic disease, dyspnea, cough.

ÖZ


Anahtar Kelimeler: Akciğer kistik hastalığı, dispne, öksürük.

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Lymphangioleiomyomatosis (LAM) is a disease with an unknown etiology that often affects women of reproductive age, and is characterized by cystic destruction of the lungs and infiltration by smooth muscle-like cells (1,2). The condition manifests with cystic lung lesions and results in respiratory failure (3), with the potential to cause pneumothorax, chylothorax, hemoptysis and hemosiderosis. The condition has a progressive course and may result in death from respiratory failure years after the initial diagnosis (4,5). Our aim intention from this case report is to emphasize that the condition should be kept in mind in the differential diagnosis of female patients of reproductive age who present with shortness of breath upon exertion.

CASE
A 42-year-old female patient presented with an approximately one-year history of progressive dyspnea and nonproductive cough that had worsened over the last three months. The patient’s symptoms were not aggravated by an allergen, and her past medical history was unremarkable for chronic conditions other than cervical cancer, for which she had undergone an operation four years earlier. She had a 25-pack/year smoking history and was a current smoker. Her family history was unremarkable. Her breathing sounds were bilaterally normal and equal. Chest X-ray and pulmonary function tests were planned, and a high-resolution thoracic computed tomography was scheduled upon the observation of bilateral, multiple air cysts on chest X-ray (Figure 1).

The pulmonary function tests revealed a forced vital capacity (FVC) of 95% (3,000 ml), forced expiratory volume in the first second (FEV1) of 57% (1,560 ml) and FEV1/FVC of 52%, while the results of an arterial blood gases analysis were pH 7.39, pO2 75.6 mmHg, pCO2 35.6 mmHg, HCO3 22.4 and oxygen saturation 94.3%. All other laboratory tests revealed normal findings. Thoracic computed tomography scans revealed multiple, thin-walled cysts scattered throughout both lungs (Figure 2). The patient was re-examined, and the system data were reviewed considering the patient’s clinical status, history and radiological imaging findings.
A pre-diagnosis of lymphangioleiomyomatosis was made based on the fact that the patient had presented with similar symptoms in the past, and thoracic computed tomography scans six months earlier had revealed similar thin-walled diffuse air cysts. A genetic analysis was conducted considering the clinical and radiological findings of the patient with unremarkable results, and transthoracic echocardiography revealed normal findings. The patient underwent left video-assisted thoracic surgery for a wedge resection and apical pleurectomy, performed in the Thoracic Surgery Department.
A histopathological examination suggested a diagnosis of lymphangioleiomyomatosis based on focal HMB-45 and diffuse smooth muscle actin positivity (Figure 3 and 4). The patient was encouraged to quit smoking and placed on close follow-up, and had subsequent repeat admissions due to exacerbations of the symptoms. No decline in oxygen saturation in room air was observed. The patient was placed on therapy with sirolimus 1 mg twice daily and continued to attend follow-up visits.

![Figure 1: Bilateral, multiple air cysts on chest X-ray](image1)

![Figure 2: Thoracic computed tomography scans revealing multiple, thin-walled cysts scattered throughout both lungs](image2)
DISCUSSION
LAM generally affects young women of reproductive age, with symptoms and signs that can vary depending on the affected organs. The most common symptoms and signs are associated with lung disease, although patients may also present with extrapulmonary manifestations, particularly those with renal angiomyolipoma and those with diseases involving the lymphatic system. LAM can be associated with typical neurocutaneous manifestations of the tuberous sclerosis complex (TSC) (i.e., angiofibroma, shagreen patches, seizures, intellectual disability) occurring sporadically. Our patient had dyspnea on exertion and dry cough, but no other complaints. Genetic analysis results were unremarkable, she had no neurocutaneous symptoms, and an abdominal ultrasound revealed normal findings.

The characteristic presenting symptoms of patients with LAM have been well-established in a registry study of 230 patients conducted in the United States, and the most common symptoms noted in the above-mentioned study have been further supported by smaller-scale studies conducted before and after the registry study (6). The most common symptoms are as follows:

- Fatigue (in approximately two-thirds of cases),
- Progressive dyspnea (in approximately two-thirds of cases),
- Spontaneous pneumothorax (in approximately one-third of cases), and
- Pleural effusion (in approximately one-quarter of cases).

Less common symptoms include:

- Chest pain (<15%),
- Cough and phlegm (<15%),
- Pulmonary hypertension (<7%),
- Chylothorax (<10%),
- Chyle in urine, feces, vaginal discharge (<10%), and
- Hemoptysis (<5%).

Dyspnea on exertion is the most common symptom of LAM, but as dyspnea is a non-specific symptom and LAM is a rare disorder, women with LAM may be started on therapy with a diagnosis of asthma, emphysema or chronic obstructive pulmonary disease (COPD) before the suspicion of LAM is raised. The results of observational studies have suggested the following findings (6-12):

- Normal spirometry (30 – 60%),
- Obstructive pattern on spirometry (25 – 60%),
- Restrictive or mixed obstructive and restrictive pattern spirometry (<25%), and
- Low lung diffusing capacity for carbon monoxide (DLCO) (60 – 90%).

Spirometry revealed an obstructive pattern in our patient with a value of 25–60%. Although a diagnosis of LAM can be established based on clinical and radiological findings, surgical lung biopsy (lung biopsy through video-assisted thoracoscopy or invasive thoracotomy) has a high diagnostic yield approximating 100 percent, and is considered the optimum approach to the diagnosis of LAM (13). In our patient, the diagnosis of LAM was confirmed from a pathological examination of a surgical specimen obtained by VATS.

The treatment options for LAM include:

**Progesterone:** Although some case series and case reports have reported favorable effects of progesterone therapy, no placebo-controlled randomized study has been conducted in this regard to date. The routine use of progesterone preparations is not recommended, although intramuscular administration can be attempted in cases experiencing a rapid decline in pulmonary function (14).

**Sirolimus:** The mTOR pathway is genetically active in patients with LAM. Although prospective studies have demonstrated that sirolimus reduces AML volume, it is not recommended as a first-line therapy for the treatment of angiomyolipoma. The effect of sirolimus on pulmonary function remains unclear, and there is a risk of side ef-
fects associated with the use of sirolimus. Although sirolimus is not routinely recommended, it can be used in experienced centers after weighing the risk of side effects against the potential benefits with close monitoring of patients who experience a rapid decline in pulmonary function (1). The lung transplantation option can be considered in patients with end-stage disease.

CONCLUSION
Through this case report the authors seek to improve the understanding of this rare condition, which should be kept in mind in the differential diagnosis of female patients of reproductive age presenting with dyspnea on exertion.

CONFLICTS OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS

REFERENCES
Acute Eosinophilic Pneumonia Associated with E-Cigarettes: A Case Report

Elektronik Sigaraya Bağlı Akut Eozinofilik Pnömoni: Olgu Sunumu

Mehmet Emin Sezgin1, Berna Duman2, Mustafa Colak1, Cengiz Özdemir3, Levent Dalar3

Abstract

Knowledge of the detrimental effects of electronic cigarettes on the lungs is increasing, especially in young adults and those who are trying to quit smoking. The lung damage caused by E-cigarettes has become known as “Electronic cigarette-associated lung injury (EVALI)” and is thought to be attributable to Vitamin E Acetate and Tetrahydrocannabinol. A female patient with no known chronic disease presented with complaints of dry cough and shortness of breath for 2 weeks. Bronchoscopy was performed on the patient, whose complaints and in-lung infiltrations were noted to increase under antibiotic treatment. Broncho-alveolar lavage (BAL) cell count showed 80% eosinophils. After 4 weeks of vaping, the patient was diagnosed with acute eosinophilic pneumonia (AEP) that was attributed to vaping. Cases of eosinophilic pneumonia, lipoid pneumonia and organizing pneumonia associated with E-cigarette use have been reported. Our patient was diagnosed with eosinophilic pneumonia associated with E-cigarette use, and we believe the specific characteristics of the case merit consideration in the body of related literature.

Keywords: Electronic cigarette, vaping, acute eosinophilic pneumonia, EVALI.

Öz


Anahtar Kelimeler: Elektronik sigara, akut eozinofilik pnömoni, akığer hasan.
The popularity and use of E-cigarettes are increasing worldwide with each passing day. While some people have taken to E-cigarettes as an alternative to smoking and as an aid to quitting smoking, their use among young people and those who are not smokers has also increased. In 2010, some 1.8% of U.S. adults reported using E-cigarettes at some time, and this figure had risen to 13.0% by 2013, while reports of “current use” increased from 0.3% to 6.8% in the same period (1). Different models of E-cigarettes have been produced in recent years to meet the increase in demand, although all comprise five main components: the battery, cartridge, microchip, sprayer and body. The operating principle is based on the microchip effect of the liquid, which consists of propylene glycol, preferably nicotine or cannabinoids, formed by propylene glycol in the cartridge, and is triggered by the flow of air inhaled to the lungs, resulting in the battery creating a cigarette-like effect (2). Although it is considered an alternative to smoking in terms of reliability, a study released by the FDA has reported a link between the propylene glycol used in E-cigarettes and carcinogenesis. Furthermore, previous studies have reported that E-cigarettes can trigger infectious and noninfectious inflammatory lung diseases (2). When E-cigarette-related lung diseases are reviewed together with case series in the literature, certain patterns are revealed, including diffuse alveolar damage, organizing pneumonia, lipid pneumonia, hypersensitivity pneumonia, bronchiolitis and acute eosinophilic pneumonia (3). There have been two cases of eosinophilic pneumonia resulting from the use of E-cigarettes reported to date in literature (4,5). The present study relates to a case that was diagnosed with eosinophilic pneumonia caused by E-cigarettes and was admitted to our clinic.

**CASE**

A 55-year-old female patient with no known disease history presented to the clinic with shortness of breath and a dry cough that had lasted for 2 weeks. The patient had a 30-packs/year smoking history but had switched to E-cigarettes around 2 months earlier. The findings of a physical examination were as follows: temperature 36.7°C, pulse: 80/min, respiratory count: 22/min and blood pressure arterial: 110/70 mmHg. The patient had no cyanosis, but bilateral common rales in the upper zones and in the left middle zone, as well as bilateral diffuse bronchi, while all other system examinations were unremarkable. Her medical history revealed pneumonia 8 months earlier for which she was hospitalized. A postero-anterior (PA) chest X-ray revealed bilaterally-dispersed infiltration, based on which she was admitted with a preliminary diagnosis of pneumonia and started on intravenous moxifloxacin treatment. Leukocyte levels (9040 mL) were normal in the hemogram, 24.4% eosinophilia was detected, CRP was 1.35 mg/dL and her biochemistry was normal. Nodular-shaped focal consolidations and blurry glass densities, accompanied by interstitial thickening, were observed in both lung parenchyma, especially in the upper lobes and peripheral lung tissue, and partially observed in the lower lobes on a Thoracic CT scan (Figure 1). The following values were recorded following a respiratory function test: FVC: 3510 mL 109%, FEV₁: 2740 mL 100% FEV₁/FVC: 78%, DLCO: 5.17 61% DLCO/VA: 0.96 62%. No endoparasites were detected in a fecal parasite examination, and cANCA and pANCA results came back negative. In a bronchoalveolar lavage (BAL), the BAL culture remained sterile and 80% eosinophil was detected in the BAL cell count. The patient was planned for treatment with 32 mg methylprednisolone based on an acute eosinophilic pneumonia diagnosis. When the patient was questioned again, it was learned that she had started using JUUL E-cigarettes 4 weeks earlier. An improvement in symptoms was noted, and a physical examination in the 1st month control under corticosteroid therapy revealed a total regression of the infiltrations on PA chest X-ray (Figure 2).

![Figure 1: Bilaterally-dispersed nodules with blurry glass densities identified from a pulmonary tomography taken before treatment](image)
Eosinophilic pneumonia is an uncommon disease, but is more common in males than in females. It is mostly idiopathic but may also develop as a result of the inhalation of allergic antigens. In diagnosis, fever lasting fewer than 5 days, common infiltrations in posteroanterior chest X-ray, eosinophil rates greater than 25% in bronchoalveolar lavage fluid and dramatic response to steroids suggest acute eosinophilic pneumonia (6). Peripheral eosinophilia, which was detected at 24.4% in the blood count in the presented case, is a rare presentation in acute eosinophilic pneumonia. The presence of diffuse alveolar infiltrations on Thorax CT, the detection of 80% eosinophils in the bronchoalveolar lavage, and the lack of bacterial or fungal growth in the culture led us to the diagnosis of acute eosinophilic pneumonia. It is well known that corticosteroids respond well to treatment. In the presented case, a rapid regression of symptoms was noted after methylprednisolone treatment and the patient was discharged within two days. At the first month follow-up, almost full recovery was observed in the radiological findings.

There have been many studies and case series to date reporting a relationship between smoking and acute eosinophilic pneumonia. The mechanism of making AEP of cigarette is explained by its activating inflammation-stimulating mechanisms. Similarly, recent studies have shown that E-cigarettes cause cytokine stimulation like IL-6 and IL-8, and this condition shows that they can trigger acute eosinophilic pneumonia and other lung diseases, similar to smoking (7,8).

Respiratory failure often accompanies the clinical manifestation in acute eosinophilic pneumonia, and two other cases diagnosed with E-cigarette-related AEP have been reported in literature to date (4,5). In these two cases, the clinical manifestation was noisy, and one case was admitted to the Intensive Care Unit with respiratory failure after hospitalization. In our case, clinical improvement was achieved without respiratory failure as a result of our rapid diagnosis and treatment.

The radiological findings associated with EVALI (E-cigarette- or vaping-associated lung injury) most often include ground-glass opacities, while rarer findings include pleural effusions, pneumomediastinum and pneumothorax. EVALI may present with organizing pneumonia, lipoid pneumonia, diffuse alveolar damage, acute respiratory distress syndrome (ARDS), diffuse alveolar hemorrhage, hypersensitivity pneumonitis and giant-cell interstitial pneumonitis, aside from acute eosinophilic pneumonia (9).

In a 2019 EVALI case series reported by the CDC including 1,299 cases from 29 states, a total of 21 deaths associated with EVALI were reported. Of the 1,043 patients whose age and sex data were available, 70% were male and 80% were under the age of 35 years (10).

CONCLUSION
The use of E-cigarettes is increasing, much of which can be attributed to the industry’s promotion of E-cigarettes as a means of “harm reduction” and a “method of quitting smoking”. Studies into the use of E-cigarettes are increasing day by day, and as a result their effects on health are becoming better understood, the harm they can do to the lungs with increased use. In cases of sudden respiratory failure, the possibility of acute eosinophilic pneumonia should be considered in cases where the person was known to be healthy before using E-cigarettes.

CONFLICTS OF INTEREST
None declared.

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

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A Case of Lung Cancer Developing in the Background of Progressive Massive Fibrosis

Progresif Masif Fibrozis Zemininde Gelişen Akciğer Kanseri Olgusu

Abstract

Pneumoconioses are parenchymal lung diseases caused by dust accumulation in the lungs and the resulting tissue reaction. A 60-year-old male patient was admitted to our clinic with complaints for 3 months of weakness, fatigue and constant pain in the right arm that did not change with movement. His professional history revealed employment in glazing processes in the ceramics industry for 28 years, while his medical history included pneumoconiosis and coronary artery bypass surgery in 2015. A recent postero-anterior chest X-ray had revealed increased opacity in the apical region of the right lung compared to a radiograph taken 3 years earlier. A high-resolution thorax computed tomography of the lungs was performed revealing a 5 cm diameter mass lesion in the upper lobe of the right lung, although no differentiation between the mass and progressive massive fibrosis (PMF) could be made. Thoracic magnetic resonance imaging was performed after mass development was suspected on the basis of PMF, and a malignant lesion that was hyperintense compared to muscle and PMF tissue was observed in the apical segment of the right lung upper lobe on T2W images. No endobronchial lesion was observed on bronchoscopy, while a transthoracic biopsy performed on the hyperintense area was reported as adenocarcinoma. We present a case of PMF pneumoconiosis presenting with lung cancer.

Keywords: Silicosis, fibrosis, cancer.

Oz


Anahtar Kelimeler: Silikozis, fibrozis, kanser.

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Pneumoconiosis refers to the accumulation of inorganic dust, fumes and fibers, originating mostly from industrial environments and causing a fibrotic tissue reaction in the lung (1). Silicosis, coal worker's pneumoconiosis (CIP), asbestosis, berylliosis, hard metal lung disease, mixed dust pneumoconiosis and talcosis are the most well-known forms of pneumoconiosis (2). They are examined in two main groups according to their radiological appearance as simple and complicated, with simple pneumoconiosis referring to the presence of round or linear opacities less than 1 cm in the chest radiograph, and progressive massive fibrosis (PMF), known also as complicated pneumoconiosis, referring to the appearance of opacities larger than 1 cm with small opacities on chest X-ray (3,4). Unilateral PMFs in particular can mimic lung cancer, and while the incidence of lung cancer in patients with pneumoconiosis is high (17.9%) (5,6), it is difficult to differentiate lung cancer from pneumoconiosis with X-ray and computed tomography (CT) imaging methods (7). With technological developments, functional information on lung masses can now be obtained with magnetic resonance imaging (MRI), leading to the description of MRI findings of PMF in recent years (8,9). Here, we present a case of pneumoconiosis in whom lung cancer was detected in the PMF lesion on thoracic MRI.

CASE
A 60-year-old male patient was admitted to our clinic with complaints of weakness, fatigue and constant pain for 3 months in the right arm that did not change with movement. The patient had a 30-pack/year smoking history but had not smoked for 8 years. On physical examination, his general condition was good and his vital signs were stable, while a chest examination revealed decreased respiratory sounds in the upper zone of the right lung. Laboratory values at admission were within normal limits. The patient had been diagnosed with pneumoconiosis in 2015 but had not attended subsequent follow-ups. His continuing employment as a glazer in the ceramic industry for 28 years involved spraying silica-containing paint onto sinks with an air-jet gun in a semi-enclosed cabin. He had undergone coronary artery bypass surgery in 2015. A PA chest X-ray revealed an increase in opacity in the apical region of the right lung compared to a radiograph taken 3 years earlier, and the patient was duly hospitalized for further examination (Figures 1a and b). Simultaneous lung HRCT revealed a solid 5-cm diameter lesion in the upper lobe of the right lung (Figure 2). In PET-CT taken in terms of malignant etiology, a pathologically increased FDG uptake was observed in the mass lesion in the right lung upper lobe and in the surrounding millimetric nodular densities, mediastinal and hilar lymph nodes, as well as a soft tissue density causing destruction in the T2-3 vertebrae, however, the mass and PMF could not be differentiated (Figure 3). MRI was performed in the belief that it could differentiate lung cancer and PMF based on their signal intensities, with Pre-contrast T1 and T2W diffusion imaging and dynamic postcontrast T1W imaging. The T2W images revealed the mass to be more hyperintense than the muscle, causing distortion in the environment, as well as contrasting that became evident towards the progressive phases in the dynamic contrast acquisition (Figure 4). No endobronchial lesion was observed in the patient on bronchoscopy, while the results of a transthoracic biopsy performed on the hyperintense area indicated adenocarcinoma. (Figure 5a, b and c). The patient was duly referred to the Oncology Department with a diagnosis of lung cancer.

Figure 1a and b: Opacity increase in the right upper zone in the newly taken chest radiograph compared to a radiograph from 3 years earlier.
A Case of Lung Cancer Developing in the Background of Progressive Massive Fibrosis | Özgün et al

Figure 2: Thoracic computed tomography revealing a 5-cm mass in the upper lobe of the right lung

Figure 3: PET-CT showing increased FDG uptake in a mass lesion

Figure 4: Thoracic MRI T2W image of a hyperintense area of a malignant lesion in the PMF lesion that is hypointense in the apical segment of the upper lobe of the right lung. (Blue arrow: Muscle, Yellow arrow: PMF, Red arrow: Malignant lesion)

DISCUSSION

Pneumoconiosis is a preventable disease that is frequently reported in Türkiye. Silica is one of the main components of rock and sand, and many different business lines, such as mining, quarrying, brick and ceramic production, and foundry operations carry the risk of silicosis (10). The cytotoxic effect of silica on alveolar macrophages would appear to be related to the pathogenesis of silicosis. Silica particles that cannot be completely cleared from the lung can damage the alveolar macrophages responsible for their removal from the lung, and these damaged macrophages are thought to release reactive oxygen and nitrogen species as well as free radicals. When the damaged alveolar macrophages containing silica ultimately die, they release the ingested silica particles and the silica particles are re-ingested by another macrophage, thus entering into a cycle of damage (11,12). PMF is an advanced form of chronic pneumoconiosis that is pathologically defined by the clustering of silicotic nodules fused with connective tissue in silicosis and in coal macules surrounded by fibrous tissue in coal worker’s pneumoconiosis (13). The International Agency for Research on Cancer is an independent scientific organization within the World Health Organization that is responsible for classifying the carcinogens that cause human cancer development, of which there are four groups. Agents that are determined to cause cancer in humans are classified as Group 1, among which inhaled crystalline silica can be counted (14). Studies have identified a high incidence of lung cancer in the background of PMF (6,8). Matsumoto et al. reported on a case of squamous cell lung cancer developing within a PMF lesion in 1996 in which the cancer tissue appeared hyperintense compared to the PMF lesion on MRI T2W images (15). In a study by Katabami et al. (16), an association with lung cancer was more likely in patients with diffuse interstitial fibrosis (DIF) pneumoconiosis than in those with pneumoconiosis without DIF. It has been found that lung cancers develop more in DIF areas, and squamous cell carcinoma in particular. In our case, lung adenocarcinoma was detected within the PMF lesion on MRI. It has been used in the diagnosis of diseases by determining the content and distribution of hydrogen protons in the water molecules of the tissues in MRI. Studies suggesting the use of MRI for the differentiation of PMF and malignant lesions have reported PMF lesions to be hypointense when compared to skeletal muscle on T2W images, while malignant lesions are hyperintense compared to skeletal muscle (17,18). In our case, malignant tissue showed high signal intensity while fibrotic masses showed low signal intensity, and the difference in signal intensity was more apparent on T2W images.

Figure 5a: A tumoral structure infiltrating the lung parenchyma as acinar, papillary and micropapillary structures is observed (HEx400)
CONCLUSION

PMF lesions can sometimes confused with malignant lesions. We recommend thoracic MRI for patients with PMF who are thought to have accompanying lung cancer, as hyperintense areas in PMF lesions on MRI T2W images can help identify the target areas of a needle biopsy.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS


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A Case of Endobronchial Tuberculosis Mimicking Lung Cancer Developing on the Background of Anthracosis

Antrakozis Zemininde Gelişen Akciğer Kanserini Taklit Eden Endobronşiyal Tüberküloz Olgusu

Sümeyra Kaplan, Ceyda Anar, Muzaffer Onur Turan, Bunyamin Sertogullarından

Abstract

Anthracite pigment accumulation in the bronchial mucosa can lead to bronchial hypertrophy and narrowing in the future. A patient pre-diagnosed with community-acquired pneumonia underwent fiberoptic bronchoscopy (FOB) and was subsequently treated with antibiotics, however no clinical or radiological response could be obtained. Fiberoptic bronchoscopy (FOB) revealed the mucosa of the lower basal segments of the right lung to be covered with black pigment, while the bronchi segments were found to be narrowed with mucosal infiltration. Based on these findings, a biopsy was performed with pre-diagnosis of malignancy developing on the basis of anthracosis. The pathological examination revealed granulomatous inflammation with caseified necrosis and acid-resistant bacilli in the bronchoalveolar lavage. The patient was diagnosed with tuberculosis on the basis of anthracosis and was thus started on quadruple anti-tuberculosis treatment, and clinical, microbiological and radiological improvement was observed in the 4th month of follow-up.

Keywords: Anthracosis, tuberculosis, bronchoscopy.

Öz


Anahtar Kelimeler: Antrakozis, Tüberkuloz, Bronkoskopı.
Anthracosis is a type of pneumoconiosis that can result from an accumulation of carbon particles, but also iron, lead, cadmium, organic or inorganic materials. Exposure to organic/inorganic particles and carbon particles can lead to their accumulation in the bronchial mucosa, resulting in bronchial hypertrophy and narrowing (1). The term “bronchial anthracosis” refers to the appearance of a black pigmentation in the bronchial mucosa (2), while “bronchial antracofibrosis (BAF)” is an accompanying anthracotic pigmentation, bronchial narrowing or obliteration (3). Bronchial anthracosis (BA) and/or antracofibrosis can be diagnosed bronchoscopically. Although biomass exposure is the leading risk factor in patients with bronchial anthracosis, a history of tuberculosis is also important. It is not clear, however, whether anthracosis causes tuberculosis or tuberculosis causes bronchial anthracosis. Uçar et al. reported the most common comorbid disease to be COPD, followed by pneumonia, tuberculosis and malignancy (4).

Endobronchial tuberculosis (EBTB) can be confused clinically and radiologically with asthma, foreign body aspiration, pneumonia and bronchial cancer, especially in those of advanced age. Another feature of EBTB is the relatively limited bacteriological diagnosis possibilities in normal sputum examinations, which can be seen in 10–40% of patients with active pulmonary tuberculosis. We present here a case who was diagnosed with endobronchial tuberculosis based on bronchoscopic material. The disease developed on the basis of anthracosis and mimicked lung cancer clinically and radiologically, and was treated successfully with anti-tuberculosis therapies.

CASE
A 77-year-old female patient presenting with cough, anorexia, weakness and weight loss had been diagnosed with pneumonia in an external center, but saw no improvement in her condition after 10 days of empirical antibiotic treatment. Upon applying to our hospital for further investigation she was subjected to a physical examination with the following findings: blood pressure: 110/70 mmHg, Pulse: 80/min and Fever: 37ºC. A respiratory system examination revealed decreased respiratory sounds in the lower right lung but no pathology in an examination of other systems. The laboratory examination findings were as follows: White Sphere be 11000/µL, Hb: 13g/dL, Hct: 33%, PLT: 250/µL, sedimentation rate: 33mm/h and C-reactive protein: 30mg/L, while biochemistry parameters were normal. The patient had no comorbidities other than a known skin basal cell carcinoma and hypertension. A homogeneous density was identified in the lower zone of the right lung on chest X-ray (Figure 1), while thorax CT revealed a consolidated area containing air bronchograms in the anterobasal right lung lower lobe (Figure 2a and b). Bronchoscopy revealed the mucosa was infiltrated with white and black anthracotic changes in the right lung lower lobe basal segment, especially in the anterior and lateral segments (Figure 3a and b), and the areas were subjected to bronchus biopsy, transbronchial fine needle biopsy and bronchoalveolar lavage.

Figure 1: A homogeneous density observed in the lower zone of the right lung on Chest X-ray

Figure 2a, and b: A consolidated area containing air bronchograms observed in the anterobasal right lung lower lobe on thorax CT

Figure 3a, and b: The mucosa was infiltrated with white and black anthracotic changes in the right lung lower lobe basal segment on bronchoscopy
Based on the bronchoscopic findings, lung carcinoma developing on the basis of anthracosis was suspected, and so a Positron Emission Tomography (PET-CT) was conducted revealing intense FDG accumulation in the consolidation area containing air bronchograms defined in the right lung lower lobe anterolateral basal, and multiple hypermetabolic lymph nodes in the mediastinum, right upper-lower paratracheal, left lower paratrahcal, prevascular, aorticed pulmonary, subcarinal, bilateral epiphrenic and bilateral hilar (Figure 4a and b). The pathology results revealed granuloma structures in the bronchial mucosa in intense lymphoplasmocytic inflammation (necrosis in the central section that could indicate caseification), and fragments of hyaline, fibrotic, anthracotic and partially necrobiosis acellular connective tissue. Mycobacterium tuberculosis PCR sent in BAL material was found to be low positive. The patient was diagnosed with pulmonary tuberculosis, developing on the basis of anthracosis, and was started on quadruple therapy (INH, RIF, EMB, PRZ). A mycobacterium tuberculosis complex grew in the tuberculosis culture of the BAL material approximately 2 weeks after the patient was started on treatment. At the 2nd month control, the sputum ARB smear was negative and there was no growth in the culture, and so the patient was switched to double anti-tuberculosis treatment (INH, RIF). A postero-anterior (PA) chest X-ray taken at the 4th-month follow-up revealed a marked regression of the infiltration area observed in the lower zone of the right lung (Figure 5). The antituberculosis treatment was planned to be completed in 6 months.

**DISCUSSION**

Endobronchial tuberculosis (EBTB) is detected in approximately 58% of patients with anthracosis, which strongly suggests that bronchial anthracosis is attributable to active or previous tuberculosis infection. Endobronchial tuberculosis continues to be a significant health problem as the diagnosis is often delayed (5,6). The presence of TB in BAF was first demonstrated by Chung et al. (3) 30 years ago. In a meta-analysis of studies investigating the relationship between TB and anthracosis, the frequency of tuberculosis in all anthracosis patients was 22.5 % (32.3 % for anthracofibrosis and 16.6 % for anthracosis), which was significantly higher than the control group (7).

It has been shown that a wheezing symptom has led EBTB to be mistakenly diagnosed as bronchial asthma, with around 24% of patients with this finding inadvertently undergoing long-term bronchial asthma treatment before a correct diagnosis (8,9). Thoracic mass lesions were observed on CT scans in 15% of patients with EBTB, but no invasive procedures were performed until active pulmonary tuberculosis was ruled out. Previous studies have revealed that bronchial anthracosis can be misdiagnosed as lung cancer based on radiological studies alone (10,11).

Singh et al. (12) reported the most common symptoms in patients with anthracosis to be dyspnea (90%) and cough (76.65%), while Chung et al. (3) reported cough (71.42%) and exertional dyspnea (60.71%) to be the predominant symptoms. Likewise, Mirsadree et al. (7) reported that 95% of the anthracosis cases in their study complained of shortness of breath while 86% had a cough. Our case had persistent cough and fatigue. The disease can increase the existing symptoms in infectious conditions such as pneumonia and tuberculosis, which may occur on the background of anthracosis.
Anthracosis has been previously documented in patients with chronic exposure to biomass fuel fumes (3,4,7). Grobbelaar et al. (13) found anthracosis to be prominent in patients chronically exposed to biomass fumes, and coined the term “Hut Lung” to describe the condition. In the study by Singh et al. (12), it showed that biomass exposure was not significantly associated with anthracosis. Our case was exposed to biomass due to the situation of burning a tandoor and a hearth. In the same study, a significant association was identified between stone mining and anthracosis, which may be attributed to the association of stone mining with silicosis, and subsequently, tuberculosis. Silica alters the macrophage function and thus prevents the clearance of inhaled particles, leading to an accumulation of pigments and changes in the immune mechanisms in the lungs, leading to Mycobacterium tuberculosis infection (14). Another hypothesis proposes that carbon and silica accumulate in the lymph nodes of people who are heavily exposed to air pollutants, cigarette smoke and biomass fuel smoke (15). When these lymph nodes become infected with M. tuberculosis, they rupture into the adjacent tracheobronchial tree, causing black pigmentation and subsequent inflammation and fibrosis.

Chest X-ray findings have been reported to be normal in only 7% of cases with anthracosis. The most common abnormalities reported on chest X-rays are inhomogeneous pulmonary infiltrations. Subsegmental atelectasis and mass lesions were found less frequently (20% and 16%, respectively, in patients) (16). Chest X-rays may be normal in 10–20% of patients with EBTB, and so the diagnosis of these patients can often be delayed or incorrectly identified as bronchial asthma or malignancy. In our case, a heterogeneous increase in density in the lower zone of the right lung was observed on chest X-ray.

CT can be considered a good diagnostic method for the differentiation of such bronchial conditions as bronchial stenosis or obstruction, with more sensitive and more specific radiological findings related to both anthracosis and EBTB. The initial reports suggested mediastinal or hilar lymphadenopathy in 94% of cases, of which 57% were calcified, and the conditions were followed by bronchial narrowing with or without atelectasis at a rate of 94% (17). In one study, the frequencies of lymph node, bronchial stenosis, atelectasis and mass lesions in BAF were significantly higher in patients with anthracosis than in non-anthracotic cases (16). Bronchial wall thickening has also been reported in 20% of BAF patients (17). Involvement may be unilateral or bilateral, although the right middle lobe has been reported as the most frequently involved lobe location, followed by the upper lobes, (16,17). In another study, mediastinal lymphadenopathy (53.3%), fibrosis (43.3%), nodules (46.67%), consolidation (33.3%) and collapse (23.3%) were detected on CT (12). In a study by Bekçi et al. (18), consolidation and atelectasis were observed at the level of the right middle lobe on CT, as in our case, and the final diagnosis was reached by bronchoscopy. Our case, on the other hand, was presented with a complaint of cough, and after no significant regression was noted on chest X-ray after 10 days of antibiotherapy treatment, an area of consolidation was observed on CT.

Bronchoscopy is the optimum approach to the diagnosis of anthracosis and EBTB. Lesion size, which has an endobronchial effect, is among the side effects of EBTB, and it is a very important point to perform a bronchoscopic examination in this direction. Anthracosis can be localized, widespread, and unilateral or bilateral. It is most often seen in the right middle lobe, followed by the upper lobe in the second order, and tracheal involvement is rare (17). Seven subtypes of EBTB have been defined based on their bronchoscopic features, being active caseous, edematous-hyperemic, fibrostenotic, tumoral, granular, ulcerative and non-specific bronchitic (19). In the study by Lee et al. (20), the most common bronchoscopic finding was lumen narrowing due to hypertrophy, and the most frequently involved areas were the right upper lobe bronchus and the right main bronchus. Our case had involvement in the lower lobe bronchus of the right lung, as well as anthracotic changes in the middle lobe and bronchus of the right lung, and bronchial narrowing and mucosal infiltration on an anthracotic background in the lower lobe. In another case who presented with hoarseness, FOB was performed to investigate the etiology of the identified mediastinal lymphadenopathy, and diffuse anthracotic pigmentation was observed in the bronchial mucosa, in addition to vocal cord paralysis. There was no finding in favor of tuberculosis or malignancy in the bronchial lavage. The pathology of the materials taken from the patient who underwent diagnostic thoracotomy revealed parenchymal anthracosis and granulomatous inflammation with caseification in the lymph nodes (21).

In our case, diagnosis was based on the identification of ARB in the bronchoalveolar lavage obtained by bronchoscopy, as well as granulomatous inflammation showing caseification on biopsy, and early treatment was initiated.

In conclusion, patients with anthracosis should be investigated and followed up for tuberculosis and malignancy. Our case of pulmonary tuberculosis mimicking anthracosis-based lung carcinoma was identified with computed tomography and bronchoscopic findings and received clinical and radiological improvement with anti-tuberculosis drug therapy. In such cases, bronchoscopic and bronchoscopic material examinations for the investigation of tuberculosis are of great importance in terms of both establishing the correct diagnosis and preventing the
development of bronchostenosis through the early initiation of treatment.

CONFLICTS OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS

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118
A Rare Cause of Mediastinal Lymphadenomegaly: Rosai-Dorfman-Destombes Disease

Mediastinal Lenfadenomegalinin Nadir Bir Nedeni: Rosai-Dorfman-Destombes Hastalığı

Abstract

Rosai-Dorfman-Destombes disease (RDD) is a rare condition that typically presents with cervical lymphadenopathy. The disease usually follows a benign clinical course, and its occurrence in mediastinal lymph nodes is extremely rare. We present here a 48-year-old female patient with Rosai-Dorfman-Destombes disease that manifested as mediastinal lymphadenomegaly, and who was diagnosed by mediastinoscopy.

Keywords: Mediastinal lymphadenomegaly, mediastinoscopy, Rosai-Dorfman-Destombes disease.

Öz


Anahtar Kelimeler: Mediastinal lenfadenomegali, mediastinoskopi, Rosai-Dorfman-Destombes hastalığı.

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Mediastinal lymphadenopathies may be encountered in such benign diseases as sarcoidosis and tuberculosis, or for reasons such as malignancies (1). Various interventional methods can be applied for diagnosis. A needle biopsy can be performed during endobronchial ultrasonography while larger biopsy specimens can be obtained with mediastinoscopy.

Rosai-Dorfman-Destombes Disease (RDD) is characterized by painless massive lymphadenopathy, leukocytosis and a high erythrocyte sedimentation rate, and follows a benign clinical course. It may occur in all lymph nodes in the body, but it is more common in those in the cervical region, while extranodal involvement can develop in approximately 25% of cases (2). It is rare in mediastinal lymph nodes. We present here a case with Rosai-Dorfman-Destombes disease, which in rare cases causes mediastinal lymphadenomegaly, in the light of literature.

CASE
A 48-year-old female patient presented with a complaint of dyspnea, but no obvious pathology was detected in a physical examination. Blood tests pointed to anemia, with Hgb: 11.3 g/dl (min:12-max:15.5), Hct: 34.3%, MCV: 71fL, MCH: 23.6pg, iron: 15 µg/dl and iron binding capacity: 402 µg/dl, while the patient’s sedimentation rate was determined as 35 mm/h. Immunoglobulin G was 17.9 g/L, and β2-microglobulin was 2.78 mg/L. Upon the detection of mediastinal enlargement on a chest X-ray, a computed tomography (CT) of the thorax was performed revealing paratracheal, subcarinal and bilateral hilar multiple lymphadenopathies (Figure 1). Due to the possibility of malignancy of the detected mediastinal lymph nodes, positron emission tomography/CT (PET/CT) imaging was performed, during which the fluoro-2-deoxy-glucose (FDG) standardized maximum uptake (SuvMax) value of the lymph nodes was identified as 15.85 (Figure 2).

No tissue diagnosis could be obtained from the paratracheal lymph node through endobronchial ultrasound (EBUS) performed in the chest diseases clinic. Mediastinoscopy was performed for lymph node sampling, which was referred to at our clinic. Multiple biopsies were taken from the right paratracheal and subcarinal lymph nodes, and the patient was discharged without any complications on the first postoperative day.

The pathology examination revealed a proliferation of CD68 (KP1) positive and CD1a immunonegative histiocytes that had destroyed the follicle structures of the lymph node. No significant atypia or mitotic activity were observed in the histiocytes, and the findings were consistent with RDD (Figures 3-4-5). The patient was followed up without treatment, and a decrease in the size and SuvMax values of the mediastinal lymph nodes was noted on PET/CT imaging 18 months later (Figure 6). The patient’s consent was obtained for this study.

DISCUSSION
RDD, first described by Rosai and Dorfman in 1969, is a rare idiopathic histiocytic proliferative disease that mostly affects children and adolescents. It is known also as sinus histiocytosis with massive lymphadenopathy (2). RDD has a prevalence of 1 case per 200,000 people, with a mean age of onset of 20.6 years, a greater prevalence in African patients and a slight preponderance in males (male/female ratio of 1:4) (3-5). It is a rare disease that tends to occur in the first or second decades of life. Although its etiology has not been clearly determined, it has been reported to be associated with disorders in the immune system, Epstein-Barr virus and human herpes virus 6 (6). Although it is usually seen in the early stages of life, it can also be detected in advanced ages due to its benign nature.
The disease most commonly presents as painless massive cervical lymphadenopathy, although its incidence is low. Extranodal involvement can occur as an isolated finding or with lymphadenopathy in the skin, soft tissue, upper respiratory tract, multifocal bone, eye and retro-orbital tissue areas (7). Rare cases of RDD occurring in mediastinal lymph nodes have been reported. Hematological disorders include microcytic or normocytic anemia, thrombocytopenia or increased erythrocyte sedimentation rate (ESR), and in some cases, autoimmune hemolytic anemia may also occur. An increased erythrocyte sedimentation rate and polyclonal hypergammaglobulinemia are detected in the majority of patients, although increased neutrophil levels and leukocytosis have also been reported (8,9).

A definitive diagnosis of RDD can be made based on a pathological examination. The detection of emperipolysis, defined as the engulfment of lymphocytes and erythrocytes by histiocyte-like cells expressing S-100, indicates an RDD diagnosis. Although positive for CD68, CD163, α1-antichymotrypsin, α1-antitrypsin, fascin and HAM-56 are detected with S-100 antigen positive, CD1a negative is detected (10,11).

In the case presented here, the pathology sample revealed a proliferation of CD68 (KP1) positive, CD1a immunonegative histiocytes that had destroyed the follicle structures in sections of the lymph node. No significant atypia or mitotic activity were observed in the histiocytes, while lymphocyte infiltration surrounding the histiocytes and locally observed intracytoplasmic were observed. All of these pathological findings supported the diagnosis of RDD. RDD may so closely resemble leukemia or lymphoma that it is clinically considered a pseudo-lymphomatous disorder. The disease is mostly benign and the enlarged lymph nodes regress spontaneously in the long term, although some mortal cases have also been reported. The emperipolysis typically observed in RDD in pathology specimens may also be seen in autoimmune hemolytic anemia, myelosclerosis, carcinoma, neuroblastoma, multiple myeloma, leukemia and malignant lymphomas, although only rarely (12).

The differential diagnosis of RDD is broad and similar to other benign or malignant lymphadenopathy etiologies. The benign causes include other histiocytic disorders such as tuberculosis, Wegener’s granulomatosis, Castleman disease, sarcoidosis and IgG4-related disease, while malignant etiologies include Hodgkin and Non-Hodgkin lymphoma, melanoma, leukemia and Langerhans cell sarcoma (8).

There are two methods used widely today for the obtaining of biopsies from mediastinal lymphadenopathies: endobronchial ultrasound-guided transbronchial needle biopsy (EBUS-TBNA) and classical cervical mediastinoscopy. EBUS-TBNA has gained popularity in recent years but is known to give false negative results in benign or malignant diseases with low FDG affinity in preoperative imaging. Furthermore, if it is performed under general anesthesia, it is not a minimally invasive procedure (13), while experienced centers can achieve successful results with high diagnosis and low complication rates through mediastinoscopy.
CONCLUSION
Since benign or malignant diseases occurring in mediastinal lymph nodes have similar radiological images, diagnosis should be based on tissue sampling when detected. Mediastinoscopy maintains a role in the current approach as it allows the direct visualization of the mediastinal structures and the taking of large biopsies. Although rare in patients with mediastinal lymphadenomegaly, RDD should be kept in mind in suspected cases.

CONFLICTS OF INTEREST
None declared.

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A Rare Cause of Stridor in the Emergency Department: Multiple System Atrophy: A Case Report

Acil Serviste Stridorun Nadir Bir Nedeni: Multipl Sistem Atrofi: Olgu Sunumu

Abstract

Multiple System Atrophy (MSA) is a less common degenerative disorder that impacts the autonomic functions of the body, such as bladder function, blood pressure, breathing and muscle control. Clinically, there are 2 types of MSA: Parkinsonian (MSA-P) and cerebellar (MSA-C). Laryngeal stridor is an important clinical finding that can aid in diagnosis and indicates a poor prognosis. We present here the case of a 53-year-old female patient who had been diagnosed with MSA-C two years earlier, and who presented to the emergency department with dyspnea.

Keywords: Multiple system atrophy, stridor, vocal cord dysplasia.

Olgun Sunumu

Acil serviste stridorun nadir bir nedeni: multipl sistem atrofi: olgu sunumu

Abstract

Multipl sistem atrofi (MSA), kan basıncı, solunum, mesane fonksiyonu ve kas kontrolu dahil olmak üzere vücudun otonomik fonksiyonlarını etkileyen nadir, dejeneratif bir nörolojik hastalıktır. Parkinsoniyen (MSA-P) ve serebellar (MSA-C) tip olmak üzere iki klinik tipi vardır. Laringeal stridor, yüksek tanısal pozitif prediktif değeri olan ve aynı zamanda kötü prognoz göstergesi kabul edilen klinik bir bulgudur. Bu yazida, acil servise nefes darlığı yakınması ile başvuran 2 yıl önce MSA-C tanısı olan 53 yaşındaki kadının hasta incelenip sunulmuştur.

Anahtar Kelimeler: Multipl sistem atrofi, stridor, vokal kord displazi.

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Multiple System Atrophy (MSA) is a less common and quickly progressive neurodegenerative disease with characteristic findings of Parkinsonism or cerebellar ataxia with autonomic failure (1). The estimated annual incidence of MSA in the general population in the United States is 0.6 cases per 100,000 people, resulting in approximately 1,900 new cases per year (2). There is a lack of definitive data on its prevalence in Türkiye. The peak onset varies between the ages of 30–90, with no difference between sexes, but occurs primarily between 55 and 60 years. The effect on autonomic functions may lead to orthostatic hypotension, bladder dysfunction, sleep disorders, sexual dysfunction, body temperature imbalances due to a deterioration in sweating balance and cardiovascular problems, while bilateral vocal cord paralysis, central respiratory failure, and central or obstructive sleep apnea syndromes in patients with multisystem atrophy are among the clinical pictures that can be seen related to respiration (3). Clinical symptoms progress rapidly, and average survival ranges from 6 to 9 years (4), while death usually results from respiratory problems, infections or pulmonary embolism (5).

Stridor is a clinical finding with a high diagnostic positive predictive value for the diagnosis of MSA, the definition of which was decided upon at the MSA International Reconciliation Conference in Bologna in 2017, and its emergence in the early period is considered an indication of short survival.

Stridor is a respiratory sound that is high-pitched and tense, and is usually heard during inhalation. It is caused by a narrowing of the rima glottis in the larynx and can occur while the patient is both asleep and awake. A laryngoscopy is advised for the elimination of the possibility of mechanical damage or functional issues in the vocal cords that may be linked to various neurological conditions. Continuous positive airway pressure and tracheostomy are recommended for the treatment of stridor as a symptom, although the impact on patient survival is unknown, and so advanced studies are needed (1).

We present here the case of a 53-year-old female with an MSA-C diagnosis to raise awareness of the possibility of this rare etiology in patients who presented to the emergency department with shortness of breath and stridor in clinical examination findings.

CASE

A 53-year-old female patient with no smoking history presented to the emergency department with a reported increase in dyspnea symptoms that had persisted for a month. Her history included an etiology of demyelinating disease and ataxia that was investigated in the neurology outpatient clinic to which she had applied with gait disturbance in 2015, and a “hot cross bun” appearance seen on cerebral Magnetic Resonance Imaging (MRI) in 2017. She was diagnosed with MSA-C, in which the cerebellar ataxia clinic is at the forefront. When questioned in detail, the patient reported long-term constipation and orthostatic hypotension. She was started on Levodopa 125 mg 3x1 but did not use it regularly and did not attend control visits. The family history was unremarkable. The patient's body temperature was 36.8°C, heart rate was 92/min, arterial blood pressure was 130/80 mmHg, respiratory rate was 32/min, and room air oxygen saturation was 85%. A physical examination revealed no abnormal findings other than inspiratory and expiratory stridor.

A posteroanterior chest X-ray revealed the diaphragms to be elevated due to insufficient inspiration, but no other significant findings (Figure 1). No major airway stenosis was observed on head, neck or thorax computed tomography imaging.

An otolaryngology examination revealed vocal cord movement to be significantly reduced but not fully paralytic, and the patient was started initially on 1 mg/kg methylprednisolone, with a recommendation for emergency intubation and tracheostomy if a decrease in saturation values was detected. The head and neck tomography findings were within normal limits.

The patient was admitted to the intensive care unit and started on 80 mg of methylprednisolone IV. After a consultation with a neurologist, levodopa 125 mg 3x1, which she had used irregularly, was added to the treatment.

The patient experienced rapid clinical improvement with a decrease in stridor and symptom severity after starting the treatment. Oxygen therapy was halted on the third day of treatment after the need declined, and room air oxygen saturation values remained static at 94–95%. The patient was transferred to the neurology clinic after the respiratory distress was relieved, and was returned to the ward with room air saturation values of 94–95% on the sixth day of treatment. A pulmonary function test was requested on the seventh day of treatment, but the patient could not cooperate. By the seventh day of methylprednisolone treatment, the patient's complaints had regressed significantly. The tracheostomy decision was postponed following an otolaryngology consultation, and she was subsequently discharged from the neurology clinic on oral and systemic steroid therapy.

The patient underwent a tracheostomy after presenting with hypoxemic respiratory failure 3 weeks after discharge due to paralysis of the two vocal cords and limitations in the passage opening, after which a significant increase in lung aeration was noted on a chest X-ray when compared to the previous image (Figure 2). In the 2-year follow-up of the patient, other symptoms related to MSA-C were followed and no respiratory distress or shortness of breath were noted.
A Rare Cause of Stridor in the Emergency Department: Multiple System Atrophy: A Case Report | Ertürk et al

**DISCUSSION**

The present study reports on a case of MSA-C with dyspnea in a female patient who presented to the emergency department. There are multiple findings associated with MSA, including autonomic failure, cerebellar ataxia and Parkinsonism (1). It is a synucleinopathy that generally starts at around the age of 50 and occurs sporadically (6). There are two subtypes of MSA disease, which are clinically dominated by autonomic and urogenital insufficiency. The cases were divided into two groups, of which 80% had MSA-P (MSA-parkinsonian) with Parkinson’s findings that were unresponsive to levodopa (L-dopa), and 20% had MSA-C (MSA-cerebellar) with cerebellar ataxia findings (7). Postural (orthostatic) hypotension, urinary-bladder dysfunction (incontinence), sleep disorders, sexual dysfunction (Libido loss - impotence), sweating balance, body temperature imbalance and cardiovascular problems can be seen (5). Our case had rarer MSA-C subtypes featuring groove disorders, orthostatic hypotension and constipation autonomic dysfunction.

Cerebral MRI is the optimum imaging method for the diagnosis of MSA. Findings such as atrophy in the putamen, pons and middle cerebellar peduncle, hypointensity in the lateral putamen on T2 sequences, and cruciform hyperintensities referred to as “hot cross bun” signs in the pons can help support the diagnosis (8). In our case, clarification secondary to atrophy in the cerebellar folia on cerebral MRI and the “hot cross bun” sign, which results typically from an increase in intensity in the T2W sequence, played an essential role in the diagnosis. MSA often involves various sleep-related respiratory conditions, such as stridor and central and obstructive sleep apnea (OSA), among which Stridor can be helpful in the diagnosis of MSA due to its high positive predictive value.

A previous study identified early onset of stridor as a predictive factor for shorter survival (9). The authors also noted that the prognostic value of stridor is a point at issue. Our case was still alive two years after the onset of stridor. The two main options for the treatment of stridor are tracheostomy and continuous positive airway pressure (CPAP). When the stridor is severe due to advanced disease or immobile vocal cords during wakefulness, tracheostomy is the preferred option (10). CPAP is a non-invasive treatment approach that can be utilized for the management of mild to moderate sleep-related stridor and OSA (9). Experts from various fields convened for a conference in Bologna in 2017 to agree on the criteria for a diagnosis of stridor, to clarify its association with MSA, to identify the prognostic value of stridor on MSA survival, to agree on therapeutic options for the management of stridor, and to systematically review the evidence so as to identify gaps for future research.

Stridor is difficult to diagnose clinically as patients are often unaware of its presence during sleep, and so a nighttime witness is often required to determine its occurrence. Manifestations such as high-pitched sounds or heavy snoring can also point to the development of stridor. Given the prevalence of snoring and obstructive sleep apnea syndrome in patients with MSA, differentiating these conditions from stridor is essential. In the present case, no polysomnography was performed prior to hospital admission, despite the patient’s report of shortness of breath for a month. To exclude other potential diagnoses and to confirm vocal cord dysfunction, laryngoscopy while the patient is awake is vital in MSA for those who present with stridor (1). A study of 136 patients with MSA revealed the development of stridor in the early period to be a negative indicator of survival.
In the presented case, a significant decrease was noted in vocal cord movement during a laryngoscopy performed by an ENT specialist, although the paralysis was not total. Accordingly, the patient was started on systemic methylprednisolone and was prepared for a tracheostomy informing the patient's relatives in cooperation with the neurology and otolaryngology department. Under close observation, however, the tracheostomy decision was not made immediately due to the dramatic clinical response of the patient to the methylprednisolone treatment. A tracheostomy was subsequently performed three weeks after discharge upon the re-development of dyspnea and stridor. There were 2 months between the initiation of steroid therapy and the opening of the tracheostomy. With this treatment, it is thought that the opening of the tracheostomy is delayed. More research and data are needed for the correct timing of tracheostomy. In conclusion, MSA patients require close follow-up, and treatment should be planned based on a multidisciplinary approach. The recognition of stridor as a poor prognostic marker and early diagnosis and treatment in a patient presenting with dyspnea can positively affect the prognosis in this progressive patient group.

CONFLICTS OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS

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COVID-19 Cytokine Storm and the Mechanisms of Immune Injury

COVID-19 Sitokin Fırtınası ve İmmün Hasar Mekanizmaları

Ali İnal, Dilaver Taş

Abstract

The first cases of COVID-19 were identified in China in 2019, and the disease subsequently spread rapidly around the world, leading it to be declared a pandemic. The disease affects the lungs through the upper and lower respiratory tracts, and with the development of pneumonia, a clinical picture leading to respiratory failure referred to as cytokine storm occurs as a result of excessive cytokine production associated with an excessive inflammatory immune response. The increase in inflammatory markers is related to acute respiratory distress syndrome, disseminated intravascular coagulation and hypercoagulation. We present here an explanation of cytokine storm and the associated immune damage mechanisms.

Keywords: Cytokine storm, COVID-19, immunopathogenesis.

Öz


Anahtar Kelimeler: Sitokin fırtınası, COVID-19, immünopatogenez.
The first case of coronavirus disease 2019 (COVID-19) was reported in the city of Wuhan, China [1], and the causative virus was identified shortly after, when an increasing number of patients presented with similar symptoms of respiratory tract infection. The causative viral agent was an RNA virus that was named subsequently “severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)“, the primary transmission route of which was identified as direct or indirect contact with the respiratory droplets of asymptomatic carriers or patients, and the rapid transmission of the virus from one person to another was the primary obstacle to disease control [1]. To date there have been 681,591,554 reported cases of the disease and 6,812,126 deaths [2]. The coronavirus has four different structural proteins that play an important role in its lifecycle: the S protein, forming the spikes on the surface of the virus, which are responsible for binding the virus to the host cell membrane (3); the M protein, which is involved in the establishment of the viral shape, and also plays a role in the formation of viral particles and budding from the cell membrane through a process known as scission [4]; the E protein, which is involved in the assembly and budding of the virion, and plays a role in viral pathogenesis; and the N protein of the virus, which has multiple functions, and is capable of binding to viral RNA through two binding domains. The N protein interacts with viral nonstructural protein 3 (nsP3) to package the genome and promote virion assembly, and maintains viral integrity against intracellular defense systems [4,5]. SARS-CoV-2 has demonstrated an ability to enter cells through different mechanisms, but mainly by direct membrane fusion, with the angiotensin-converting enzyme 2 (ACE2) receptors being the main binding site and playing a crucial role in the entry of the virus into the cell and viral replication [6]. The S protein of SARS-CoV-2 binds to ACE2 receptors and fuses with the plasma membrane and is proteolytically processed after binding to the ACE2 receptor, which is an important stage in the lifecycle of the virion [5]. Our understanding of how SARS-CoV-2 enters cells remains open to further refinement, although it is known to gain entry through the formation of viral inclusion bodies upon contact with cellular surface elements.

In addition to membrane fusion, both clathrin-mediated and clathrin-independent endocytosis mechanisms have been reported. Clathrin is a basic protein that plays a role in the assembly of extracellular vesicles into a specific shape. Once the single-stranded positive-sense RNA genome gains entry to the cell, it is released into the cytoplasm, and as a result, the transcription and translation of viral products take place [7]. ACE2 receptors are expressed in various tissues, including alveolar cells, bronchial epithelial cells, and the liver, neurons, glia, pancreas, stomach, bowel, heart and kidneys [8]. The internalization and cleavage of ACE2 during the entry of the virus into the host cell affects also the renin-angiotensin system (RAS) and results in an increased serum level of angiotensin-2. ACE2 receptors are also expressed in endothelial cells, and viral inclusion bodies can be observed in the endothelial cells upon contact with the virus. The endothelitis, apoptosis and imbalance in RAS resulting from endothelial cell infection have been linked to a variety of conditions, such as ischemia, edema and hypercoagulability [9,10]. Antibody-dependent enhancement (ADE) is another potential route for the entry of SARS-CoV-2 into cells. In the presence of anti-S antibodies, the virus enters the host cells that harbor Fcγ-2 (CD32) receptors on their surfaces in the form of an antibody-virus complex, and thus exerts cytopathic effects. It is thought that the entry of SARS-CoV-2 into monocytes and macrophages through ADE could play a role in cytokine and chemokine release and apoptosis [11,12].

The body’s natural immune response elements are the first-line defense in the recognition and clearance of viral infectious agents. The leading factor in the activation of a natural immune response is the recognition of the pathogen-associated molecular pattern (PAMP) of the virus in the form of lipid, protein and nucleic acid by toll-like receptors (TLRs). It has been suggested that the S protein can be recognized from TLR4, that ssRNA can be recognized from TLR7/8, and that the dsRNA that forms during replication can be recognized from TLR3. TLR3 and TLR4 induce interferon regulatory factor 3 (IRF3) over the toll-interleukin1 receptor (TRIF) domain-containing adaptor-inducing interferon-β and the TRIF-related adaptor molecule (TRAM), leading IRF3 to accumulate in the nucleus and initiate interferon (INF) synthesis. Upon recognizing a foreign or a disrupted molecule, the cell instructs the neighboring cells to correct the problem, and these pathways are crucial elements in the innate immune response to viruses. Coronaviruses are capable of concealing pathogen-associated molecular patterns (PAMPs) and can also prevent intracellular receptors from recognizing them [13]. They have also developed various mechanisms through which they can evade recognition by host cells, such as by concealing themselves within double-layered endosomal structures and disrupting the timing and magnitude of the host's interferon (IFN) response to infection. Despite being vulnerable to the immune responses mediated by interferon (IFN), SARS-CoV and other coronaviruses have evolved multiple mechanisms that make them resistant to type-I IFN-mediated responses, allowing the virus to evade the host's immune defenses and cause significant damage to the infected patient [14,15]. Studies investigating the role played by T and B lymphocytes in mice infected with SARS-CoV have revealed that T cells play a crucial role in clearing the virus and supporting the
host’s immune defense, and that the weak virus-specific T cell response is linked to the development of severe disease. In cases of SARS-CoV infection, approximately 80% of the cells that infiltrate the lungs are CD8 cytotoxic T cells (16). The importance of a robust T cell response for the successful clearance of viral infections is well understood, and this is the case also in SARS-CoV-2 infections. The development of lymphopenia in COVID-19 patients has been well-documented and is of prognostic significance (17). The CD4/CD8 cell ratio appears to remain stable in patients with COVID-19, with no notable changes identified in CD4 marker expressions to date, while an upregulation in the intensity of CD8 on the surface of lymphocytes has been observed. Given the crucial role of the CD8 protein in mediating cytotoxic activity, it has been suggested that cytotoxic T lymphocytes (CTLs) increase CD8 expression to facilitate effective antiviral activity (18). In humans, memory T cells specific to SARS-CoV have been detected in the blood up to 6 months after infection, while conversely, there would appear to be a significant deficiency in the specific memory B cell response. During the course of the disease, patients exhibit decreases in total lymphocyte count, CD4-positive and CD8-positive T cells (while the CD4/CD8 ratio is preserved), as well as B-lymphocytes and natural killer cells in the peripheral blood (19,20). Furthermore, memory helper T cell and T-regulator cell counts are remarkably low, and patients with more severe infections have been found to exhibit lower total lymphocyte, CD4-positive and CD8-positive T-cell, and B-lymphocyte counts than those with milder forms of the disease (6,20,21). Peripheral blood analyses of patients with severe forms of the disease have revealed increased expressions of HLA DR in both CD4- and CD8-positive cells, and increases in CD4+, CCR4+, CCR6+ and Th17 cell counts have also been observed (22). Notably, autopsy studies have revealed the destruction of secondary lymphoid organs over the course of the disease, while examinations of lung specimens have revealed prominent infiltrations of CD4-positive cells (23).

Patients with severe COVID-19 infections who require admission to the intensive care unit (ICU) tend to have increased erythrocyte sedimentation rates (ESR), and C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and IL-1β, IL-8 and IL-2R levels, and such observed increases in inflammatory markers have been linked to the development of acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC) and hypercoagulability. Another study reported significant differences in the IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), inducible protein 10 (IP10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α) and TNF-α levels of patients requiring admission to the ICU when compared to those who do not require such care. Severe COVID-19 has been linked to increased inflammatory cytokine response. ARDS is induced by an exaggerated inflammatory response rather than the viral load (24). There are two primary reasons for the development of immune regulation disorders: one is the overproduction of proinflammatory cytokines by monocytes, and the other is related to the acquired immune system disorder that arises due to the depletion of CD4-positive lymphocytes. IL-6 is released in excessive amounts upon the hyperactivation of monocytes, leading to a decrease in the expression of HLA-DR on the antigen-presenting cells, especially in CD14-positive monocytes, and reduced IFN-γ (interferon-γ) secretion by CD4-positive cells. The inhibition of the IFN pathway and excessive viral load, together with the decreased viral response of the host and the persistent proinflammatory response can lead to deterioration in the patient as a result of excessive inflammation. IFN response can thus be understood to play a vital role in limiting SARS-CoV-2 infection and in activating innate and acquired immune responses. In SARS-CoV-2 infections, these responses are often delayed and inadequate, which is believed to be associated with the development of cytokine storms. While the exact mechanism by which viruses enter cells is not yet fully understood, studies have suggested that both previous coronavirus and the novel SARS-CoV-2 induce apoptosis by triggering an overproduction of such proinflammatory mediators as IL-6, GM-CSF, IL-1s and TNF, as well as activating the NLRP3 inflammasome in monocytes and macrophages, which can, in turn, lead to cytokine storm, referred to also as cytokine release syndrome (25). It has been suggested that elevated serum ferritin, IL-6, IL-1β, IFN-γ, IP-10 and MCP-1 levels play a role in the pathogenesis of severe COVID-19 (26,27), and point to the activation of Th1 lymphocytes, which are involved in the differentiation of mature B lymphocytes into plasma cells, the transformation of growth factor-β (TGF-β)-mediated differentiation of naive CD4-positive T lymphocytes into Th17 lymphocytes, and the initiation of the production of acute phase proteins such as CRP, fibrinogen, serum amyloid A and hepcidin. IL-6 initiates the maturation of megakaryocytes into platelets and the activation of hematopoietic stem cells within the bone marrow (28,29), and increased serum IL-6 levels have been linked to respiratory failure, ARDS and unfavorable clinical outcomes. It has been noted that COVID-19 patients with high IP-10, MCP-1 and TNFα levels often require monitoring in the ICU, while those with lower levels of these markers tend to have a milder disease course that does not require ICU admission. Unlike SARS caused by SARS-CoV, there is an increased immune-focused release of IL-4 and IL-10 from the TH2 lymphocyte in COVID-19 caused by SARS-CoV-2 that suppresses inflammation. The excessive release of
pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α and TGF-β) and chemokines (CXCL10, CXCL8, CXCL9, CCL2, CCL3 and CCL5) is associated with accelerated and persistent abnormal systemic inflammatory response. The cytokine storm observed in severe COVID-19 patients is a significant risk factor for increased mortality, multi-organ failure, acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC). In particular, IL-6, which is released from macrophages, has been reported to contribute to the development of macrophage activation syndrome (MAS) (28). Studies have reported that plasma levels of IL-6, which is considered a critical cytokine for the development of MAS, are increased in both mild and severe COVID-19 cases, while significantly higher IL-6 levels have been observed in those with a severe form of the disease. IL-6 is a pleiotropic cytokine that is produced by a variety of immune cells, mesenchymal cells, endothelial cells and fibroblasts in response to infections and tissue injury. Monocytes, macrophages and dendritic cells become activated upon infection with beta coronavirus, and this leads to a release of IL-6 and other inflammatory cytokines that can trigger a cytokine storm. IL-6 is capable of signaling through various pathways, however, in the classic (cis) signaling pathway, IL-6 binds to the IL-6 receptor expressed on the surface of lymphocytes that form a complex with glycoprotein 130 (gp130), activating the Janus kinase (JAK) signal transducer and the activator of the transcription (JAK/STAT) pathway. The secondary message affects the B and T cells, suppressing the development of T-regulator cells by increasing the differentiation of T helper 17 (Th17), T follicular helper (Tfh) and CD8-positive cytotoxic T cells, as well as activated B cells. Such decreases in T-regulator cells complicate the control of immune response, and IL-6 may exert different effects on the acquired and innate immune systems via this pathway. In the trans-signaling pathway, IL-6 binds to soluble IL-6 receptors and triggers the JAK/STAT pathway over the gp130 complex in cells that do not express IL-6R (mIL-6R) on their membranes, such as endothelial cells. This pathway affects endothelial cells in the blood vessels with vascular endothelial growth factor (VEGF), increasing the release of MCP-1, IL-8 and IL-6, and decreasing E-cadherin synthesis, leading to increased vascular permeability and vessel leakage. These effects contribute to the development of hypotension and ARDS, and lead to a further deterioration in the patient’s clinical condition. IL-6 has also direct effects on the synthesis function of the liver, increasing the release of CRP, serum amyloid A, hepcidin, fibrinogen, thyroid peroxidase (TPO), C3 and ferritin from the organ. Both the classic (cis signaling) and trans-signaling pathways contribute to the development of cytokine storm, leading to pulmonary dysfunction and the emergence of SARS symptoms, while cytokine storm leads also to the depletion of T lymphocytes (CD3, CD4, CD8), apoptosis and the development of lymphopenia. Studies examining the pulmonary infiltrates of COVID-19 patients who develop ARDS have suggested a link between extensive lung damage and increased IL-6 levels, and a decrease in CD4, CD8, natural killer (NK) and NKT counts in peripheral blood samples (30,31). Innate lymphoid cells (ILCs) are effector cells that respond to environmental cytokines and regulate immune response, and that do not express the antigen receptors found on the surface of T and B cells. Tissue-resident ILCs are categorized as cytotoxic and non-cytotoxic, among which the cytotoxic cell group comprises conventional natural killer cells, whereas the non-cytotoxic cell group, the main function of which is cytokine release, is made up of three subgroups. Similar to T-helper cells, the ILC1 cell group is composed of IFN-γ-producing cells, the ILC2 cell group is composed of cells that produce IL-4, IL-5 and IL-13, and the ILC3 cell group is composed of those producing IL-17/IL-22 (32). There are limited data on the roles played by cytotoxic natural killer cells and ILCs in COVID-19, although it has been demonstrated that ILC1 and ILC3 express such ligands as CD26, CD147 and cyclophilins that interact with SARS-CoV-2. Studies of COVID-19 have produced different data on the number of natural killer cells in patients. While there are several studies reporting no significant difference in the number of NK cells in COVID-19 patients when compared to healthy controls, only a single study has reported a remarkable increase in NK cell counts, and the authors suggest that this may have triggered a cytokine storm (33-34). There are many other studies, however, that have reported low or significantly decreased NK cell counts in patients with severe SARS-CoV-2 (35,36), and the functional depletion of NK and cytotoxic CD8-positive T cells has been linked to severe SARS-CoV-2 infection. Although the production of CD107a, IFN-γ, IL-2, granzyme B and TNF-α was decreased in the depleted NL and CD8-positive T cells, an overexpression of CD94/NK group 2 member A (NKG2A), acting as an inhibitory receptor, was reported in these cells (20). HLA-E is an NKG2A ligand expressed by epithelial cells, and NKG2A is known to inhibit cytotoxicity and prevent the control of infection by binding to the non-classic HLA-E molecule (37). The complement system is a component of the innate immune response that plays a critical role in host defense, although an uncontrolled and exaggerated response of the complement system can lead to acute lung injury. C5a activates phagocytic cells, stimulating cytokine release from the activated cells and can lead to a cytokine storm. C5a exerts its effects through C5aR in antigen-
presenting cells, which affects the proliferation and differentiation of CD4-positive T-helper cells and is also involved in the activation of cytotoxic CD8-positive T cells. Considering all these aspects, C5a can be said to contribute to the development of cytokine storm and ARDS by increasing the release of proinflammatory cytokines into both the innate and acquired immune systems, and it is believed that an excessive release of C5a may play a role in the development of severe respiratory failure, resulting in the release of such proinflammatory cytokines as IL-12, TNF-α and MIP-1α by inducing the mast cells, neutrophils, monocytes and macrophages. It has also been reported to induce the release of such cytokines as TNF-α, IL-1β, IL-6 and IL-8 by stimulating B and T cells (38,39).

The immune response mediated by cytotoxic CD8-positive T cells in COVID-19 neutralizes all cells infected by the virus, while CD4-positive T-helper cells help B cells initiate humoral responses. SARS-CoV-2 infects T lymphocytes through the binding of the spike protein (S1) to the CD147 ligands found on the surface of T lymphocytes. CD147 is expressed in a diverse range of tissues and cell types, and is involved in cell proliferation, apoptosis and tumor cell migration, metastasis and differentiation, especially under hypoxic conditions. The spike protein of SARS-CoV-2 has been reported to interact directly with CD26 in host cells (40). CD26 is a surface glycoprotein that contributes to T-cell activation and proliferation by interacting with the T cell receptor, and is expressed in high levels in CD4-positive and CD8-positive T cells, while displaying lower expression levels in dendritic and NK cells. The binding of the S protein of SARS-CoV-2 to the CD26 and CD147 molecules that play a role in T-cell activation suggests that the depletion of T cells by the infection can lead to cell death. It would seem plausible to suggest that the development of lymphopenia in patients with SARS, MERS (Middle East respiratory syndrome) and COVID-19 could be associated with the depletion of T cells (41,42). Following the infection of respiratory tract epithelial cells by SARS-CoV-2, viral peptides are presented to cytotoxic CD8-positive T cells via class I major histocompatibility complex (MHC) molecules. CD8-positive T cells become activated and begin to proliferate, developing virus-specific effector and memory T cells through clonal expansion. Cytotoxic CD8-positive T cells eliminate virus-infected cells through various cytotoxic mechanisms, including perforins and granzymes (43). CD8-positive T cells are of critical importance in mediating clearance following various acute viral infections in the lungs, while memory CD8-positive cells protect against secondary infections. There have been studies reporting, however, that total CD8 T and NK cell counts are diminished in COVID-19 due to lymphopenia, and cytotoxic lymphocytes are functionally depleted in SARS-CoV-2 infections in association with lymphopenia. The upregulation of NKG2A is believed to be responsible for the loss of NK and CD8-positive T-cell functionality, and it has been reported that NK and CD8-positive T-cell levels normalize in parallel with the downregulation of NKG2A in COVID-19 patients whose clinical status improves following treatment. These findings suggest that compromised antiviral response may contribute to the severity and pathogenesis of COVID-19. An immune response that is insufficient in suppressing viral replication and eliminating virus-infected cells can have systemic implications, including the development of clinically severe ARDS and disseminated intravascular coagulation, which can lead also to severe inflammatory response and may culminate in a cytokine storm (44).

Regulatory T cells (Tregs) play an important role in the suppression of excessive immune responses to pathogens, cancer cells and transplanted tissues, while also preventing the development, and controlling the progression of autoimmune and allergic diseases. The role of molecular mechanisms underlying the regulation of fork head box P3 (FOXP3) expressions and the antigen-specific response of Treg cells in COVID-19 remains ambiguous, and so further investigations are required to establish their clinical significance in this sense. On the other hand, a decrease in circulatory Treg cells (CD3+, CD4+, CD25+, CD127) has been observed aside from lymphopenia in COVID-19 patients (43-45). B and T lymphocytes are activated in response to SARS-CoV-2 infections, leading to the production of neutralizing antibodies. Initially, macrophages, acting as professional antigen-presenting cells, present the virus and its peptides to CD4-positive T helper cells via MHC class II molecules, while B cells can also become activated through the direct recognition of the SARS-CoV-2 nucleocapsid protein. The detection of primary virus-specific IgM antibodies is possible within the first week (4–8 days) of the onset of symptoms, and this initial IgM response is followed by the production of IgA and then IgG antibodies (10–18 days). The production of mucosal IgA antibodies plays a role in the prevention of re-infection with SARS-CoV-2, whereas IgA in the circulation may be effective in suppressing infection by contributing to the systemic neutralization of SARS-CoV-2 (46,47). The quality and extent of the IgG antibody response play a critical role in the neutralization of SARS-CoV-2. Given the limited time since the COVID-19 outbreak, the effective duration of the protective levels of virus-blocking antibodies is currently unknown. A study examining the data of previous SARS-CoV infections reported that the neutralizing IgG antibodies may be specific to the S protein of SARS-CoV-2, and that levels should be detectable in serum 2–3 weeks after infection (47). Neutralizing antibodies interact with various components of the immune system, including the complement cascade, phagocytes and NK cells. IgM antibodies are linked.
mainly to complement activation and the release of pro-
inflammatory cytokines, whereas IgG antibodies stimulate
an immune response through FcR-expressing cells (48). A
study examining the IgG and IgM antibodies that are
generated to counter the SARS-CoV-2 proteins found an
early and robust antibody response, characterized by high
titers, to be associated with the development of severe
disease, while a weak IgG response was found to be
associated with higher viral clearance. These findings
indicate an unforeseen relationship between robust anti-
body response and disease severity, and a relationship
between weak antibody response and viral clearance (49).
ACE2, which is suppressed and sheds to the environment
during the entry of the virus into the cells, affects pulmo-
nary permeability via RAS, leading to the development of
pulmonary edema, and can play a role in immune dys-
function through the promotion of excessive T-cell activa-
tion. Anti-S-IgG can increase systemic inflammatory re-
sponses by stimulating a variety of cell types via the ADE
phenomenon, leading to the development of viral sepsis
and multiorgan failure. The effects of COVID-19 on ves-
sels, however, is a component of the disease that has yet
to be fully understood, although existing data suggest that
COVID-19 may cause microangiopathy, independent of
thrombosis, and is not limited to the pulmonary system.
Immune dysfunction, systemic inflammatory response and
RAS dysfunction can all contribute to the development of
a cytokine storm, and COVID-19 can lead to death due
to ARDS and respiratory failure unless cytokine storm,
pulmonary edema and organ injuries can be well con-
trolled (50). A hypercoagulable state has been demon-
strated in many cases of severe pneumonia associated
with SARS-CoV-2 infection, and the increased mortality
associated with COVID-19 patients with coagulopathy
suggests that the coagulation cascade may play a signifi-
cant role in the pathogenesis of the disease (51). These
observations are supported by clinical findings indicating
that patients with D-dimer levels exceeding 3 μg/mL ben-
efit from heparin therapy, and that anticoagulant thera-
pies have been successful in reducing mortalities. A hy-
percoagulable state may have serious consequences,
including cerebrovascular events such as stroke and car-
diovascular events such as pulmonary thromboembolism,
as well as miscarriage, arterial and venous thrombosis
and osteonecrosis. Hypoxia resulting from respiratory
failure can trigger a signaling pathway related to the
hypoxia-inducible transcription factor (HIF) or may directly
increase blood viscosity, while pulmonary hyperinflamma-
tion can cause elevated TPO levels, leading to a predis-
position to thrombocytosis and thrombosis (52,53).
A cytokine storm can cause the overactivation of the co-
agulation cascade. Previous studies have suggested that
such viral infections as hepatitis C virus, human immuno-
deficiency virus (HIV), cytomegalovirus (CMV), varicella-
zoster virus, Epstein-Barr virus, adenovirus and parvovirus
B have the potential to increase the production of an-
tiphospholipid antibodies. Antiphospholipid syndrome
stimulated by the virus has also attracted attention in
COVID-19 patients, with studies conducted in this direc-
tion detecting anti-cardiolipin IgA, anti-β2-glycoprotein 1
IgA and IgG antibodies in the older patient group with
such underlying comorbidities as hypertension and diabe-
tes and a history of multiple cerebral infarctions, as well
as findings consistent with antiphospholipid syndrome.
That said, whether SARS-CoV-2 contributes significantly
to the production of such antibodies requires further study
(54). It has also been suggested that systemic and local
increases in angiotensin 2 levels observed after the inter-
nalization and destruction of ACE2 upon the entry of the
virus into the cell may facilitate the development of
thrombosis (10). The activation of a coagulation cascade,
triggered by the destruction of the endothelium, would
appear to be one of the primary factors contributing to
the development of a hypercoagulable state (9).
In conclusion, COVID-19 can stimulate the production of
severe pathologies in many tissues, aside from the de-
struction it causes in the respiratory tract and can result in
widespread systemic complications that may culminate in
multiorgan failure. While SARS-CoV-2 infection can be
asymptomatic, it can also lead to such serious conditions
as ARDS, respiratory failure, MAS, DIC, widespread
thromboembolism and even death. Although there are
still several unknown factors related to the virus that re-
quire further research for elucidation, studies to date have
done much to clarify the immunopathogenesis underlying
the emergence of this severe disease in humans. The
long-term consequences of the disease can be a point of
particular interest in future studies.

CONFLICTS OF INTEREST
None declared.

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## Author Index of Respiratory Case Reports

**Volume Eleven, 2023**

<table>
<thead>
<tr>
<th>Author Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdullah Kansu</td>
</tr>
<tr>
<td>Abdullah Sezer</td>
</tr>
<tr>
<td>Abdurrahman Şeniyigit</td>
</tr>
<tr>
<td>Adem Koyuncu</td>
</tr>
<tr>
<td>Ağbaba Ahmedov</td>
</tr>
<tr>
<td>Ahmed Shahin</td>
</tr>
<tr>
<td>Ahmet Ucvet</td>
</tr>
<tr>
<td>Akin Çinkooğlu</td>
</tr>
<tr>
<td>Ali İlal</td>
</tr>
<tr>
<td>Ali Riza Fatih Büyükkutlu</td>
</tr>
<tr>
<td>Alper Güzóbük</td>
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<tr>
<td>Arzu Mirici</td>
</tr>
<tr>
<td>Ashok P Arbat</td>
</tr>
<tr>
<td>Ataa Albaroudi</td>
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<tr>
<td>Atilla Can</td>
</tr>
<tr>
<td>Aydın Şanlı</td>
</tr>
<tr>
<td>Ayman Ahmed</td>
</tr>
<tr>
<td>Ayşegül Akgün</td>
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<tr>
<td>Ayşenur Ertaş</td>
</tr>
<tr>
<td>Bahar Ağaoğlu Şanlı</td>
</tr>
<tr>
<td>Barış Akçül</td>
</tr>
<tr>
<td>Berna Akınç Özürek</td>
</tr>
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<td>Berna Duman</td>
</tr>
<tr>
<td>Betül Kınık</td>
</tr>
<tr>
<td>Bilge Akgündüz</td>
</tr>
<tr>
<td>Bunyamin Sertogullarindan</td>
</tr>
<tr>
<td>Burcu Özdemir</td>
</tr>
<tr>
<td>Bushu Haruna</td>
</tr>
<tr>
<td>Cengiz Özdemir</td>
</tr>
<tr>
<td>Ceprail Şimşek</td>
</tr>
<tr>
<td>Ceyda Anar</td>
</tr>
<tr>
<td>Deniz Hırçın Cenger</td>
</tr>
<tr>
<td>Dilaver Taş</td>
</tr>
<tr>
<td>Dündar Özalp Karabay</td>
</tr>
<tr>
<td>Ebru Aykan</td>
</tr>
<tr>
<td>Ebru Çakır Edis</td>
</tr>
<tr>
<td>Ecem Naz Ertürk</td>
</tr>
<tr>
<td>Efsun Gonca Uğur Chousein</td>
</tr>
<tr>
<td>Emrah Korkutcu</td>
</tr>
<tr>
<td>Erol Başaranoğlu</td>
</tr>
<tr>
<td>Esma Sevil Akkurt</td>
</tr>
<tr>
<td>Esra Akkutuk İngel</td>
</tr>
<tr>
<td>Eylem Sercan Özgür</td>
</tr>
<tr>
<td>Fahad Al Amoudi</td>
</tr>
<tr>
<td>Fatih Tamer</td>
</tr>
<tr>
<td>Fatma Tokgoz Akyıl</td>
</tr>
<tr>
<td>Fazlı Yanık</td>
</tr>
<tr>
<td>Funda Demirağ</td>
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<tr>
<td>Gauri Gadge</td>
</tr>
<tr>
<td>Gülcen Sari</td>
</tr>
<tr>
<td>Güven Sadi Sunam</td>
</tr>
<tr>
<td>Hadice Selimoğlu Şen</td>
</tr>
<tr>
<td>Hakan İşlık</td>
</tr>
<tr>
<td>Hakan Polat</td>
</tr>
<tr>
<td>Halil Şen</td>
</tr>
<tr>
<td>Hande Güçlü</td>
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<tr>
<td>Hasan Oğuz Kapcibaşı</td>
</tr>
<tr>
<td>Hasan Yavuz</td>
</tr>
<tr>
<td>Hatice Kutlay Özceylan</td>
</tr>
<tr>
<td>Hema Yarman Ramarmuty</td>
</tr>
<tr>
<td>Hülya Abali</td>
</tr>
<tr>
<td>Hülya Şahin</td>
</tr>
<tr>
<td>Hüseyin Yıldırım</td>
</tr>
<tr>
<td>İlker Yılmaz</td>
</tr>
<tr>
<td>İsmail Sert</td>
</tr>
<tr>
<td>Kaan Kara</td>
</tr>
<tr>
<td>Kosuma Mohamed Nordin</td>
</tr>
<tr>
<td>Kenan Can Ceylan</td>
</tr>
<tr>
<td>Kerem Ensarioğlu</td>
</tr>
<tr>
<td>Khai Lip Ng</td>
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<tr>
<td>Kübra Karaca</td>
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<tr>
<td>Kunji Kannan Sivaraman Kannan</td>
</tr>
<tr>
<td>Lale Duman</td>
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<tr>
<td>Lalit Gupta</td>
</tr>
<tr>
<td>Levent Dalar</td>
</tr>
<tr>
<td>Levent Özdemir</td>
</tr>
<tr>
<td>Mehmet Emin Sezgin</td>
</tr>
<tr>
<td>Mehmet Orhan Ayıldız</td>
</tr>
<tr>
<td>Merve Erol Gülseven</td>
</tr>
<tr>
<td>Merve Fidan Ağış</td>
</tr>
<tr>
<td>Merve Şengül İnan</td>
</tr>
<tr>
<td>Mustafa Colak</td>
</tr>
<tr>
<td>Muzaffer Onur Turan</td>
</tr>
<tr>
<td>Nai Chien Huan</td>
</tr>
<tr>
<td>Nazan Beyhan</td>
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<tr>
<td>Nermin Zeman</td>
</tr>
<tr>
<td>Neslihan Fener</td>
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<tr>
<td>Nigar Alizade</td>
</tr>
<tr>
<td>Nurlana Mikayilova</td>
</tr>
<tr>
<td>Ömer Serdar Bekdemir</td>
</tr>
<tr>
<td>Osman Emre Ersin</td>
</tr>
<tr>
<td>Özgün Aran</td>
</tr>
<tr>
<td>Özkan Devran</td>
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<tr>
<td>Parimal Deshpande</td>
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<tr>
<td>Pınar Karabağlı</td>
</tr>
<tr>
<td>Pınar Mutlu</td>
</tr>
<tr>
<td>Rabia Hande Avcı</td>
</tr>
<tr>
<td>Şaban Uşsal</td>
</tr>
<tr>
<td>Savas Gegen</td>
</tr>
<tr>
<td>Seda Bingöl</td>
</tr>
<tr>
<td>Seda Koç Şahin</td>
</tr>
</tbody>
</table>
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