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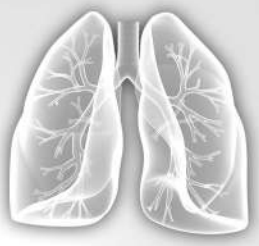

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RESPIRATORY CASE REPORTS

Treatment of Bronchopleural Fistula with Watanabe Spigots

Bronkoplevral Fistülün Watanabe Tıkaçları ile Tedavisi

Julia Fattore, David Ngo, Bruce French, Sultana Syeda, Jonathan Williamson

Abstract

Bronchopleural fistula (BPF) is a known complication of necrotizing pneumonia that is treated primarily with pleural drainage and antimicrobial therapy, while surgical treatments are generally reserved for those who do not respond to conservative management. Endobronchial spigots – a potentially less invasive approach to the treatment of bronchial occlusion – can be utilized when the culprit bronchi can be isolated and successfully blocked. We describe here the case of a 44-year-old female with a persistent right lower lobe bronchopleural fistula complicating necrotizing MRSa pneumonia, despite pleural drainage and directed antimicrobial therapy. The use of an endobronchial spigot for the bronchial occlusion of two bronchopulmonary segments led to an immediate reduction in the size of a large pleural cavity, contributing to significant symptomatic and biochemical improvement. The treatment can thus be considered an alternate cost-effective minimally invasive approach to the management of non-resolving bronchopleural fistula.

Keywords: *Bronchopleural fistula, bronchoscopy, interventional pulmonology, Watanabe spigot.*

Öz

Bronkoplevral fistül (BPF), nekrotizan pnömoninin bilinen bir komplikasyonudur. BPF için ilk tedavi, plevral drenaj ve antimikrobiyal tedaviyi içerir. Cerrahi tedaviler konservatif tedavinin başarısız olduğu durumlarda kullanılmaktadır. Daha az invazif bir alternatif tedavi seçeneği olan endobronşiyal tıkaçlar fistülün problematik bronş düzeyinde oklüzyonunu sağlamak amaçlı kullanılabilmektedir. Bu olgu sunumunda MRSa pnömonisine sekonder gelişen ve plevral drenaj ve antimikrobiyal tedaviye rağmen devam eden sağ alt lob bronkoplevral fistülü olan 44 yaşında bir kadını sunuyoruz. İki bronş segmenti spigot ile oklüde edilerek, hastada klinik ve laboratuvar düzelme ile birlikte plevral boşluğun boyutunda önemli ölçüde bir azalma sağlandı. Bu yöntem iyileşmeyen bronkofistüllerin tedavisi için alternatif, uygun maliyetli ve minimal invazif bir yaklaşım olabilir.

Anahtar Kelimeler: *Bronkoplevral fistül, bronkoskopi, girişimsel göğüs hastalıkları, Watanabe spigot.*

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A bronchopleural fistula (BPF) is an aberrant connection between the main stem, lobar or segmental bronchus and the pleural space resulting from an infectious, iatrogenic or structural etiology, and is associated with several risk factors (Table 1) (1-3). Depending on the etiology, presentation can range from subacute progressive symptoms of infection, including fever, purulent sputum, dyspnea and persistent air leak, to features of acute tension pneumothorax with respiratory failure (2).

Radiography may reveal intrapleural air, air-fluid levels, pneumothorax, pneumomediastinum and underlying pathologies such as pulmonary consolidation, as well as evidence of thoracic surgery and possibly the fistula itself (4,5). Bronchoscopy can allow the direct visualization of the defect, or the site of the fistula may be identified through other techniques, such as segmental balloon occlusion, demonstrating the cessation of a persistent air leak when a particular bronchus is blocked.

The first-line management of BPF when an infectious cause is suspected involves the insertion of an intercostal catheter (ICC) and antimicrobial therapy. Minimal suction, or a simple underwater seal drain, should be used to minimize air leakage through the BPF, as Pierson et al. (7) report that smaller air leaks provide a better prognosis. (6) Surgical repairs should be performed early (within 14 days) in patients with surgery-related BPF. Autologous blood patch pleurodesis and bronchoscopic therapies such as one-way valves, spigots, glues and other instilled agents are seeing increased use for the sealing of persistent BPFs.

CASE

A 44-year-old female with asplenia endured a prolonged 11-week hospitalization secondary to Influenza A complicated by methicillin-resistant Staphylococcus aureus (MRSA) necrotizing pneumonia and empyema, resulting in a bronchopleural fistula (BPF). The patient had a recent history of gastrointestinal spirochete infection and had lost 25 kg in weight over 6 months, a 10-pack/year smoking history, cannabis use via a water pipe and previous heavy alcohol consumption.

The patient had to date been treated with empiric antibiotics (moxifloxacin) in conjunction with antiviral oseltamivir, followed by directed therapy for MRSa (cultured from pleural fluid) in the form of a 10-week course of vancomycin. A right-sided intercostal catheter (ICC) was inserted for drainage of the empyema, with a resultant 9-day air leak that resolved spontaneously, and the drain was subsequently removed. A newly diagnosed left ventricular dysfunction was then detected on transthoracic echocardiography with a left ventricular ejection fraction of 18% (Simpson biplane). Notably, the patient had recorded normal ventricular function 1 month earlier.

The condition progressed to complicated pneumonia, despite the use of antibiotics, with a right-sided pleural effusion and empyema, and a subsequent large non-resolving pleural cavity with a bronchopleural fistula identified on thorax CT (Figure 1).

After 7 weeks of non-surgical management of the necrotizing pneumonia and BPF, including a prolonged course of antibiotics and ICC insertion, a large cavity persisted, and there had been minimal clinical improvement (Figure 1), and multidisciplinary team discussions led to the proposal of four treatment options for consideration:

1. Ongoing conservative therapy
2. Insertion of an ICC into the pleural cavity
3. Thoracic surgery with muscle flap repair of the BPF
4. Endoscopic options for the management of the BPF without an active air leak

Initially, a right-sided pulmonary resection with a large pectoralis major flap surgery was planned for the repair of the defect. Surgery was delayed, however, due initially to a mild nosocomial COVID-19 infection, and subsequently in consideration of the high anesthetic risk due to newly diagnosed heart failure, leading to the pursuit of the endoscopic option.

The bronchoscopic insertion of two Watanabe spigots for BPF closure under general anesthetic with muscle paralysis was performed 12 weeks after the initial presentation using a rigid 12mm tracheoscope. These included a 5mm Watanabe spigot (Figure 2) that was advanced into the right lower lobe to occlude the right posterobasal bronchus (RB10), sliced obliquely to facilitate its manipulation into the segment; and a 7mm spigot inserted into the posterolateral bronchus (RB9) (Figure 2). Intravenous vancomycin was continued for 5 days followed by trimethoprim/sulfamethoxazole for a further 2 weeks. The RB10 spigot spontaneously expectorated 72 hours after insertion, and so a larger (6mm) spigot was inserted (also obliquely sliced), with no further complications.

The patient attended a 6-week follow-up, during which a serial chest computed tomography (Figure 3) revealed a marked reduction in the size of the bronchopleural cavity. The symptoms showed a marked improvement, including a resolution of the cough, chest pain, fevers and night sweats, and the patient had gained 10 kg in weight and recorded an albumin increase from 23g/L (nadir during admission) to 40g/L at the time of review. Her functional status improved further, and she became able to consistently walk 12,000 steps per day. Repeat imaging at 6 months following the endobronchial Watanabe spigot insertion (Figure 3) revealed further improvements, with the resolution of the cavity defect, leaving only minor pleural thickening. The spigots were successfully removed 6 months after insertion.

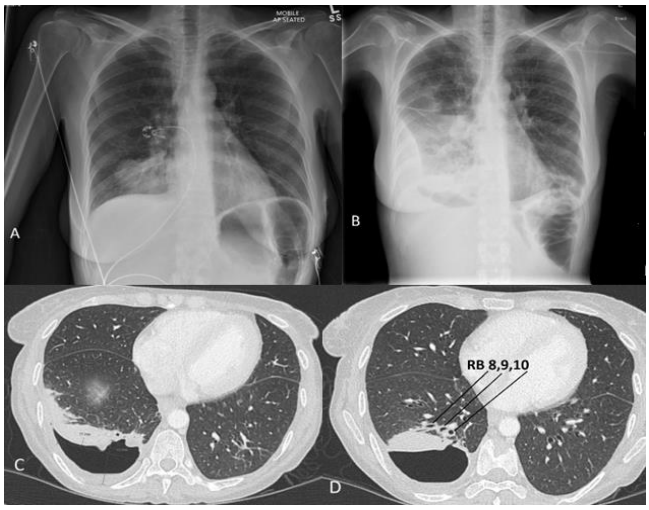

Figure 1: Progression of imaging demonstrating the development of the bronchopleural fistula. A: Initial chest radiograph on presentation. B: Progress radiograph <7 days following initial presentation. C: Computed tomography scan of the chest demonstrating the size of the defect. D: Computed tomography scan of the chest at the level of RB8/9/10

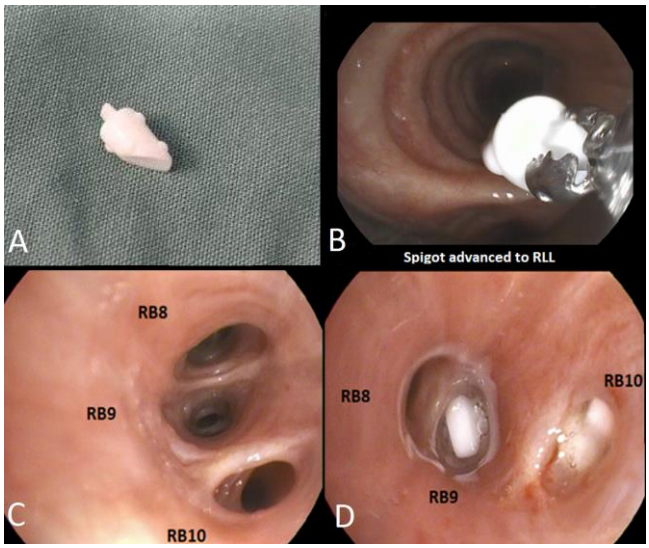

Figure 2: Watanabe Spigot insertion. A. Obliquely sliced Watanabe spigot. B. Spigot grasped by forceps endobronchially C. RB8,9,10 prior to spigot insertion. D. RB 8,9,10 following spigot insertion

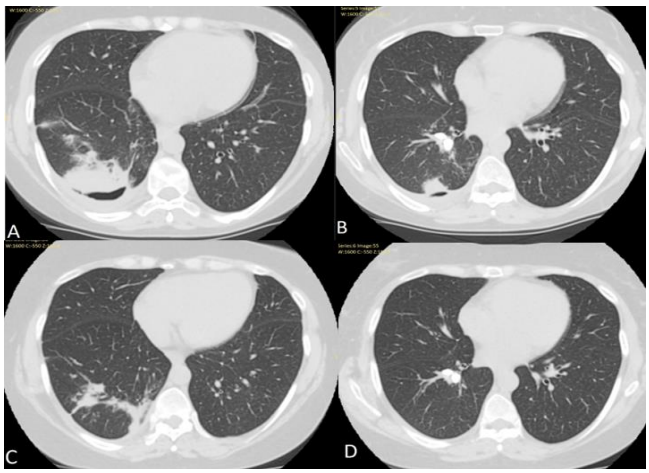

Figure 3: Follow-up imaging: A: Reduction in size of the BPF at 6 weeks (A) and 6 (C) months. B: Watanabe spigots in-situ (RB9 and RB10) at 6 weeks (B) and 6 (D) months

Figure 4: Variable sizes of the spigots available. Image sourced from Novatech online; https://www.novatech.fr/en/ewstm/ewstm/

DISCUSSION

To the best of our knowledge, this is the first registered use of Watanabe spigots for the treatment of a bronchopleural fistula (BPF) in Australia. These minimally invasive, endobronchially inserted spigots can be considered an effective treatment option for those who are unable to undergo standard thoracic surgery for the treatment of BPF. This case describes the clinical benefits and a reduction in the size of a large BPF cavity in a patient six months after insertion.

The use of Watanabe spigots was first described in 2001, after being developed in Japan by Yoichi Watanabe (8). The endobronchial Watanabe spigot was developed with three key features supporting successful bronchial occlusion, including (1) the spigot shape of the device and the studs on its surface that support the fixture of the spigot in place, (2) the presence of graspable segments at either end to facilitate placement and/or removal, and (3) the variety of sizes available to suit different bronchus sizes (Figure 4).

Watanabe investigated the use of bronchial blockades with spigots in 63 cases (9) for the treatment of intractable pneumothorax (in 40 cases), pyothorax with bronchial fistula (12 cases), pulmonary fistula (7 cases) and one case each for bronchial fistula, broncho-biliary fistula, broncho-esophageal fistula and broncho-gastric fistula. The technical success of the bronchial occlusion was reported in 97% of cases, with the total cessation of the air leakage reported in ~40% of the cases, and a marked reduction in ~38% of the cases. It was noted that it took 2–3 days for the air leakage to resolve in some patients following the insertion of the spigots. The average number of spigots inserted in each case was ~4. The complications that developed following spigot insertion included dyspnea (3.3%), pneumonia (3.3%) and fever (1.7%). The spigots were removed 2–4 weeks after being inserted, where possible.

Further cases treated with endobronchial Watanabe spigots were reviewed over a 13-year period in a study by Himeji et al. (10) in which all cases had intractable pneumothorax or pyothorax with a bronchial fistula, had failed appropriate drainage for 2 weeks and were unsuitable for thoracic surgery. Of the total 21 cases identified, 10 had intractable pneumothorax, seven had pyothorax with a bronchial fistula, and four had postoperative air

leakage. The successful treatment rates by primary disease were 80% for intractable pneumothorax, 100% for pyothorax with a bronchial fistula and 75% for postoperative air leakage. The limitations of the study include the concurrent use of additional therapies, which included washings, bronchial injection of fibrin glue and pleural adhesion. Similar to Watanabe, the air leak resolved immediately in some cases, but took up to 2 days in others following spigot insertion, and several spigots were often required (mean 6.5 per patient). The complications encountered included spigot migration and a single case of aspergillus infection 4.5 years following the insertion of the endobronchial Watanabe spigots, suggesting that the spigots should be considered for removal from clinically appropriate patients with a good long-term prognosis.

Alternative bronchoscopic treatment modalities for the management of BPF include adhesives, hemostatic agents, sclerosing agents, thermal occlusions, stents and one-way valves. There is a lack of quality data on these techniques, and there have been no randomized controlled trials to date. One-way endobronchial valves (EBVs) were first used for bronchial occlusion in the early 2000s. A one-way endobronchial valve can be inserted via a flexible bronchoscope, and can prevent air from entering the affected segmental bronchus, but allowing the egress of air and mucus. These features of the one-way valve have secured it a pivotal role in endobronchial lung volume reduction procedures. One retrospective study reviewed data from over a 3-year period on the use of EBV for the treatment of BPF in 26 patients (11). Prior to insertion, a Chartis assessment was performed to identify the culprit lobe/segment, and a total of 46 EBVs were inserted, with a median of two valves per procedure. The underlying causes of BPF included post-operative (50%), pneumothorax (15%) and the remaining infective precipitants; non-tuberous mycobacterial disease (19%) and tuberculosis (12%). Prior to valve insertion, 16 patients were fitted with a chest tube. The average duration of ICC drainage was 88 days (range 14–222) prior to EBV. Following valve insertion, the ICC remained in place for an average of 28.2 days (range 2–98). The authors concluded that EBVs succeeded in improving the rate of BPF resolution by 73.1%, while five of the 26 underwent additional procedures to assist with management at different time points, which were not specified. These included the use of silicone plugs, lauryl alcohol, argon laser plasma coagulation, ventricular septal and umbrella occlusion devices. Complications included bronchial bleeding requiring embolization following the removal of the EBV in one patient, while two further patients required thoracic surgical intervention. Previous studies have reported complications associated with EBVs, and a systematic review of EBV for the treatment of persistent air leaks revealed such complications as migration or expectoration of the valves, moderate oxygen desaturation, as well as infection of the related lung (12).

A prospective, randomized unblinded study was conducted investigating the success rates of treatments of persistent air leaks following secondary spontaneous pneumothorax using either selective bronchial autologous blood patches (ABP) with the addition of thrombin, silicone bronchial spigots (BS) or prolonged ICC (13). All of the 150 patients included in the study had persistent air leaks for 7 days following the insertion of an ICC, and had at least one of the following conditions: chronic obstructive pulmonary disease (n=65), pulmonary bullae (n=47), pneumonia (n=24), pulmonary cancer (n=20), bronchiectasis (n=11), asthma (n=9) and/or pulmonary fibrosis (n=6). The size of the pneumothorax was not statistically significant between the three groups; all patients were observed for up to 14 days following intervention. The resolution of the pneumothorax within 14 days was achieved most frequently in the silicon spigot group (84%), followed by the ABP (82%), and least frequently in the ICC alone group (60%). Comparatively, ABP and BS were significantly superior to chest tube drainage alone ($p = 0.008$), and were also statistically superior in terms of the duration of air leak cessation; lung re-expansion and hospital stay vs. chest tube drainage ($P<0.001$ for all). Fever, cough and chest pain complications were similar between the three groups. Temporary hemoptysis of <10mls was significantly more prevalent in the blood patch and silicon spigot groups, occurring in 100% of cases in both groups, compared to 12% in the ICC alone group. Spigot displacement occurred in 8% of cases. As endobronchial Watanabe spigots were not available from China, the silicon spigots used were individually trimmed to create dumbbell-shaped plugs from chin silicone implants.

Watanabe spigots differ significantly from EBVs. They are customizable, and can be cut to optimize airway fit. As outlined in our case, we were able to obliquely slice the spigot to ensure an optimal fit and thus successful insertion into the target bronchus. EBVs are not modifiable, however the insertion procedure is technically less complex. Cost-effectiveness is vastly different – EBVs are significantly more expensive per unit, but have the benefit of one-way drainage, allowing the clearance of secretions while potentially minimizing post-obstructive pneumonia.

CONCLUSION

We conclude that the endobronchial insertion of Watanabe spigots, a customizable option for the management of bronchopleural fistula, can result in the successful treatment of fistulae leading to clinical and radiological improvement, and so should be considered in

appropriate patients as a minimally invasive and cost-effective therapy.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - J.W., J.F., D.N., S.S., B.F.; Planning and Design - J.W., J.F., D.N., S.S., B.F.; Supervision - J.W., J.F., D.N., S.S., B.F.; Funding -.; Materials -; Data Collection and/or Processing -; Analysis and/or Interpretation -; Literature Review -; Writing -; Critical Review -

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Is Surgery a Must? A Case of Endobronchial Leiomyoma Removed via Rigid Bronchoscopy

Tek Seçenek Cerrahi mi? Rijid Bronkoskopi ile Çıkarılan Endobronşiyal Leiyomyom

Aytekin İdikut, Gamze Göktaş, Oğuz Karcıoğlu, Ziya Toros Selçuk

Abstract

Pulmonary leiomyoma is a very rare benign lesion that usually develops as a result of bronchial metastasis in women with a history of uterine leiomyoma or myomectomy. Although primary pulmonary leiomyomas are less common than the metastatic forms, they can be detected incidentally or when complaints such as cough and dyspnea are present. The structure of the lesion and its relationship with the bronchial mucosa play an important role in the determination of the treatment option. Endobronchial methods such as rigid bronchoscopy and electrocauterization may be superior to surgery as they are less invasive.

Keywords: *Leiomyoma, rigid bronchoscopy, tracheobronchial tumors.*

Öz

Akciğer leiyomyomu oldukça nadir görülen ve genellikle uterusta leiyomyom veya miyomektomi öyküsü olan kadınlarda bronşa metastaz sonucu görülen benign lezyonlardır. Primer pulmoner leiyomyom, metastatik olana göre daha nadir görülmek ile beraber, öksürük ve nefes darlığı gibi şikayetler olması üzerine ya da insidental olarak akciğer görüntülemelerinde saptanabilmektedir. Lezyonun yapısı ve bronş mukozası ile ilişkisi, tedavi seçeneğinin belirlenmesinde önemli bir rol oynamaktadır. Rijid bronkoskopi ile elektrokoterizasyon gibi endobronşiyal yöntemler kullanılması, daha az invazif olması nedeni ile cerrahiye üstünlük sağlayabilmektedir.

Anahtar Kelimeler: *Leiyomyom, rijid bronkoskopi, trakeobronşiyal tümörler.*

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Leiomyomas are benign tumors that occur in smooth muscle and that can arise in the airway in the absence of a history of uterine leiomyomas (1). First described by Frokel in 1909, pulmonary leiomyomas are benign tumors originating in the mesoderm (2,3). The optimum treatment of leiomyomas depends on the location of the lesion and the clinical symptoms present (4). In our case, an endobronchial tumor excised by rigid bronchoscopy was diagnosed as leiomyoma.

CASE

A 71-year-old non-smoking male patient with a history of hypertension, type 2 diabetes mellitus and kidney donation were admitted to the Department of Chest Diseases with dyspnea, an occasional dry cough and no other symptoms, and a physical examination revealed no remarkable findings. Pulmonary function test results revealed FEV1 2.6 L (93%), FVC 3.4 L (95%) and FEV1/FVC 76.4%. A 16x12 mm polypoid lobulated lesion occupying the entrance of the left lower lobe bronchi (Figure 1) was identified on thorax CT, while fiberoptic bronchoscopy revealed a polypoid, soft, non-vascular and mobile endobronchial lesion originating in the lateral wall of the end of the left main bronchus that was almost completely blocking the lumen (Video 1, Figure 2). PET-CT confirmed a very low FDG uptake (11x16 mm, SUVmax: 2,7), and no findings compatible with metastasis. Since the lesion had a narrow base and did not extend beyond the bronchi, it was electrocauterized via rigid bronchoscopy using a 30-watt cautery, during which the base of the lesion was captured with a snare and almost all of it was resected (Video 2). The presence of neoplastic cells that stained positively with desmin and H-Kaldesmon and negatively with ALK, CD34 and S100 confirmed the diagnosis of leiomyoma. A thorax CT conducted 1 month after the procedure revealed no lesion within the lumen. The patient was scheduled for follow-up of symptoms with a physical examination and imaging procedures every 6 months.

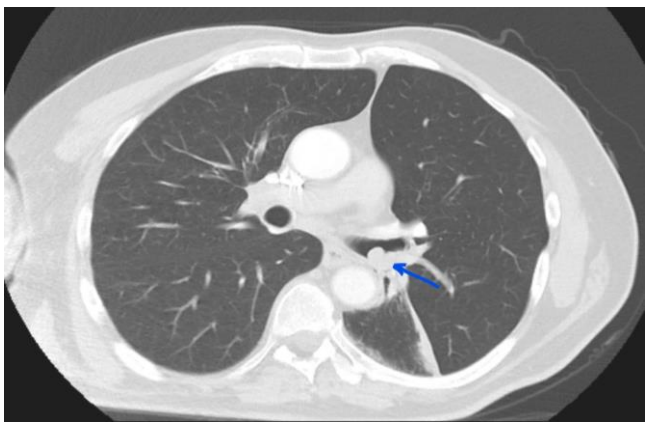

Figure 1: *Tumor in the distal left main bronchus on Thorax CT*

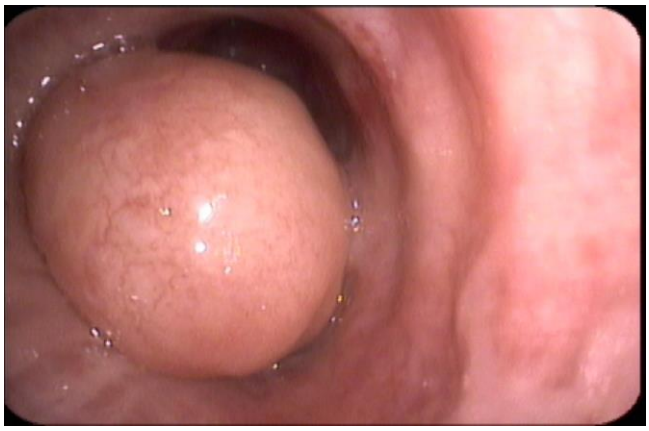

Figure 2: *Appearance of Endobronchial Leiomyoma in Fiberoptic Bronchoscopy*

DISCUSSION

Leiomyomas are benign tumors comprised of smooth muscle cells that are immunohistochemically stained by actin and desmin. They are usually well-circumscribed and larger than 1 cm (5,6) and may also affect the respiratory system in rare cases, originating from pulmonary parenchyma, as well as the airways (7). Leiomyomas occurring only in the lung are referred to as primary pulmonary leiomyomas (PPL), and as benign metastasizing leiomyoma (BML) if found in the lungs of women with a history of uterine leiomyoma (1,4). Although they can radiologically be confused with malignant lesions, they can be pathologically proven to be benign based on a low mitotic index and no evidence of invasion.

Pulmonary leiomyomas are referred to as endobronchial when they emerge in the proximal airways (up to the segmental level), and as parenchymal when they originate in peripheral airway tissue and spread to the rest of the lung (8). The most common symptoms of endobronchial leiomyoma are cough, wheezing, dyspnea, chest pain and recurrent respiratory infections, and may be misdiagnosed as asthma, reflux and post-infectious cough due to such non-specific symptoms. Their local effect can cause atelectasis by blocking the bronchus in their location and can lead to post-obstructive pneumonia (4), and some patients may also experience hemoptysis (4,9,10). In two-thirds of patients with PPL, the condition manifests as an endobronchial lesion in the proximal airways. There are as yet no published guidelines advising on the management of endobronchial leiomyomas. Resections may vary depending on the size and location and the relationship between the lesion's base and the airway wall. Rigid bronchoscopy is a well-established method that facilitates the resection of endobronchial tumors while protecting airway patency (4,11). In cases with narrow-based lesions, advanced bronchoscopic techniques such as electrocautery, laser and argon plasma coagulation may be used during rigid bronchoscopy to resect the tumor (12). Surgical resection is the general-

ly preferred technique for wide-based lesions, endobronchial lesions, tumors located in the distal bronchial tree and parenchymal tumors (4). Prognosis is, on the whole, favorable following the full excision of the lesion (4,10–12), although patients should be followed up at regular intervals to confirm that no recurrence has occurred (7).

CONCLUSION

PPL, as one rare tumor of the tracheobronchial tree, may present with symptoms such as cough, dyspnea, hemoptysis and chest pain resulting from the local effect on the tree, although they may also be detected incidentally on thorax imaging. The bronchoscopic appearance of the lesion should raise suspicion for diagnosis and guide the appropriate treatment option. The endobronchial approach stands out as the optimum approach to narrow-based lesions due to lower tissue loss than with surgery. PPL can be followed radiologically or undergo bronchoscopic or surgical resection, depending on the clinical manifestations. Assessment of treatment options should consider the impact.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - A.İ., G.G., O.K., Z.T.S.; Planning and Design - A.İ., O.K., G.G., Z.T.S.; Supervision - A.İ., O.K., Z.T.S., G.G.; Funding - G.G., A.İ. ; Materials - G.G., A.İ.; Data Collection and/or Processing - A.İ., G.G., O.K.; Analysis and/or Interpretation - A.İ., O.K.; Literature Review - A.İ., O.K., Z.T.S.; Writing - A.İ.; Critical Review - A.İ., O.K., G.G., Z.T.S.

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RESPIRATORY CASE REPORTS

Unilateral Hemotympanum after Bronchoscopy: A Case Report and Review of the Literature

Bronkoskopi Sonrası Tek Taraflı Hemotimpanum: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

Dorina Esendağlı, Polina Nezalzova

Abstract

Hemotympanum, referring to the presence of blood in the middle ear, is an unusual complication of bronchoscopy procedures usually performed on the airways for diagnostic or therapeutic purposes. We present here a report of a 45-year-old male who presented with fever, hemoptysis and back pain in whom a mass was detected in the right middle lobe of the lung. During a bronchoscopy procedure performed for diagnostic purposes, the patient had an excessive coughing episode that may have increased middle ear pressure, leading to hemotympanum only in the right ear, evidenced by bleeding from the ear canal. The patient had a past history of myringotomy, which may have contributed to this complication, about which little is known. We draw attention to this rare complication and propose additional risk factors for the underlying pathophysiology, and stress the need for better cough suppressor strategies to avoid occurrence.

Keywords: *Bronchoscopy, hemotympanum, complication, cough.*

Öz

Orta kulakta kan varlığını ifade eden hemotimpanum, genellikle hava yollarında tanısal veya terapötik müdahaleler için yapılan bronkoskopi prosedürünün çok nadir bir komplikasyonudur. Bu yazıda ateş, hemoptizi ve sırt ağrısı ile başvuran ve akciğerin sağ orta lobunda kitle saptanan 45 yaşında bir erkek hasta sunulmuştur. Tanı amaçlı yapılan bronkoskopi işlemi sırasında hastada orta kulak basıncını artırabilecek aşırı öksürük vardı ve ilginç bir şekilde kulak yolundan kanama ile fark edilen sadece sağ kulak hemotimpanumu meydana geldi. Geçmişinde miringotomi girişiminin öyküsü olması, hakkında çok fazla şey bilinmeyen bir komplikasyona katkıda bulunan başka bir risk faktörü olabilir. Bu nadir komplikasyona dikkat çekiyoruz ve altta yatan patofizyoloji için ek risk faktörleri olabileceği ve ortaya çıkmaması için daha iyi öksürük baskılayıcı stratejilere ihtiyaç olduğunu öne sürüyoruz.

Anahtar Kelimeler: *Bronkoskopi, hemotimpanum, komplikasyon, öksürük.*

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Bronchoscopy is a medical procedure for the examination of the airways in the lungs, allowing not only the visualization and inspection of the airways, but also the collection of samples of lung tissue or fluids, and the performance of various diagnostic and therapeutic procedures. Bronchoscopy is commonly used to diagnose and evaluate such conditions as lung infections, tumors, chronic cough and lung diseases, but can also be used for therapeutic reasons, such as for the removal of foreign objects or the relief of airway obstruction, and for the endobronchial staging of lung cancer (1,2). The procedure is typically performed under local anesthesia, while sedation may be used in some cases.

Hemotympanum refers to the presence of blood in the middle ear that usually occurs as a result of trauma or injury to the ear or head. It can be caused by various factors, such as a direct blow to the ear, skull fracture or barotrauma (sudden changes in air pressure) (3,4). The diagnosis of hemotympanum is based typically on a physical examination of the ear, and proper evaluation and management are essential for optimal recovery and the prevention of complications.

The most common complications of bronchoscopy are bronchospasm, laryngospasm, hypoxemia, elevated airway pressure, hemorrhage, aspiration and medication/comorbidities-related symptoms, but here we report an unusual complication of a procedure in a patient with unilateral hemotympanum in the right following diagnostic bronchoscopy.

CASE

A 45-year-old male presented to the emergency department with fever and hemoptysis, complaining of back pain that had become more prominent within the last week and difficulty in breathing. He had hypertension in his past medical history and a myringotomy during childhood, but no bleeding disorder or any usage of anticoagulation or antiplatelet drugs. A physical examination was unremarkable, while laboratory results revealed leukocytosis (11400 /μL) with neutrophil predominance (84 %) and a high CRP level of 58.8 mg/L (R: 0-5) with normal liver and kidney function and normal D-dimer levels. Thorax computed tomography (CT) revealed a spiculated mass in the right middle lobe and surrounding ground glass opacity, together with right paratracheal, pre-carinal and subcarinal lymphadenopathies. The patient was hospitalized with a plan for diagnostic bronchoscopy, but because of the resistant fever the COVID-19 PCR and the multiplex PCR for respiratory tract infections together with sputum, blood and urine culture were performed but no pathogen could be isolated. The patient was started on ceftriaxone and clarithromycin treatment, and a diagnostic bronchoscopy was planned to investigate the airways and for the acquisition of a biopsy. The patient was given midazolam intravenously and local lidocaine for sedation, but had a pronounced coughing episode during the procedure. The bronchoscopy showed no endobronchial lesion or bleeding site. Bronchoalveolar lavage (BAL) was obtained from the right middle lobe, but the procedure was interrupted due to the sudden appearance of bleeding from the right ear. The otorhinolaryngology was consulted immediately, and an investigation with an otoscope revealed a hematoma in the anterior of the right tympanic membrane with perforation (Figure 1). Local adrenaline was applied, and a second investigation after 2 hours revealed no active bleeding, and the left tympanic membrane was intact. Ciprofloxacin ear drops were recommended for 3 days and the hemotympanum was self-limited with no other complications. A positron emission tomography–computed tomography (PET-CT) showed that the lesion (75x44 mm) had the highest SUVmax of 13.5 and all lymphadenopathies described previously on thorax CT had a SUVmax in the range of 3.9–5.9. BAL cultures were negative, and after one week of empirical antibiotic administration the mass was found to have regressed on X-ray. Due to the complication experienced during the bronchoscopy, the patient was recommended for transthoracic needle biopsy (TTNB) rather than endobronchial ultrasound bronchoscopy (EBUS), which he denied and was discharged upon his request.

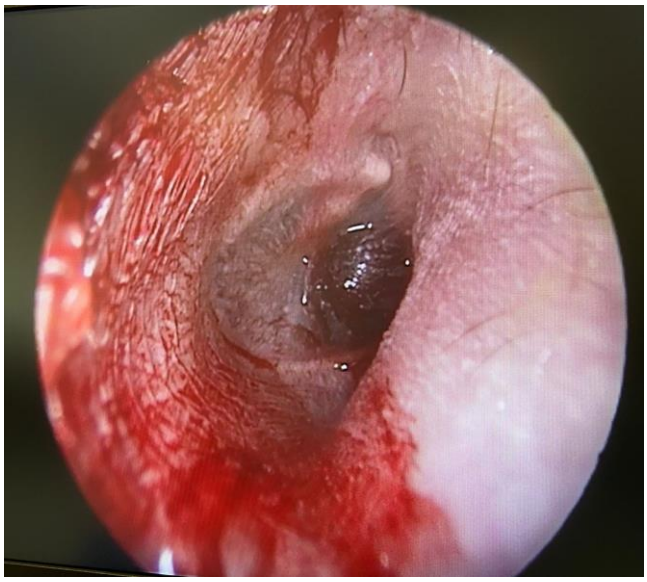

Figure 1: Otoscopic evaluation of the right tympanic membrane with a hemotympanum

Table 1: Common Characteristics of Reported Cases with Hemotympanum Related to Bronchoscopy

Reference	Year	No. of Patients	Age	Gender	Procedure	Sedation	Complication	Possible risk factors
Bhardwaj H et al.	2016	1	72	Male	Diagnostic Bronchoscopy	Moderate sedation and topical lidocaine	Bilateral HT and reversible hearing deficit, supportive care	Excessive Cough
Maqsood U et al.	2018	1	64	Male	EBUS-TBNA	Midazolam, alfentanil and topical lidocaine	Self-limited Bilateral HT	Aspirin and Cough
Hussain H et al.	2020	1	53	Female	EBUS and Biopsy	Propofol, midazolam and topical lidocaine	Right ear HT, supportive care	Cough

Abbreviations: EBUS: endobronchial ultrasound bronchoscopy; TBNA: transbronchial needle aspiration; HT: Hemotympanum

DISCUSSION

We report here a very unusual complication of a bronchoscopy procedure in which a male patient experienced right hemotympanum, referring to the presence of blood in the middle ear that accumulates and gives the tympanic membrane a bluish or black color, depending on the time of the bleeding (3). The condition may sometimes be accompanied by tympanic membrane perforation, thus resulting in bleeding observable from the outer ear canal. Previous studies in literature have reported hemotympanum occurring due to trauma, especially head trauma, epistaxis or chronic otitis media (4). The presence of any bleeding disorder or the usage of anticoagulant drugs may also play a role in spontaneously occurring forms of hemotympanum, while barotrauma is another risk factor for hemotympanum. Cases have been reported in scuba divers and following air travel, although sneezing and excessive cough may also increase middle ear pressure, and thus may also be a predisposing factor for hemotympanum (5). Bronchoscopy procedures are used mainly for the visualization of the airways, and to sample pulmonary lesions within the bronchial system. While the procedure is usually safe, many complications have been reported that are mainly classified as either mechanical or systemic. Mechanical complications are related to airway manipulations or bleeding, whereas systemic complications arise from the procedure itself, medication administration (sedation) or patient comorbidities (1,2). The most common complications of bronchoscopy are bronchospasm, laryngospasm, hypoxemia, elevated airway or intracranial pressure, hemorrhage, aspiration, arrhythmia and pulmonary insufficiency, although death may occur in less than 0.1% of cases (1,2). A review of literature revealed only three cases of hemotympanum developing as a complication of bronchoscopy (Table 1) (5–7). Due to the rarity of the condition there is insufficient knowledge to support a discussion of the underlying pathophysiology, and so literature would benefit from further case reports contributing to the identification of the risk factors and the development of avoidance measures.

The first reported case, published in 2016, described a male with bilateral hemotympanum during a diagnostic bronchoscopy without any sampling and without any risk factor despite excessive coughing (5). The second case was published in 2018, and described a male on aspirin in whom bilateral hemotympanum developed during EBUS with transbronchial needle aspiration (TBNA), with cough identified as the main risk factor for the complication (6). The most recent case was reported in 2020 by Hussain H et al. who described a female patient who developed right ear hemotympanum after EBUS and the taking of a biopsy (7). Barotrauma in the middle ear due primarily to excessive cough was described as responsible in all three cases. Our case had undergone a myringotomy intervention during childhood, which may have been an additional risk factor, together with the pronounced cough during bronchoscopy. Coughing is encountered quite often during diagnostic and interventional bronchoscopy procedures, but not all the patients with a persistent cough have a history of hemotympanum, and so additional risk factors most probably exist that predispose a certain specific group of patients to this complication, such as aspirin usage, for example, as in one the above cases. Fortunately, all the cases had self-limiting bleeding and reversible side effects that were cured with supportive care (5–7). Observation and conservative management may be sufficient in most cases, while more severe cases may require drainage of the blood or surgical intervention.

Another important issue to be discussed is the amount and type of sedation that should be used to suppress the cough in such patients. All the cases had been moderately sedated with midazolam, and some were given propofol or alfentanil together with topical lidocaine (6,7). While these drugs are sufficient for most patients, they might not be enough to suppress cough in others, and so new strategies for cough suppression should be developed to avoid cough-related complications.

CONCLUSION

This case report draws attention to a very rare complication in the form of hemotympanum occurring during a bronchoscopy procedure. While self-limited and reverse side effects have been reported, there is still a lack of data regarding the pathophysiology and risk factors associated with the condition, and the measures that can be taken to prevent such complications.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - D.E., P.N.; Planning and Design - D.E., P.N.; Supervision - D.E., P.N.; Funding -; Materials - D.E., P.N.; Data Collection and/or Processing - D.E., P.N.; Analysis and/or Interpretation - D.E.; Literature Review - D.E., P.N.; Writing - D.E., P.N.; Critical Review - D.E.

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Clustering in a Small Business. Diagnosis of Pneumoconiosis: Heads or Tails?

Küçük Ölçekli bir İşletmede Kümelenme. Pnömokonyoz Tanısı: Yazı mı Tura mı?

Merve Demirci Atik

Abstract

Occupational diseases and accidents are lagging indicators of occupational health and safety (OHS), and clustering in certain areas suggests that OHS policies have failed in this regard. A cluster of pneumoconiosis cases employed at a refractory concrete factory was noted among those admitted to an occupational disease clinic, with 12 of the total 22 blue-collar workers (54.5%) employed by the small-scale enterprise (SSE) being followed up with a diagnosis of pneumoconiosis. The first case in the SSE was detected in 2017 and regular health audits were initiated following workplace inspections. The median exposure time was 8.5 years, with a range of 4–22 years. During follow-up, one-third of the cases progressed (median 3.5 years). To summarize, the probability of a blue-collar worker in the SSE developing pneumoconiosis is greater than the chance of a coin landing on either heads or tails when they first start their job. Workers in developing countries in particular are more prone to problems related to OHS, particularly in SSEs.

Keywords: *Clustering, occupational disease, occupational health and safety, pneumoconiosis, small scale enterprise.*

Öz

Meslek hastalıkları ve iş kazaları, iş sağlığı ve güvenliğinin (İSG) ardıl göstergeleridir. Belli alanlardaki kümelenmeler, İSG politikalarının bu noktalarda başarısız olduğunu göstermektedir. Meslek hastalıkları polikliniğine başvuran pnömokonyoz olguları arasında aynı refrakter beton fabrikasında bir kümelenme tespit edildi. Bu küçük ölçekli işletmede (KÖİ) çalışan toplam 22 mavi yakalı çalışanın 12'si (%54,5) pnömokonyoz tanısıyla takip ediliyordu. Bu KÖİ'de ilk olgu 2017 yılında tespit edilmiş ve iş yeri denetimlerinin ardından düzenli sağlık gözetimi başlatılmıştı. Maruz kalım süresi 4-22 yıl arasında değişmekle birlikte ortalama 8,5 yıldı. İzlemde (ortalama 3,5 yıl) her 3 olgudan 2'sinde progresyon saptandı. Özetle, bu işletmedeki mavi yakalı çalışanların pnömokonyoz olma olasılığı, işe başladıkları gün havaya attıkları paranın yazı ya da tura gelme olasılığından daha yüksekti. Özellikle gelişmekte olan ülkelerde KÖİ'lerde İSG açısından daha ciddi sorunlar yaşanmaktadır.

Anahtar Kelimeler: *Kümelenme, meslek hastalığı, iş sağlığı ve güvenliği, pnömokonyoz, küçük işletme.*

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The majority of the global workforce is employed in small-scale enterprises (SSEs), being companies with fewer than 50 employees. Such enterprises employ an average of 40% of the workforce in industrialized OECD (Organization for Economic Cooperation and Development) countries, and 60% in developing countries (1). For various reasons, however, these businesses often face significant challenges in the assurance of occupational health. Although the hazards present in smaller workplace environments are similar to those in larger businesses, the risk of exposure is often significantly higher in SSEs (1,2). Various studies have reported a greater frequency of occupational disease in SSEs (3). Occupational diseases serve as lagging indicators of occupational health and safety (OHS), highlighting a need for comprehensive retrospective analyses. This case series presented here examines the clustering of pneumoconiosis cases within a single SSE.

CASES

This report delineates the characteristics of 12 pneumoconiosis cases, all of whom were employed in the same refractory concrete factory. After obtaining informed consent from the patients for their inclusion in the study, their current and past working conditions were meticulously detailed during their admission, and an in-depth retrospective review of their clinical follow-ups was carried out based on hospital records. Approval for the study was obtained from the Necmettin Erbakan University Non-Pharmaceutical and Non-Medical-Device Research Ethics Committee (No:2023/4406). Chest X-ray assessments were conducted according to the guidelines published by the International Labor Organization (ILO) International Classification of Radiographs of Pneumoconiosis (2022), by a certified specialist. High-resolution computed tomography (HRCT) images of the cases were retrieved from the hospital's radiology archive, and progression was categorized based on the reports of experienced radiologists. Pulmonary function tests (PFT) and carbon monoxide diffusion capacity (DLCO) measurements were performed in our facility using a ZAN 100 spirometer device (Oberthulba, Germany) and following the current guidelines (4). Descriptive statistics of the cases were presented, ratios were compared with Pearson's Chi-square and Fisher's exact tests, and a Mann-Whitney-U test was used to compare the means of the two groups. A significance level of $p<0.05$ was defined.

Workplace Features

According to patient statements, 34 people are employed by the SSE, including 12 administrative staff, eight maintenance and repair workers (MRWs), and 14 manufacturing workers (MWs). The company makes use of such raw materials as quartz, magnesite and bauxite in the production of heat-resistant bricks and concrete, known also as fire bricks. The production facility is equipped with crushers, sieves, mills and filling-packaging machinery, and all associated tasks are performed by the MWs on a rotational basis. Dust control was not managed through wet work. The MWs spend the entire working day (8 hours/day) in the production area, while the MRWs spend only a portion of the working day (4–5 hours/day) in this area while engaged in repair and assembly work, while the rest of the day (3–4 hours/day) is spent in the mechanical maintenance workshop performing metal cutting, assembly and welding works. It was noted that in 2017, after the identification of the first case of silicosis in the workplace (case no.12), the health monitoring of all employees was initiated, and OHS services were procured from a private joint health and safety center, and 11 further cases of pneumoconiosis were subsequently identified. It was understood that following the workplace inspections, local exhaust ventilation systems were established at several points in the facility and dust masks were provided to the employees.

Of the 22 blue-collar workers in the plant, 12 were diagnosed with pneumoconiosis and were under follow-up. The mean age of the pneumoconiosis cases was 46.5 (±6.69), the mean age at diagnosis was 42.75 (±7.03), and the median exposure time (period from employment to diagnosis) was 8.5 (4–22) years. One-quarter of the cases had no respiratory complaints, and breathing sounds were normal on physical examination in two-thirds of the cases. The affected workers included eight MWs and four MRWs (Table 1).

During the median follow-up period of 3.5 years (2–6) post-diagnosis, radiological progression was observed in eight (66.7%) of the cases, seven of whom were MWs. Large opacities were observed in three cases and Ax opacity in one case. Follow-up HRCT images of some of the pneumoconiosis cases are presented in Figure 1. A file containing HRCT imaging of all cases over time is presented as supplementary material (Figure 3).

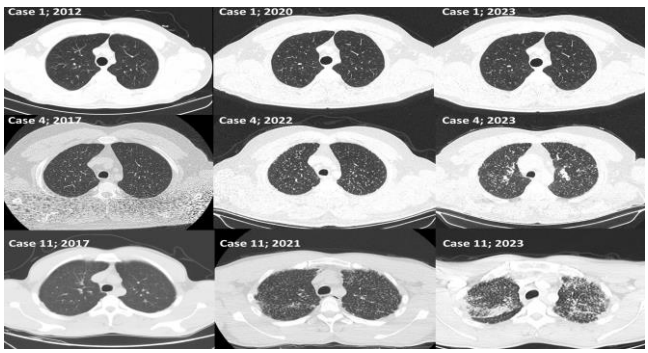

Figure 1: *HRCT images of some pneumoconiosis cases in the follow-up*

Table 1: Characteristics of the pneumoconiosis cases

Case no	Age, sex	Comorbidite	Smoking history	Task	Dust/smoke exposure at previous job history	Exposure time before diagnosis	Respiratory symptom	Physical examination	Any change in job/task status
1	44, male	Yes, Hypertension	Ex-smoker, 20 pack years	MW	Never	4 years	Exertional dyspnea	Rhonchi	Had changed as gardener, 2014
2	58, male	Yes, Hypertension	No	MW	Never	11 years	None	Normal	Had changed as administrative staff, 1994
4	48, male	No	Ex-smoker, 14 pack years	MRW	Yes; 19 years, welding fume	12 years	Exertional dyspnea	Normal	No change
5	46, male	Yes, lumbar discopathy	Ex-smoker, 1 pack years	MW	Yes; 6 years, brick manufacturing	8 years	Exertional dyspnea	Normal	No change
6	49, male	No	Ex-smoker, 20 pack years	MRW	Yes; 12 years, welding fume	12 years	Exertional dyspnea	Normal	No change
7	52, male	No	Smoker, 15 pack years	MRW	Yes; 5 years, welding fume	10 years	Exertional dyspnea and wheeze	Normal	No change
8	39, male	Yes, sacroiliitis	Smoker, 20 pack years	MW	Never	4 years	None	Normal	No change
9	33, male	Yes, celiac	No	MW	Never	6 years	Exertional dyspnea	Normal	No change
10	51, male	No	Smoker, 28 pack years	MRW	Never	22 years	None	Normal	No change
11	50, male	Yes, Hypertension and diabetes	Ex-smoker, 20 pack years	MW	Yes; 20 years, brick manufacturing	8 years	Exertional dyspnea	Rhonchi	Retired, 2023
12	40, male	Yes, Asthma	Ex-smoker, 15 pack years	MW	Never	9 years	Exertional dyspnea, wheeze and cough	Rhonchi	No change

Note: Age, smoking exposure, symptoms and physical examination findings are the data of current (2023) applications.
MW: manufacturing worker; MRW: maintenance and repair worker

Table 2: Radiologic and functional examinations of the pneumoconiosis cases

Case no	Follow-up time after diagnosis	Radiological findings			Current pulmonary functional evaluation				
		ILO radiology at diagnosis	ILO radiology currently	HRCT follow-up findings	FEV1 % predicted	FVC % predicted	FEV1/FVC ratio	DLCO	DLCO/VA
1	5 years	p/p 1/0	p/p 1/2	Progression	53	60	73.2	68	121
2	4 years	p/p 1/2	p/p 1/2	Stable	88	82	85.6	98	128
4	2 years	p/p 1/1	p/p 1/1	Stable	109	103	85.0	113	108
5	6 years	q/p 2/2	r/q 3/2, B	Progression	63	74	69.5	85	128
6	3 years	p/s 1/0	p/q 2/1	Progression	94	100	77.4	-	-
7	2 years	p/s 1/2	p/p 1/2	Stable	83	91	73.2	124	127
8	5 years	p/s 1/0	p/p 2/1	Progression	104	101	85.6	86	112
9	3 years	p/s 1/0	q/q 2/3, Ax	Progression	100	103	81.7	128	109
10	2 years	p/p 0/1	p/p 0/1	Stable	85	100	69.6	-	-
11	4 years	p/q 1/1	q/q 3/2	Progression	87	89	80.1	-	-
12	3 years	p/q 1/1	q/q 3/3, B	Progression	67	86	65.4	-	-

FEV1: Forced expiratory volume in the first second. FVC: Forced vital capacity; DLCO: Diffusing capacity of the lung for carbon monoxide (% of predicted); DLCO/VA: Diffusing capacity per litre alveolar volume (% of predicted)

After the cessation of exposure of three MWs, two (66.7%) showed progression, while the other five MWs (100%) whose exposure continued demonstrated progression (p=0.37). Case 10 was included in the group with continued exposure as he had just retired. Conversely, all MRWs had continued exposure, and progression was observed in one (25%) (Table 2). The exposure time was significantly shorter in MWs than in MRWs (p=0.010, means 7.25 years ±2.43 and 14 years ±5.42, respectively) (Table 3).

Table 3: Comparison of the features of pneumoconiosis cases according to tasks

	Total N=12 (100 %)	MWs N=8 (66.7 %)	MRWs N=4 (33.3 %)	p value
HRCT follow-up findings				
• Progression	8 (66.7)	7 (87.5)	1 (25.0)	0.067
• Stable	4 (33.3)	1 (12.5)	3 (75.0)	
ILO opacity at diagnosis				
• < 1.5 mm (p or s)	8 (66.7)	4 (50.0)	4 (100.0)	0.208
• > 1.5 mm (q,r,t,u)	4 (33.3)	4 (50.0)	0 (0.0)	
ILO profusion at diagnosis				
• Category 1	10 (83.3)	6 (75.0)	4 (100.0)	0.325
• Category 2	1 (8.3)	1 (12.5)	0 (0.0)	
• Category 3	1 (8.3)	1 (12.5)	0 (0.0)	
ILO opacity currently				
• < 1.5 mm (p or s)	6 (50.0)	3 (37.5)	3 (75.0)	0.545
• > 1.5 mm (q,r,t,u)	6 (50.0)	5 (62.5)	1 (25.0)	
ILO large opacity currently				
• No	9 (75.0)	5 (62.5)	4 (100.0)	0.491
• Yes	3 (25.0)	3 (37.5)	0 (0.0)	
ILO profusion currently				
• Category 1	5 (41.7)	2 (25.0)	3 (75.0)	0.070
• Category 2	3 (25.0)	2 (25.0)	1 (25.0)	
• Category 3	4 (33.3)	4 (50.0)	0 (0.0)	
Age of diagnosis of pneumoconiosis¥	44 (30-54)	39.5 (30-54)	47.5 (46-50)	0.060
Exposure time before diagnosis (years)¥	8.50 (4-22)	8 (4-11)	12 (10-22)	0.010
Cigarette exposure (pack/year)¥	14.5 (0-28)	7.5 (0-20)	17.5 (14-28)	0.141
Pulmonary functional assessment¥				
• FEV1 % [a]	87 (53-109)	87 (53- 104)	89.5 (83-109)	0.450
• FVC % [a]	91 (60-103)	86 (60-103)	100 (91-103)	0.154
• FEV1/FVC[a]	77.4 (65.4- 85.6)	80.1 (65.4-85.6)	75.3 (69.6-85)	0.776
• DLCO % [b]	98 (68-128)	86 (68-128)	118.5 (113-124)	0.245
• DLCO/VA % [b]	121 (108-128)	121 (109-128)	117.5 (108-127)	0.434

¥The median and min-max values of the variables are presented in the table

[a] Values of 11 cases with current PFT are included

[b] Values of 7 cases with current diffusion test are included

***MWs:** manufacturing workers; **MRWs:** maintenance and repair workers; **FEV1:** Forced expiratory volume in the first second; **FVC:** Forced vital capacity. **DLCO:** Diffusing capacity of the lung for carbon monoxide; **DLCO/VA:** Diffusing capacity per litre alveolar volume*

All cases applied to the social insurance institution, and four (case no 4,8,10,11) were granted permanent partial disability compensation. Case 12 had retired after being granted permanent total disability, and had recurrent hospitalizations with a diagnosis of pneumothorax, and is currently under follow-up at the lung transplant center to which he was referred. Long-term chest X-ray images of Case 12 are presented in Figure 2.

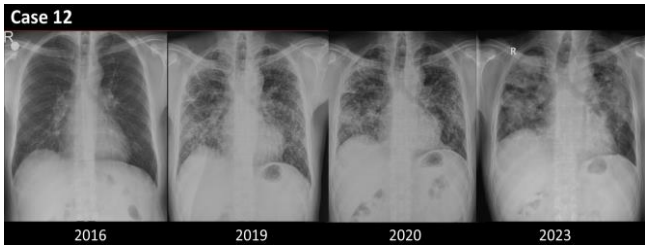

***Figure 2:** Chest x-ray images of Case 12. Rapid progression is observed over approximately seven years*

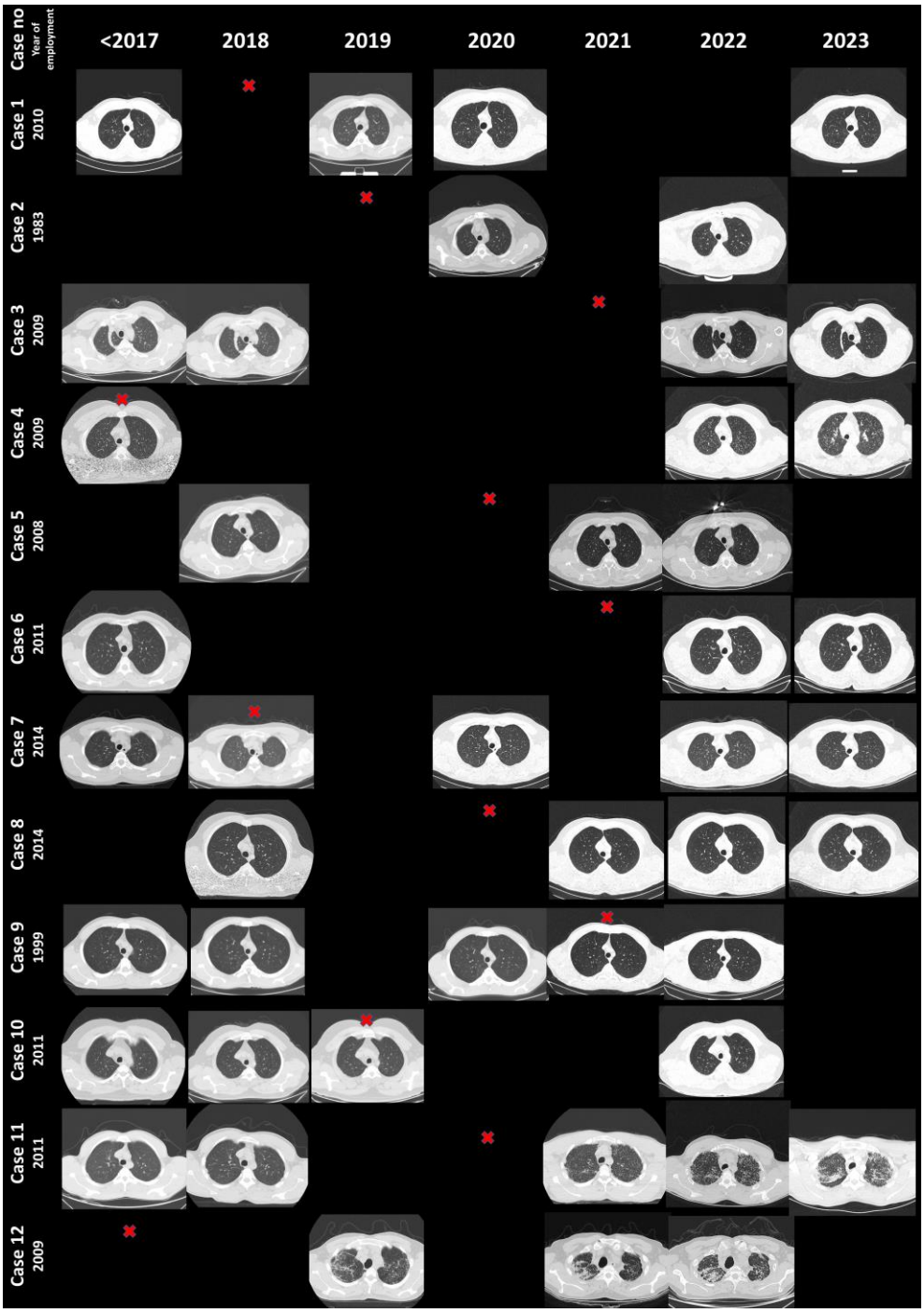

Figure 3: HRCT images of pneumoconiosis cases in the follow-up x = Years of the diagnosis. Note: Due to the problem in the archive system, some external center radiology examinations could not be reached

DISCUSSION

This case series tells a real-life story of how the health of workers in a small business could not be protected, with more than half of the blue-collar workers in this small business being diagnosed with pneumoconiosis. The maintenance of OHS in SSEs can be challenging due to the limited human, financial and technological resources (1,2), and the need to enhance the knowledge and skills of employers, who play a key role in OHS, has been frequently emphasized. In a qualitative study, an inspector was reported to state that owner-managers in SSEs have only limited awareness of the risks associated with their business, citing the frequently used phrase, "As long as nothing happens, it's all good" (5).

The risk of pneumoconiosis in the refractory brick production sector is well known, for example, Vien et al. reported a prevalence of 10% in a medium-sized enterprise (6). Silicosis can rapidly develop due to the increased oxidative stress, and pro-inflammatory and pro-fibrotic response associated especially with the inhalation of high-density freshly crushed silica (7). Gravimetric dust measurements have shown that respirable dust concentrations

increase intensively especially in such processes as quartz crushing, chopping/mixing and weighing/filling operations (6,8). The exposure intensities of the MWs were similar in the present study, as all these processes took place in the same production area, and all tasks were done on a rotational basis. It was observed that pneumoconiosis developed and progressed much faster in MWs than in MRWs, who spent only half of the working day in the dusty production department. It clarifies the dose-response relationship. Undesirable consequences can develop more rapidly with increased frequency or intensity of exposure (6).

The other substances to which MRWs are exposed, such as metal dust and welding fumes, should not be overlooked in this generalization. In welder's pneumoconiosis, which has a reported prevalence of 0.8–8% (9,10), no progressive massive fibrosis develops, and regression is experienced by almost one-third of the cases after the cessation of exposure (10,11). That said, the MRWs in the present study were also exposed to silica, which has proven fibrogenic effects (7), in addition to welding fumes, and their exposure did not cease, leading to progression in one of the four MRWs, while the findings were stable in the other three.

In the follow-up of the MWs, progression was observed in all five (100%) of the cases with continued exposure, and in two of the three (66.7%) whose exposure was terminated. Similarly, León-Jiménez et al. (12) reported progression in 56% of 106 silicosis patients at a mean follow-up of 4.01±2.1 years after exposure cessation, while Kimura et al. (13) described progression in 207 retired coal miners with pneumoconiosis, specifically 62% in the first decade and 29% in the second decade.

Most cases in the study recorded normal physical examination and PFT results, with functional abnormalities observed in four cases (cases 9 and 11=obstructive; case 1=restrictive; case 4=mixed). Early-stage pneumoconiosis may present with no PFT abnormalities, while obstructive, restrictive or mixed abnormalities may develop as the disease progresses. Smoking history, a common confounder, is also significant alongside workplace exposure (14).

The prevention and early exposure termination is crucial due to the lack of effective treatment for pneumoconiosis (13). Despite the launch of health audits in this SSE in 2017, exposure could not be prevented, and employees continued to work under almost the same conditions, even after new cases of pneumoconiosis were identified and the significant progression of previous cases. Health audits without preventative actions are meaningless, and the owner's actions, such as the provision of dust masks and local ventilation, were insufficient for effective dust control. The environmental monitoring of workplaces is a dynamic process requiring ongoing risk assessments and improvements (15). Apart from two retired employees, none of the workers have resigned from the company.

The lack of national policies regarding employment protection and occupational rehabilitation may have led workers diagnosed with pneumoconiosis to continue working as an alternative to unemployment.

The present study reports on the follow-up of a pneumoconiosis cluster with similar exposures due to their employment in the same workplace. Although statistical significance could not be determined between the task groups other than in the exposure time due to the limited number of cases, differences in the subgroups were well-defined. The exposure times in this workplace were the only ones included in the analyses, as five cases with defined dust/fume exposure in previous jobs lacked pre-employment medical records, which is a limitation that should be considered.

CONCLUSION

Difficulties are experienced related to the monitoring of health in SSEs. Further studies of this subject are required, especially in developing countries, due to their potential contribution to the development of primary and secondary prevention and rehabilitation policies.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - M.D.A.; Planning and Design - M.D.A.; Supervision - M.D.A.; Funding - M.D.A.; Materials - M.D.A.; Data Collection and/or Processing - M.D.A.; Analysis and/or Interpretation - M.D.A.; Literature Review - M.D.A.; Writing - M.D.A.; Critical Review - M.D.A.

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Pulmonary Mucormycosis Mimicking a Lung Tumor in a Patient with Advanced Retroviral Disease

İleri Retroviral Hastasında Akciğer Tümörünü Taklit Eden Pulmoner Mukormikozis

Shuk Ching Chai[1], Khai Lip Ng[1], Nai Chien Huan[2], Wee Fu Gan[1], Diyana Abdullah[3], Kasuma Mohamed Nordin[1]

Abstract

Pulmonary mucormycosis is a relatively rare disease that may become more common with the increasing number of immunocompromised patients. The male case presented here, with advanced retroviral disease, presented with persistent cough and acute respiratory distress. A chest radiograph and computed tomography (CT) of the thorax revealed a right apical pneumothorax and a mass in the right main bronchus. Flexible bronchoscopy revealed an endobronchial mass, occluded entirely the right main bronchus. Histopathological examinations of multiple biopsies revealed fungal bodies suggestive of mucormycosis. The patient was treated with Posaconazole, leading to a complete clinical and radiological cure.

Keywords: *Pulmonary mucormycosis, lung mass, retroviral disease, bronchoscop.*

Öz

Pulmoner mukormikozis nadir bir hastalık olmakla birlikte immunsuprese hasta sayısının artması ile birlikte görülme sıklığı beklenilenden fazla olabilmektedir. Bu olgu sunumunda, öksürük ve nefes darlığı şikayetleri ile acil servise başvuran akut solunum yetmezliği nedeniyle entübe edilen ilerlemiş retroviral hastalığı olan bir erkek olgu sunuldu. Toraks bilgisayarlı tomografisinde sağ ana bronşta total oklüzyona yol açan endobronşial lezyon ile birlikte sağ apikal pnömotoraks mevcuttu. Fleksibl bronkoskopide tomografi ile uyumlu olarak sağ ana bronşu tamamen tıkayan endobronşiyal lezyon izlendi. Bronkoskopik biyopsi histopatolojik incelemesinde mukormikozis ile uyumlu mantar cisimcikleri görüldü. Posakonazol ile tedavi edilen hastada klinik ve radyolojik olarak tam iyileşme görüldü.

Anahtar Kelimeler: *Pulmoner mukormikozis, akciğerde kitle, retroviral hastalık, bronkoskopi.*

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Mucormycosis is a rare but potentially life-threatening fungal infection that most frequently affects immunocompromised patients. Infection can progress rapidly, leading to substantial morbidity and mortality owing to the angioinvasive properties of the condition. Rhino-orbital-cerebral sites are the most common targets of mucormycosis-related infections, followed by the pulmonary system. The clinical symptoms, physical signs and radiological findings of pulmonary mucormycosis are often non-specific, and can closely mimic other respiratory conditions, including endobronchial malignancies to pulmonary infections and/or airway diseases. As a result, distinguishing pulmonary mucormycosis from other competing differentials can be challenging, and often requires a high index of clinical suspicion. We present here the case of a middle-aged male with advanced retroviral disease who was referred for a tumor-like endobronchial lesion in the right lung.

CASE

A 56-year-old male with a history of chronic obstructive pulmonary disease and advanced retroviral disease (CD4+ T-cell count of 53 cells/mm^3 and viral load of 11,615 copies/mL) presented with a 1-week history of worsening shortness of breath and productive cough. The patient, who reported no fever, night sweats, chest pain and hemoptysis, was in acute respiratory distress upon presentation to the emergency service, requiring urgent intubation and mechanical ventilation. A physical examination revealed generalized rhonchi in both lung fields, along with reduced air entry on auscultation of the entire right lung. Blood investigations produced the following results: total white cell count of 5200/uL, hemoglobin 10.6 g/dL, platelet 326x109/L, and C-reactive protein at 11.6 mg/L.

The patient's history included a diagnosis of retroviral disease in 2008 for which he was treated with antiretroviral medications (tenofovir-emtricitabine and efavirenz), however, the patient's compliance with the medications was poor and he was lost to follow-up in 2018. The patient had also undergone a 6-month course of antituberculous medications for smear-positive pulmonary tuberculosis in 2013. He is an active chronic smoker of 35 pack/years and has a history of intravenous drug abuse.

An urgent chest radiograph in the emergency department revealed a right apical pneumothorax that prompted a decision to proceed with a chest drain insertion and broad-spectrum intravenous antibiotics, and regular nebulization together with intravenous corticosteroids. The patient responded to the above treatments and was successfully extubated after 5 days of hospitalization. A repeat chest radiograph on day 6 of admission, however, revealed a persistent non-expandable right lung, raising clinical suspicion of either a trapped right lung due to a pleural pathology or an obstructing endoluminal airway lesion. His chest drain was fluctuating with respiration but was not actively bubbling, ruling out the possibility of an active pneumothorax with persistent air leak (Figure 1). The patient remained oxygen dependent with oxygen saturations of only 85–90% on nasal prong oxygen running at 3 L/min. A computed tomography (CT) of the thorax revealed an occluding endoluminal lesion in the right main bronchus (Figure 2).

Flexible bronchoscopy revealed a whitish endobronchial mass causing total occlusion of the right main bronchus, and the origin of the mass was identified as approximately 1cm distal from the main carina (Figure 3). Multiple biopsies were performed using flexible forceps, which resulted in a patent right main bronchus and, therefore, a fully expanded right lung post-procedure. A histopathological examination revealed fungal bodies with predominantly non-septate hyphae and yeasts (Figures 4A and B). Ziehl-Neelsen stain for acid-fast bacilli was negative. The overall findings were suggestive of pulmonary mucormycosis. Since the patient was deemed unfit to undergo surgery due to poor physical fitness secondary to advanced retroviral disease, he started systemic antifungal treatment with oral Posaconazole for 2 weeks. The patient was weaned off oxygen and was discharged well.

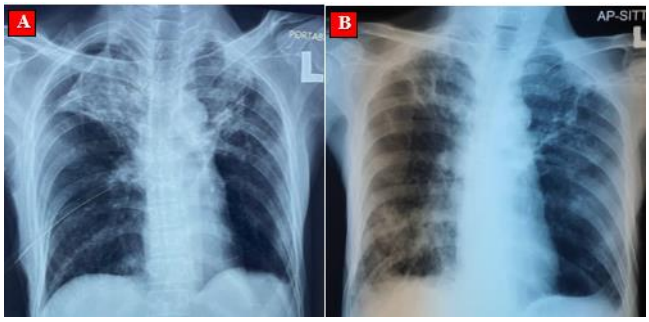

Figure 1: Persistent pneumothorax and right upper lobe consolidation after antibiotic treatment, despite chest tube insertion (A). Chest X-ray after antifungal treatment revealing resolved right upper lobe consolidation (B)

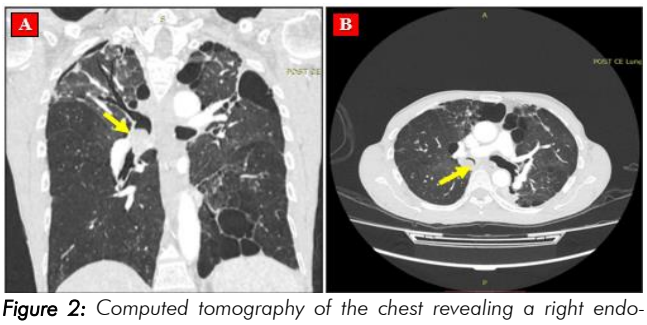

Figure 2: Computed tomography of the chest revealing a right endobronchial mass (1.3 × 1.9 cm)

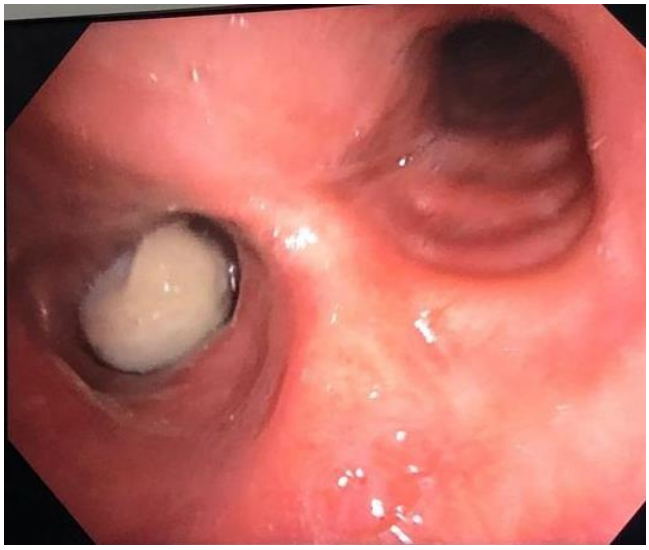

Figure 3: Fiberoptic bronchoscopy revealing an endobronchial mass in the right main bronchus

DISCUSSION

Mucormycosis is a rare and often opportunistic infection caused by fungi of the Zygomycetes class, which can be further subdivided into 3 subtypes: namely, *Mucor*, *Rhizopus* and *Lichtheimia*. Mucormycosis is prevalent among patients diagnosed with diabetes, hematological malignancies and other immunocompromised conditions. Patients may present with various clinical forms, the most common of which are rhino-cerebral and pulmonary mucormycosis, which are usually acute and fulminant, and are associated with mortality rates as high as 76% (1–3). Patients with HIV are much less likely to develop pulmonary mucormycosis than neutropenic cancer patients undergoing induction chemotherapy or recipients of hematopoietic stem cell transplants (HCST) (4), as neutrophils, as opposed to T lymphocytes, play a significant role in defense against Mucorales. In a study by Antinori et al. (5), only two patients were diagnosed with mucormycosis in a comprehensive retrospective investigation of the autopsy reports of 1,630 patients who died of AIDS from 1984 to 2002. Mucormycosis in HIV patients is usually associated with intravenous drug use and is more common in young men with lower CD4+ cell counts (6), as in our case, although iron overload and deferoxamine therapy also play a major role in the pathogenesis of mucormycosis (6,7). Rare cases of mucormycosis have also been reported among immunocompetent patients. Ng et al. (8) reported on an immunocompetent pregnant female with pulmonary mucormycosis that initially masqueraded as an endobronchial tumor who responded well to a 2-week course of intravenous amphotericin-B. The non-specific radiological and clinical attributes of pulmonary mucormycosis may make it difficult to distinguish it from other lung diseases, such as angio-invasive aspergillosis and lung cancer (2). Dyspnea, fever, chest pain and cough are some of the more common symptoms noted among those suffering from pulmonary mucormycosis (3). Pulmonary mucormycosis may rarely present as an endobronchial lesion, as in the present case (8–10). Endobronchial mucormycosis can cause airway obstruction, leading to pulmonary collapse, and has the potential to invade the hilar blood vessels, resulting in extensive hemoptysis (2). Aside from isolated masses, X-rays frequently reveal wedge-shaped consolidations, nodules, pleural effusion, halo signs and cavitation, with the upper lobe of the lungs being the most commonly affected area (11). High-resolution chest computed tomography (CT) is considered the most effective approach to the assessment of the extent of pulmonary mucormycosis, and can often detect infection before it becomes apparent on chest X-rays (4). The case presented here is a chronic smoker who suffers from COPD, which puts him at high risk of developing lung cancer and is vulnerable to opportunistic conditions such as fungal infection due to his immunodeficiency.

The diagnosis of the presented case was confirmed from histopathological findings obtained from a biopsy of the mass in the right bronchus. The culture method is important but with low sensitivity (3). Recent multi-center trials have revealed consistently low bronchoalveolar lavage (BAL) culture yields, with a sensitivity in the range of 20–50% (12). For this reason, biopsy and histological examination can be considered the optimum approach to the detection of pulmonary mucormycosis (4). A histopathological examination of biopsy material revealing non-septate hyphae is suggestive of such Zygomycete species as *mucor*, *rhizomucor* and *cunninghamela*, and degenerating *Aspergillus* is another probable mimic. In our case, a fungal PCR was ordered, although the biopsy was contaminated with a formalin solution. Our patient's predisposing condition (HIV infection), acute clinical presentation, radiographic appearance (endobronchial lesion) and histological findings of non-septated hyphae, as well as his rapid remission with posaconazole, all pointed to mucormycosis.

Factors supporting the successful treatment of pulmonary mucormycosis include the prompt administration of antifungal therapy, timely diagnosis, the early and broad surgical debridement of infected areas, and the adoption of a multidisciplinary approach. In the presented case, surgery was inappropriate due to the patient's premorbid condition, and so only medicinal therapy was prescribed. A study investigating the survival rate of pulmonary mucormycosis revealed a huge variance between the rate of 31.2% among patients undergoing only medicinal therapy and 69.1% among patients treated with both surgical and medicinal therapies (13). It is worthy of note that only a handful of reports to date have reported successful antifungal treatment in isolation (14,15).

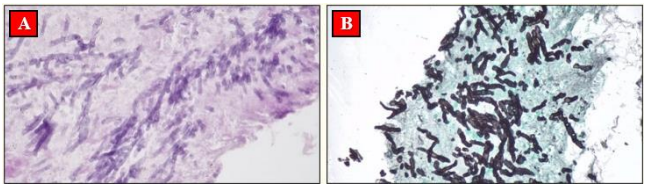

Figure 4: Non-septated hyphae (x600 PAS) (A). Non-septated hyphae (x600 GMS) (B)

Reversing the underlying risk factors that can lead to mucormycosis is also critical, aside from the administration of antifungal therapy. Interventional pulmonological procedures such as snaring, cryodebulking and laser ablations of the mass were unavailable at our center. Fortunately, the quick turnaround time of the histopathological analysis facilitated early and accurate diagnosis and treatment, preventing such devastating complications as hemoptysis and airway obstruction. Our patient responded well to the antifungal treatment, which supported an improvement in symptoms and the resolution of the pneumothorax, although no further chest CT or flexible bronchoscopy were made as the patient did not turn up for his follow-up appointments.

In conclusion, in rare cases, pulmonary mucormycosis may present as a right bronchus lesion on bronchoscopy showing a pedunculated mass mimicking a bronchial malignancy. Biopsy and histopathological examination are key to the confirmation of the diagnosis. The case presented here emphasizes the need to keep pulmonary mucormycosis firmly in mind when assessing immunocompromised patients, as early recognition and antifungal treatments are important for the avoidance of complications and mortality.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - S.C.C., K.L.N., N.C.H., W.F.G., D.A., K.M.N.; Planning and Design - S.C.C., K.L.N., N.C.H., W.F.G., D.A., K.M.N.; Supervision - S.C.C., K.L.N., N.C.H., W.F.G., D.A., K.M.N.; Funding - K.M.N.; Materials - D.A.; Data Collection and/or Processing - S.C.C., K.L.N.; Analysis and/or Interpretation - S.C.C., K.L.N.; Literature Review - W.F.G., N.C.H.; Writing - S.C.C., K.L.N., N.C.H.; Critical Review - S.C.C., K.L.N., N.C.H.

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Septic Pulmonary Embolism Due to Dialysis Catheter

Diyaliz Kateterine Bağlı Septik Pulmoner Emboli

Mücahit Güleç, Muhammed İnanç, Ahmet Cemal Pazarlı, Handan İnonu Köseoğlu, Halil Ibrahim Yakar, Gökhan Aykun

Abstract

A septic pulmonary embolism develops with non-specific pulmonary symptoms, including pulmonary infiltrations, fever, chest pain and cough as a secondary effect of any infectious focus, leading to the hematogenous spread of coagulated blood containing microorganisms from the right heart to the lungs. The condition can lead to the formation of infarctions and abscesses in patients with such predisposing conditions as congenital heart disease, intravenous drug use and long-term catheter use. We present here a case of septic pulmonary embolism resulting from the use of a dialysis catheter.

Keywords: *Septic pulmonary embolism, catheter, dialysis.*

Öz

Septik pulmoner emboli herhangi bir enfeksiyon odağına ikincil olarak gelişen akciğer infiltrasyonları, ateş, göğüs ağrısı, öksürük gibi non spesifik akciğer semptomları ile karakterize bir hastalıktır. Konjenital kalp hastalığı, IV ilaç kullanımı, uzun süreli katater kullanımı gibi predispozan durumlarda, mikroorganizmaları içeren koagüle kanın sağ kalpten hematojen yolla akciğerlere yayılımı ile infarkt ve abse formasyonları oluşturmasıyla karakterize klinik bir tablodur. Diyaliz katater uygulamasına sekonder gelişen bir septik pulmoner emboli olgusu sunulmuştur.

Anahtar Kelimeler: *Septik pulmoner emboli, kateter, diyaliz.*

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Septic pulmonary embolisms (SPE) generally develop as a result of microorganisms being transported through the pulmonary vascular system from an extrapulmonary infection source to the lungs, passing through alveolar capillaries, arterioles and venules. A blood clot filled with microorganisms, which originates from an infection focus such as infective endocarditis, tonsillitis, jugular, dental, or pelvic region, or an infected central venous catheter, becomes trapped in the pulmonary arteries leading to several nodular, cavitary or wedge-shaped infiltrates in the lung tissue. Such infiltrates are usually located near the edges and close to the blood vessels (1). SPE can present with nonspecific clinical findings with a gradual onset, and diagnosis may be delayed if SPE is not considered as a potential cause of bilateral and peripheral nodular or wedge-shaped infiltrates within the lung parenchyma along with a secondary focus of infection (2). Histopathological findings do not support a clinical diagnosis of SPE.

CASE

A 58-year-old female patient was admitted to an external healthcare facility with complaints of lower back pain and was subsequently referred to our clinic with a preliminary diagnosis of malignancy and pulmonary tuberculosis based on clinical and radiological findings. The patient had no acute or chronic respiratory symptoms at the time of presentation to our clinic. The patient had experienced a 3 kg loss of body weight, loss of appetite and night sweats in the past month. Her comorbidities included hypertension, diabetes mellitus and chronic kidney disease, and she was undergoing dialysis treatment three times a week. There was no reported history of malignancy, tuberculosis or contact with affected family members. The findings of an investigation of the respiratory system were normal, revealing an oxygen saturation level of 97% measured by pulse oximetry.

A computed tomography (CT) scan of the patient's thorax revealed new findings of bilateral cavitary and nodular structures that were absent from a CT scan 1 year earlier, as shown in Figure 1. The patient had several conditions, including rheumatological disease, lung involvement, tuberculosis and malignancy, identified from laboratory results of C-reactive protein at 180mg/dl and Creatinine at 5.5mg/dL. Blood cultures were performed due to elevated infection levels and sub-febrile temperature, and piperacillin-tazobactam 3x0.5 was initiated after calculating the creatinine clearance. Rheumatological markers were negative for the pulmonary involvement of concomitant rheumatological disease. Echocardiography was arranged as a preliminary diagnosis of suspected subacute bacterial endocarditis (SBE), but no signs of vegetation or thrombus were evident. Acid-resistant bacteria (ARB) staining for tuberculosis was negative, and tumor markers revealed no signs of malignancy. Methicillin-sensitive *Staphylococcus aureus* (MSSA) was identified in a blood culture taken from the patient's hemodialysis catheter, and the existing treatment regimen of piperacillin-tazobactam was continued.

As the patient was presented with high levels of C-reactive protein, negative rheumatological markers, and no vegetation or thrombus on echocardiography, and there were no findings supporting infective endocarditis or malignancy. Tuberculosis ARB use was ruled out. While undergoing routine dialysis, a culture of the blood sample taken from the hemodialysis catheter displayed MSSA growth, and the patient was consequently diagnosed with a septic pulmonary embolism due to the infected dialysis catheter. Oral treatment was planned to control the patient's condition with a switch to fusidate sodium. A posteroanterior chest radiograph revealed a decrease in the number and size of the nodules in the upper lobe of the right lung (Figure 2). The patient's fusidate sodium treatment was scheduled for completion within six weeks.

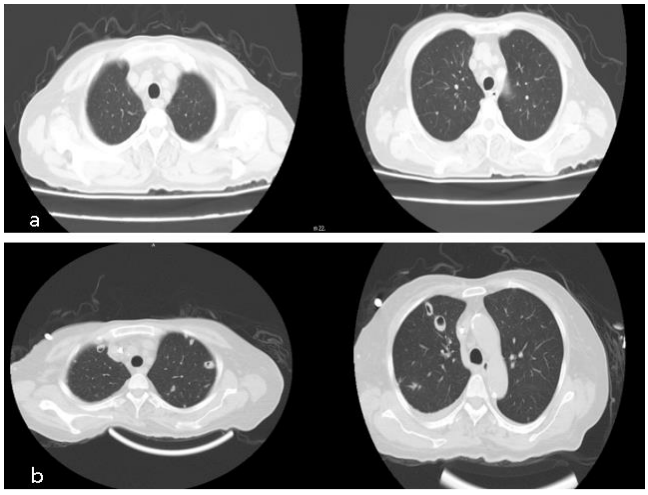

Figure 1: Bilateral cavitary lesions and nodular appearances on the new CT scan, compared with a previous CT scan of the patient

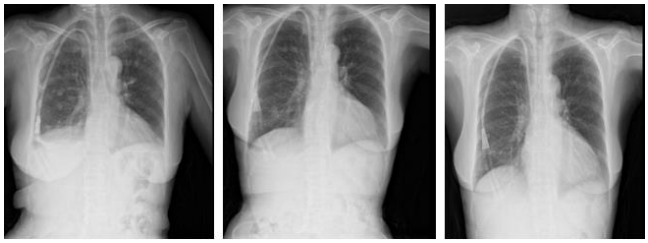

Figure 2: Almost complete regression noted on posteroanterior radiographs after antibiotic treatment

DISCUSSION

SPE is a rare disease for which diagnosis is complicated due to the non-specific symptoms and signs, although early diagnosis and treatment are vital in the management of the condition for the achievement of optimal outcomes and the avoidance of potentially catastrophic complications. IV drug addiction, infective endocarditis, alcoholism, lymphoma, severe skin infections, the presence of an A-V shunt in hemodialysis patients, osteomyelitis, immunodeficiencies, mastoiditis, toxic shock syndrome, Lemierre's syndrome, liver abscess and periodontal disease have all been shown to play a role in the etiopathogenesis of SPE (3). In a study in Japan analyzing 11,367 cases of PE identified on postmortem examination, SPE was identified in 247 (2.2%) (4). A 1978 case series study analyzing 60 SPE patients found 78% of the cases to be active intravenous drug users (5), while a 2013 study of 137 SPE cases reported only 26% to be intravenous drug users, and this decline may be attributable to the increased use of indwelling catheters and pacemakers in recent years (6). Typical lesions in infective endocarditis involve vegetation of platelets, fibrin, microorganisms and inflammatory cells. The association between pre-existing heart disease and bacteremia and the occurrence of infective endocarditis has been known since ancient times (7). In a study conducted to determine the clinical features of SPE, a re-examination of the cases revealed the most common clinical findings of SPE to be fever, dyspnea, chest pain and cough, leading to SPE being reported to be a rare disease without specific clinical findings (6). Radiology is highly important in the differential diagnosis of SPE. Although peripheral parenchymal nodules and thin-medium thick cavitations with irregular walls are typical on posteroanterior chest radiography, tomography is superior to chest radiography for the diagnosis of SPE. Cavitation is an important indicator of the infectious origin of an infarct. Thorax CT can also be useful for the visualization of such complications as the extension of abscesses into the pleural cavity and is superior to other imaging modalities in the identification of disease progression (8). *Staphylococcus aureus* is often the etiological agent of SPE, while in addition to *Staphylococci*, *viridans streptococci* and *Klebsiella pneumoniae* may also be causative agents (2). This is consistent with the higher incidence of skin and soft tissue infections as the primary extrapulmonary source. The microbiology of SPE can vary depending on a number of factors, including the underlying source (*Fusobacterium necrophorum* and anaerobes in Lemirre's syndrome, *Bacteroides sp.* in pelvic thrombophlebitis, etc.), geography (predominance of Klebsiella in Korea and Southeast Asia) and host (*non-typhoidal Salmonella* in HIV/AIDS). Empirical antibiotic therapy should be initiated immediately, initially with glycopeptides and with the addition of broad-spectrum antibiotics where appropriate. Antibiotics can then be modified based on culture results and continued for 4–6 weeks, in the presence of clinical improvement and based on the results of follow-up cultures, inflammatory markers and imaging studies (4,5). The differential diagnosis of SPE should include metastasis, tuberculosis, fungal and gram (-) infections, parasitic infections (hydatid cyst), rheumatological conditions, such as rheumatoid arthritis, and Wegener's granulomatosis.

CONCLUSION

SPE is a rare clinical condition in which early diagnosis, the prompt initiation of appropriate antimicrobial therapies and the treatment of extrapulmonary sources of infection are important. As SPE is a rare condition that is difficult to diagnose and treat, it should be considered as a priority, especially in high-risk patients, in whom careful evaluation is required.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - M.G., M.İ., A.C.P., H.İ.K., H.I.Y., G.A.; Planning and Design - M.G., M.İ., A.C.P., H.İ.K., H.I.Y., G.A.; Supervision - M.G., M.İ., A.C.P., H.İ.K., H.I.Y., G.A.; Funding - M.G., M.İ., A.C.P.; Materials - M.G., M.İ., A.C.P.; Data Collection and/or Processing - M.G., M.İ.; Analysis and/or Interpretation - A.C.P.; Literature Review - M.G., M.İ., A.C.P.; Writing - A.C.P.; Critical Review - A.C.P.

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Assessment of Docetaxel- and Paclitaxel-Related Diffuse Parenchymal Lung Disease: Two Case Reports

Dosetaksel ve Paklitakselin Neden Olduğu Diffüz Parankimal Akciğer Hastalığı: İki Olgu Sunumu

Gulcin Yilmaz, Hikmet Çoban, Mustafa Çolak, Merve Yumrukuz Şenel, Fuat Erel, Nurhan Sarioglu

Abstract

Previous studies have reported the development of hypersensitivity pneumonia, interstitial pneumonia and organized pneumonia, two parenchymal lung diseases that are clinically and radiologically interchangeable, secondary to docetaxel and paclitaxel (Taxane) use. Parenchymal lung diseases secondary to docetaxel treatment are rare, but may have serious and even fatal consequences, and any delay in diagnosis and treatment can result in a poor prognosis. Docetaxel treatment should be discontinued and corticosteroid therapy should be initiated as soon as lung involvement becomes a concern. We present here two different cases who developed diffuse parenchymal lung toxicity associated with Taxane use, considering the information in literature.

Keywords: *Docetaxel, paclitaxel, pulmonary toxicity, pneumonia.*

Öz

Dosetaksel ve paklitaksel (taksan grubu) kullanımına bağlı olarak literatürde, hipersensitivite pnömonisi, intersitisyel pnömoni ve organize pnömoni geliştiği bildirilmiştir. Bu grup hastalıklar diffüz parankimal akciğer hastalıkları içinde ele alınmakta olup bu hastalıklar arasında klinik ve radyolojik olarak geçişkenlik olabilmektedir. Taksan grubu tedavisine sekonder gelişen diffüz parankimal akciğer hastalıkları nadir görülür fakat ciddi ölümcül sonuçları olmaktadır. Tanıda gecikme ve geç tedaviye başlama kötü prognoza neden olmaktadır. Akciğer tutulumu olduğu anda ilaç tedavisi kesilmeli ve kortikosteroid tedavi başlanmalıdır. Bu yazıda, iki farklı olgu ile taksol kullanımına bağlı gelişen diffüz parankimal akciğer toksisitesi literatür bilgileri eşliğinde sunulmuştur.

Anahtar Kelimeler: *Dosetaksel, paklitaksel, pulmoner toksisite, pnömoni.*

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Paclitaxel and docetaxel (a semisynthetic derivative of paclitaxel) are taxane-group anti-neoplastic agents with antitumor properties that increase the aggregation of microtubules in the cell, preventing depolymerization and forming stable microtubule communities. Taxane therapy has been linked to such adverse effects as peripheral neuropathy, bone marrow suppression (mainly neutropenia), arthralgias, myalgias, interstitial pneumonia, organza pneumonia, noncardiogenic pulmonary edema and skin reactions. We present here two case reports, discussing lung toxicities in the first case who was diagnosed with breast cancer and who underwent docetaxel chemotherapy, and a second case who was diagnosed with NSCLC and who was placed on paclitaxel chemotherapy, due to the rarity of their conditions.

CASE

Case 1: A 50-year-old female patient underwent a protective mastectomy after being diagnosed with invasive ductal carcinoma, with a T2N1MO staging. Following mastectomy, the patient was placed on 100mg/m^2 docetaxel therapy every three weeks but developed a cough and shortness of breath after the third cycle with no fever, and the family physician prescribed non-specific antibiotherapy. The complaints persisted, leading her to be referred to the pulmonology polyclinic, where significant exertional dyspnea was identified during her initial examination. A complete blood count showed normal WBC and neutrophil levels. HGB was 10.1.

A lung radiograph revealed increased bilateral reticular densities in all zones of both lungs. The patient was admitted to the ward for monitoring. She had no fever, while arterial blood gas measurements showed moderate hypoxia (pO_2: 55.3 mmHg). Thorax CT revealed no pulmonary embolism, while extensive ground glass densities and reticulonodular involvement were noted in both lungs (Figure 1). The serum cytomegalovirus (CMV) antibody, legionella antibody/antigen, and anti-human immunodeficiency virus (HIV) antibody were all negative, and C-ANCA, P-ANCA, ANA, ANTI DS DNA, ANTI AMA, ASMA, total Ig E and RF levels were normal.

No bronchoscopy or lavage could be performed since the patient had respiratory distress. Differential diagnoses of infection and metastasis were ruled out based on clinical, radiological and laboratory data, and prednisolone therapy was initiated at a dose of 1 mg/kg as the patient developed lung damage secondary to docetaxel treatment. As the patient started to recover from respiratory distress, the steroid therapy decreased gradually and stopped at the end of one month.

Check-up radiographs showed almost complete recovery of the lung parenchyma.

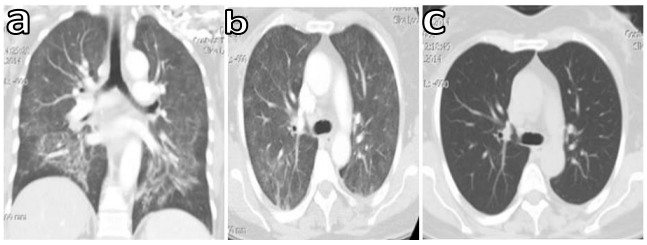

Figure 1: Thorax CT images prior to, and after treatment: an increase in ground glass appearance and interstitial reticulonodular densities can be seen with protected regions of sub-pleural and costophrenic sinuses (a and b). Lung parenchyma appears completely normal 1 month after corticosteroid therapy (c)

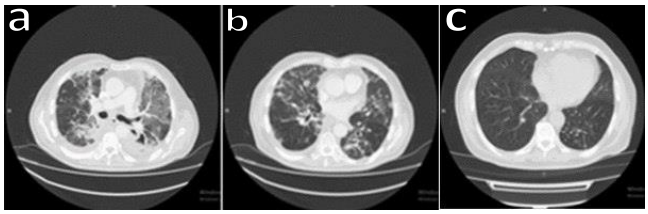

Figure 2: Areas with slightly ground glass density and fibrotic recessions extending to the pleura observed in both lungs (a and b). On control Thoracic CT, near-complete improvement in lung parenchyma was detected (c)

Case 2: A 71-year-old female patient diagnosed with NSCLC, with a staging of T3N2MO, was started on RT and CT treatment. After surgery, the patient was treated with 100 mg/m^2 paclitaxel once every three weeks, and complaints of cough and dyspnea developed after the third course. An emergency physician started the patient on non-specific antibiotic treatment, who had no fever, and she was referred to the pulmonology polyclinic after her complaints did not regress. The patient was hospitalized in an external center and followed up with pneumonia treatment many times, but no decrease was noted, and the frequent emergency applications continued. The patient was presented with dyspnea during her initial examination in the polyclinic. Hb:9 g/dL RDW: 20.9% HCT: 30.7% RBC: 3,42x104 MCH: 26.3 pg Plt: 40x103. A lung radiograph showed increased bilateral reticular density in all zones of both lungs, and the patient was admitted to the ward for monitoring. She had no fever, while arterial blood gas measurements revealed moderate hypoxia. Thoracic CT showed marked emphysematous changes in the upper lobes in both lungs, and ground-glass density areas, pleural parenchymal sequelae, fibrotic retraction and bronchiectatic changes in the superior lower lobe of the left lung. Areas with slight ground glass densities and fibrotic recessions extending into the pleura were observed in both lungs. (Figures 2a and b)

The serum cytomegalovirus (CMV) antibody, legionella antibody/antigen and anti-human immunodeficiency virus (HIV) antibody were negative. Considering the clinical,

radiological and laboratory data, differential diagnoses of infection and metastasis were ruled out.

Prednisolone therapy was initiated at a dose of 1 mg/kg, as the patient had developed lung damage secondary to paclitaxel treatment. After the respiratory distress regressed, the steroid therapy was gradually reduced at the end of one month.

Thoracic CT revealed a near-complete improvement in the lung parenchyma (Figure 2C).

DISCUSSION

Docetaxel is a chemotherapeutic agent used for the treatment of breast, head and neck, gastric, prostate and non-small cell lung cancers. Cells that cannot pass into the mitotic phase during the cell cycle cannot divide and are directed to apoptosis by the G1 control point. There have also been studies showing that paclitaxel inhibits blc-2 by binding to a protein called blc-2, which blocks apoptosis, thus allowing apoptosis to continue (1,2). The most common side effects of docetaxel include neutropenia, hypersensitivity reactions, mucosal inflammation (stomatitis), peripheral neuropathy and fluid retention. Cases of docetaxel-related hypersensitivity, and interstitial and organized pneumonia have been reported, and while pulmonary side effects are rare, they remain as potentially fatal complications of docetaxel therapy. Docetaxel-related pneumonia is characterized by prolonged symptoms and respiratory distress (3). It has been shown that patients with NSCLC treated with a combination of docetaxel with other chemotherapeutic agents or radiotherapy can develop drug-related lung damage (4,5).

In Von Hoff et al.'s (6) study of mice with human pancreatic cancer xenografts, Nab-PTX alone and in combination with GEM consumed the desmoplastic stroma, whereas in mice receiving Nab-PTX plus GEM, the intratumoral concentration of GEM was 2.8 times greater than in those who received GEM alone.

The process underlying drug-related lung damage is not fully understood. According to one hypothesis, docetaxel causes hypersensitivity-type lung damage by stimulating a proliferation of cytotoxic T cells which act against the pulmonary antigens produced by the tumor. It has been further suggested that docetaxel causes damage through its reactive oxygen metabolites (3). Interstitial pneumonia is the most common form of diffuse parenchymal lung toxicity discussed in literature. Ochoa et al. (7) analyzed 30 case reports (12 NSCLC, 12 breast CA, 4 prostate CA, 2 gastrointestinal carcinomas) published prior to 2012 and found an overall mortality rate of 40%, while two case reports published later described the development of interstitial pneumonia in three patients with NSCLC, all three of whom recovered under corticosteroid therapy (8,9).

Interstitial involvement appears to be more common in patients with NSCLC. The incidence of docetaxel-related interstitial involvement is 4.6%, however, this rate rises to 25.9% in patients with prior interstitial changes. Docetaxel is not recommended for NSCLC patients with interstitial changes, as demonstrated by CT (chest computed tomography) (10). A study of 40 patients (35 patients diagnosed with breast cancer, and none with lung cancer) newly started on docetaxel treatment reported significant decreases in DLCO, FEV1, FEV1/FVC and HRCT scores after treatment. Despite the significant decreases in pulmonary function tests and HRCT scores, none of the patients developed respiratory symptoms in the study (11).

The diagnosis of hypersensitivity pneumonia secondary to docetaxel and paclitaxel treatment is made based on the exclusion of other potential causes. In an article reporting four cases, the diagnosis of hypersensitivity pneumonia was made based on the presence of diffuse interstitial infiltration, a lack of response to antibiotherapy, the exclusion of metastatic tumors, potential hypersensitivity reactions to other medications, and rare infectious agents such as CIMV, HIV or legionella (12). A case of docetaxel hypersensitivity pneumonia that resulted in mortality has also been reported in which docetaxel treatment was continued despite the development of lung symptoms, and the diagnosis was subsequently made based on autopsy results (13). Since the diagnosis in that case was delayed, it is likely that treatment was begun at the late stage of the disease, which may have contributed to a lack of treatment response. Hypersensitivity pneumonia has been described previously in five patients in literature, all of whom, including four with NSCLC and one with breast cancer, had a mortal course (12,13).

Organized pneumonia can also develop as a result of docetaxel treatment (14–16).

Laboratory results, radiological findings and bronchoalveolar lavage can be helpful in a differential diagnosis to rule out infections and malignancies, but do not lead to a definitive diagnosis. It has been previously reported that a transition from docetaxel-related pulmonary fibrosis to organized pneumonia may occur (15). Previous cases of docetaxel-related organized pneumonia have been treated with steroids and discontinuation of treatment. All three cases described in literature developed in patients with lung carcinoma who recovered upon corticosteroid therapy.

Broncho Alveolar Lavage (BAL) was not performed in either of the cases in the present study, no diagnostic lung tissue biopsy could be carried out, and carbon monoxide diffusion capacity (DLCO) test results of the lung were unavailable, which can be considered limitations of the present study.

CONCLUSION

The most significant challenge encountered in cases of docetaxel- and paclitaxel-related pneumonia is the complexity of differential diagnoses. The first diagnosis that comes to mind in such patients is pneumonia due to the immunosuppression associated with chemotherapy and antibiotherapy, and this can result in a loss of time, increasing the risk of mortality. In patients undergoing docetaxel treatment, the symptoms should be questioned, and steroid therapy should be initiated immediately. Docetaxel is a common chemotherapeutic agent owing to its ease of use, its high efficacy and its high tolerance among patients. Docetaxel-related lung damage should be considered particularly in patients with respiratory symptoms and confirmed pulmonary infiltrations. Since neutropenia is common in this patient group, the diagnosis should not be mistaken for infections or radiation pneumonia when docetaxel is used in combination with radiotherapy for the treatment of lung cancer. Since docetaxel can result in organized pneumonia, the condition can incorrectly be considered as a lack of response to treatment or progression when docetaxel is used for the treatment of lung cancer. In such cases, the initial action must be the cessation of docetaxel treatment, after which potential infections, hypersensitivities and interstitial lung diseases must be ruled out. It should be remembered that docetaxel-related interstitial pneumonia can have fatal consequences if there is a delay in differential diagnosis and treatment. Early diagnosis, the discontinuation of docetaxel and the administration of corticosteroid therapy may allow complete recovery.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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Diffuse Alveolar Hemorrhage Due to Drugs: Two Case Reports

İlaçlara Bağlı Olarak Gelişen Diffüz Alveoler Hemoraji: İki Olgu Sunumu

Sümeyra Kaplan, Ceyda Anar, Muzaffer Turan, Bunyamin Sertogullarindan

Abstract

We present here two cases who developed diffuse alveolar hemorrhage (DAH) after using inhaled anesthetic sevoflurane and warfarin as an anticoagulant. The first patient was a 32-year-old male who underwent general surgery for appendicitis, and who developed sudden hypoxemia and bleeding at the end of the operation. Bilateral diffuse alveolar infiltrates were identified on chest X-ray, and decreased serum hemoglobin in the postoperative period. The hypoxemia resolved on the fifth day, and alveolar infiltrates disappeared from the chest X-ray. The second case was prescribed Coumadin for the treatment of atrial fibrillation and was found to have an INR value of 12.6 upon presentation to the emergency department with a complaint of hemoptysis. The patient was administered intramuscular vitamin K, and the pulmonary infiltrates were noted to have regressed radiologically on the fifth day. Although DAH is rare with both drugs, early diagnosis and treatment can be lifesaving.

Keywords: *Alveolar hemorrhage, warfarin, sevoflurane.*

Öz

Antikoagülan olarak inhale anestezik sevofluran ve varfarin kullanımına bağlı yaygın alveoler kanama (DAH) gelişen iki olguyu sunmayı amaçladık. Hastanın ilki apandisit nedeniyle genel cerrahiye başvuran 32 yaşında bir erkekti. Ameliyat sonunda ani hipoksemi ve kanama tespit edildi. Akciğer grafisinde bilateral diffüz alveoler infiltratlar görüldü. Postoperatif dönemde serum hemoglobin seviyesinde düşüş gözlendi. Beşinci günde hipoksemi düzeldi ve akciğer grafisinde alveolar infiltratlar kayboldu. İkinci olgumuzda atriyal fibrilasyon nedeniyle coumadin kullanılmış olup, acil servise hemoptizi şikayeti ile başvuran hastanın INR değeri 12.6 idi. Hastaya intramusküler K vitamini verildi. Beşinci günde radyolojik olarak akciğer infiltratlarında gerileme gözlendi. Her iki ilaca bağlı DAH yaygın olmasa da erken tanı ve tedavi hayat kurtarıcı olabilir.

Anahtar Kelimeler: *Alveoler hemoraji, warfarin, sevofluran.*

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Diffuse alveolar hemorrhage (DAH) is a rare syndrome that presents with different symptoms that can lead to life-threatening hemoptysis. While immune-mediated systemic vasculitis, such as Wegener's granulomatosis, and some drugs may play a role in its etiology, its exact pathogenesis is as yet unknown (1). We present here two cases of DAH that developed following the use of inhaled anesthetic sevoflurane and warfarin for atrial fibrillation during appendectomy operations.

CASE

Case 1: A 32-year-old male patient was admitted to the general surgery outpatient clinic with a preliminary diagnosis of appendicitis. Preoperative clinical, physical examination and laboratory values were within normal limits, and there was no additional disease. Arterial blood pressure was 135/92 mmHg; oxygen saturation was 98%, and heart and respiratory rates were 84 and 15 per minute, respectively. Contrast-enhanced upper and lower abdomen computed tomography (CT) imaging during the preoperative evaluation revealed normal lung parenchyma areas (Figure 1). The patient was given midazolam 1mg and remifentanil 0.5mg/kg for procedural sedation, and was intubated, and anesthesia was achieved with sevoflurane (3%) and remifentanil 0.125 mg/kg/min. Post-surgery, the patient developed bronchospasm and hypoxemia during extubation, and the following values were recorded in room air blood gas, pH: 7.36 PCO_2: 41.3 mmHg, PO_2: 51.5 mmHg, HCO_3: 22.6 mEq/L and saturation: 80.4%. A postoperative thorax CT of the patient in the intensive care unit revealed central weighted alveolar ground-glass consolidated densities in the bilateral parenchyma (Figure 2). Hemoptysis was noted in the intubation tube, and the patient was given oxygen support with a double jack (with nasal + mask support) after extubation. The preoperative hemoglobin value of the patient was 14.7 g/dL, and the hemoglobin value was 13.8 g/dL on the postoperative 1st day, 13 g/dL on the 2nd day and 12g/dL on the 3rd day. The postoperative coagulation parameters were INR: 1.2, the partial thromboplastin time (a PTT) was 15 seconds, and a platelet count of 222 000/μl was recorded. The patient was treated postoperatively with antibiotherapy, and antitussive and tranexamic acid, and had no significant hemoptysis in the following days. Serological tests for vasculitis and connective tissue disease were within normal limits. Bronchoscopy was considered for the patient, however the patient's hypoxemia regressed on the fifth postoperative day, and a control Posterior-anterior chest X-ray showed regression of bilateral parenchyma infiltrates (Figure 3), and so no bronchoscopy was performed.

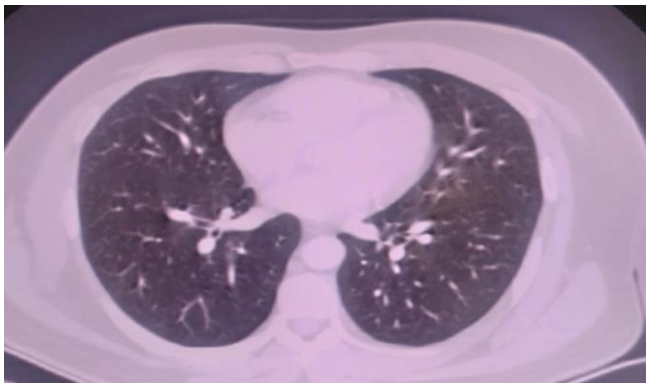

Figure 1: *Preoperative contrast-enhanced upper and lower abdomen computed tomography (CT) imaging, revealing the lung parenchyma in the examination area to be within normal limits*

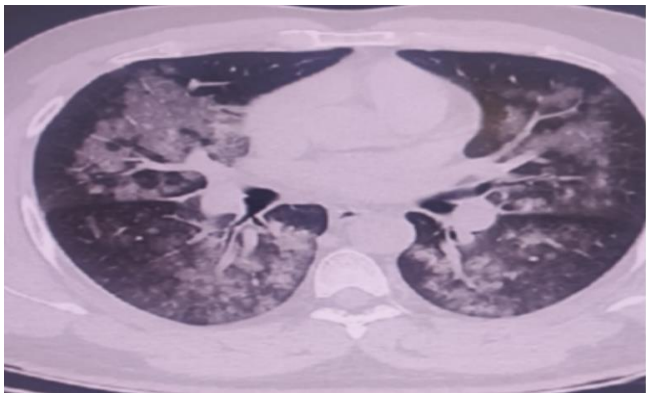

Figure 2: *Postoperative thorax CT revealing consolidated alveolar ground glass densities in the bilateral parenchyma*

Case 2: A 78-year-old female patient applied to the emergency department with cough and bruising in parts of the body with no hemoptysis or dyspnea. Around 5 days before applying to the emergency department the patient complained of 2–3 events of bleeding with sputum. The patient had atrial fibrillation, asthma and hypertension comorbidities, her arterial blood pressure was 153/82 mmHg, oxygen saturation was 93 with nasal support from 7L/min, heart rate was 73/min and respiratory rate was 16/min. A thorax CT revealed bilateral diffuse central and ground glass infiltrations (Figure 4). Laboratory values were INR 12.6, PTT 147.2, partial thromboplastin (a PTT) 88.5, hemoglobin 11.2 g/dL and platelet 242,000/μl. Due to the high INR and the present symptoms, the patient was given 1 ampoule of vitamin K administered intramuscularly in the emergency department, after which her INR was 3.03, PTT 36.2 and hemoglobin 11.6 g/dL. The patient started on antitussive treatment and the warfarin was stopped. On follow-up, the patient's hemoglobin values were recorded as 11.6 g/dL on day 1, 11.1 g/dL on day 2 and 12.1 g/dL on day 3. A PA chest X-ray taken on the 5th day revealed that the infiltrates in the bilateral parenchyma had regressed (Figure 5). Diffuse alveolar hemorrhage due to warfarin was thought to be due to the improvement of the

infiltrating areas radiologically and the regression of hemoptysis and bruising in the body in such a short time.

DISCUSSION

DAH has been described as bleeding originating from the microvascular structure of lung parenchyma (2). Although immune causes related to vasculitis are frequently, there are also non-immune causes such as heart disease, coagulation disorders, infections and drugs (1). In addition to asymptomatic radiological abnormalities, massive hemoptysis can also be seen in DAH. In most cases, a history of hemoptysis, low hemoglobin and bilateral diffuse patchy radiological infiltrates should alert physicians to the possibility of DAH. Bronchoscopy may rule out other causes of hemoptysis. The fact that BAL is hemorrhagic can contribute to a diagnosis of DAH (1). Both of the presented cases had low serum hemoglobin levels. The clinical and radiological evaluations of the patients supported the diagnosis of DAH and ruled out other causes in the etiology. At the same time, the rapid radiological improvement led us to consider drug-related etiology. Both cases had clinical dyspnea and hemoptysis. In our patient (case 2), who was dependent on warfarin, it was thought to be the lung involvement of COVID-19 pneumonia, given the ongoing pandemic, however, the rapid radiological regression in just 5 days, the low hemoglobin level and the high INR level at the time of admission also suggested DAH. Active pulmonary symptoms other than dyspnea were not observed in either of our cases. The oxygen needs of both patients, who were followed up with high oxygen support on the first day, continued to decrease.

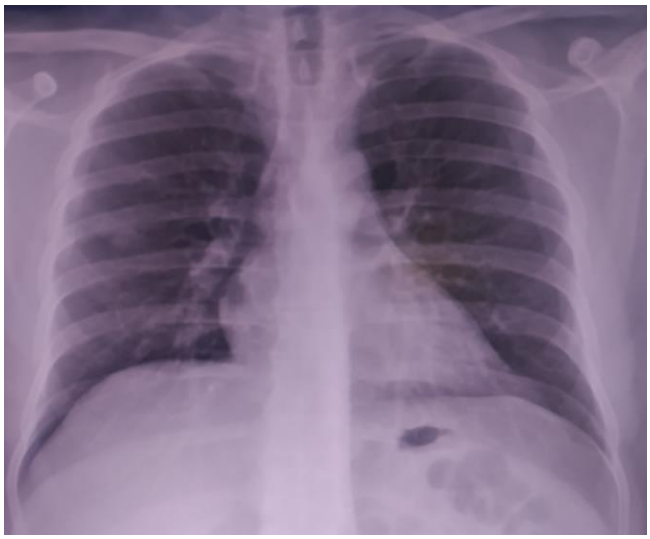

Figure 3: Posterior-anterior chest X-ray on the fifth postoperative day in which the bilateral parenchyma infiltrates can be seen to have almost completely regressed

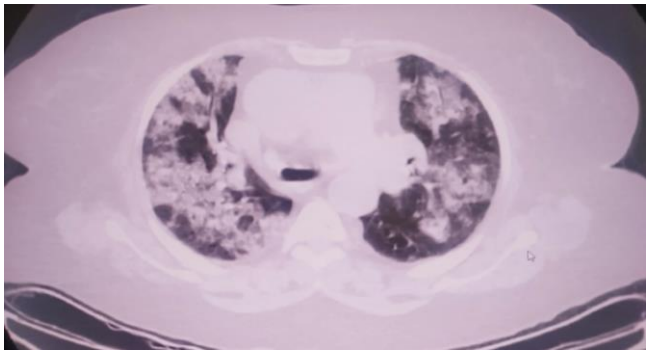

Figure 4: Bilateral diffuse central and ground glass density infiltrates on thorax CT imaging

Given the unexplained early onset of postoperative alveolar bleeding, we can conclude that the causative agent was sevoflurane, an inhaled anesthetic agent used for general anesthesia. Although sevoflurane has been associated with a number of respiratory side effects, including cough, apnea, laryngeal spasm and respiratory depression, alveolar hemorrhage occurs in only a small number of cases. Fat-soluble volatile gases may increase the inflammatory response by increasing the arachidonic cascade in the cell membrane, increasing alveolar permeability and oxidative stress (3,4), and previous studies have suggested that the mechanism causing DAH by sevoflurane may be related to this (5,6). It has also been shown that sevoflurane inhibits platelet function and decreases platelet aggregation rates (7,8).

Cases of DAH linked to sevoflurane have been reported in literature, although it has been suggested that cocaine and marijuana use accompanying sevoflurane may also lead to DAH in some cases (5,9,10,11), although the relationship between drug use and DAH in these studies remains speculative.

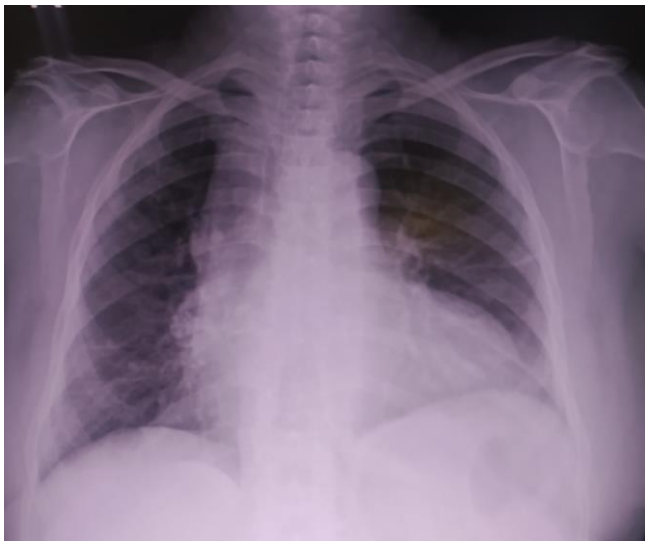

Figure 5: Regressed infiltrates observed in the bilateral parenchyma on PA chest X-ray

Mersh et al. (12) and Hao et al. (13) both suggested that alveolar hemorrhage may be associated with sevoflurane and negative pressure pulmonary edema. In two cases, none of the predisposing factors or causal causes were present as in our patient. Austin et al. (6) presented a case of a young male patient who underwent cystoscopy to widen the urethral stenosis, Cengiz et al. (14) reported on a young male patient who underwent orthopedic surgery and Yıldız et al. (15) reported on a 29-year-old male patient who applied for plastic surgery due to gynecomastia. All of these patients were males aged 20–40 years.

The drug in the second case presented here that caused DAH was Warfarin – an anticoagulant that is frequently prescribed all around the world. Warfarin-associated alveolar hemorrhage was first described by Brown et al. (16), and several warfarin-related cases of DAH have been reported since in literature (17,18).

The early diagnosis of DAH can be lifesaving, as the prognosis worsens over time. Treatment involves the destruction of the alveolar capillary membrane and the underlying cause, for which corticosteroids and immunosuppressives are used (1). Clinical and radiological regression was observed in both cases in the present study within a few days of drug discontinuation, since the underlying cause was drug related. In a patient with sevoflurane-induced DAH treated with daily methylprednisolone (1 g) administered intravenously for 3 days, the alveolar infiltrates disappeared on chest X-ray on the fourth day (15). In cases with bleeding due to oral anticoagulant use, the aim is to reverse any decreases in vitamin K-dependent coagulation factors. At this point, vitamin K antagonists should be stopped, oral or intravenous vitamin K supplementation should be provided, and clotting factors should be increased with Fresh Frozen Plasma. Prothrombin complex concentrates are used in cases with major bleeding (19). Intravenous vitamin K was administered to the patient in the present study who developed DAH due to warfarin. As supportive treatments, coagulation disorders should be corrected, and platelet replacement, careful fluid support and adequate oxygenation should be provided. In the event of hypoxemia, the NIMV support of patients is relatively contraindicated due to the risk of aspiration, and high-level oxygen support or high-flow oxygen support may be more appropriate. High oxygen support was provided to both of the presented cases due to the development of hypoxemia.

CONCLUSION

Since there was no underlying disease in either of our cases, we concluded that the responsible agents behind DAH were the inhaled anesthetic sevoflurane in the first case, and warfarin in the second case. The DAH development associated with either drug is uncommon, however, early diagnosis and treatment can be lifesaving. The possibility of DAH should be considered in patients receiving warfarin therapy and using sevoflurane as a general anesthetic agent in the presence of sudden onset respiratory failure and hemoptysis or low hemoglobin, as well as the identification of diffuse alveolar infiltrates in the bilateral lung parenchyma on radiological imaging.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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Pulmonary Langerhans Cell Histiocytosis Proceeding with Inguinal Lymph Node Infiltration: A Case Report

İnguinal Lenf Nodu Tutulumu ile Seyreden Pulmoner Langerhans Hücreli Histiyositoz: Olgu Sunumu

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Abstract

Langerhans cell histiocytosis (LCH) is a myeloproliferative disorder characterized by the clonal neoplastic proliferation of dentritic cells containing CD1a/S100/Langerin proteins. The BRAF V600E mutation causes hyperactivation in the MAPK pathway, and plays a role in misguided myeloid cell differentiation in LCH development. The incidence of the disease in the adult population is 2/1 million. Multi-organ involvement can be seen, although bone involvement is the most common site, and lung, skin and central nervous system involvement can also be seen. Isolated pulmonary involvement (pulmonary LCH) occurs between the ages of 20 and 40 years in adults, and more than 90% of cases are heavy smokers. We present here a case of pulmonary LCH identified with a bilateral micronodular infiltration on chest radiograph with details of clinical-radiological follow-ups.

Keywords: *Langerhans cell histiocytosis, MAPK, micronodular infiltration.*

Öz

Langerhans hücreli histiyositoz (LHH); CD1a/S100/Langerin proteinlerine sahip dendritik hücrelerin klonal neoplastik çoğalması ile karakterize miyeloproliferatif bir hastalıktır. LHH gelişiminde; bozulmuş miyeloid hücre diferansiasyonuna yol açan, hücre sinyalizasyonunda rol alan MAP kinaz yolağında uygunsuz aktivasyona neden olan BRAF V600E mutasyonu rol almaktadır. Hastalığın erişkin yaş grubundaki insidansı milyonda 2 olarak bildirilmiştir. LHH, çoğu organı etkilemekle birlikte kemik en sık tutulum yeridir. Akciğer, cilt, merkezi sinir sistemi tutulumları görülebilmektedir. İzole akciğer tutulumu (pulmoner LHH) çoğunlukla 20-40 yaş arası genç erişkenlerde görülmektedir ve %90'ından fazlasında sigara öyküsü bulunmaktadır. Bu olgu sunumunda radyolojik olarak her iki akciğerde mikronodüler infiltrasyonlar ile başvuran bir bir pulmoner LHH olgusu ve klinik-radyolojik takibindeki süreçten bahsedilmiştir.

Anahtar Kelimeler: *Langerhans hücreli histiyositoz, MAPK, mikronodüler infiltrasyon.*

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Histiocytic disorders originate from mononuclear phagocytic cells as macrophages and dendritic cells, and Langerhans cell histiocytosis (LCH) has been defined as a subgroup of these disorders. LCH is a myeloproliferative disorder that is characterized by the clonal neoplastic proliferation of dendritic cells containing CD1a/S100/Langerin proteins (1).

Different classifications of the disease have been put forward due to its clinical-histopathological heterogeneity. Unifocal, multifocal and multisystemic disease forms were first reported by the Histiocyte Society based on disease progression and organ involvement, and in this classification liver, spleen and hematopoietic system involvements were accepted as risk-organ involvements (2). The disease can occur at any age, although it is more common among pediatric patients aged 1–3. The incidence of the disease among children is 4/1 million, compared to 2/1 million in adults (3,4). It is thus considered uncommon in the adult population, and clinicians may not consider the disease as an entity.

LCH can affect various organs, although bone involvement is the most common form (5), while lung, skin and central nervous system involvements may also be seen (6). Isolated pulmonary involvement (pulmonary LCH) occurs between the ages of 20 and 40 years in adults, and more than 90% of cases are heavy smokers. The relationship between the disease and smoking is considered to be associated with bombesin-like peptide production and tobacco glycoproteins, which are thought to trigger an immune response resulting in chemotaxis and cytokine release (7), leading to infiltration of the lung parenchyma by Langerhans cells (8).

The pulmonary LCH case presented was identified with a bilateral micronodular infiltration on chest radiograph, and is reported with details of the clinical-radiological follow-ups.

CASE

A 43-year-old male patient with a 20/pack-year smoking history and a background in ship construction with work-related galvanization exposure was admitted to the outpatient clinic with symptoms of breathlessness and cough for 2 months. A chest radiograph revealed bilateral micronodular infiltrations and bilateral centrilobular micronodular infiltrations were detected on thorax computerized tomography (CT) (Figure 1). A fiberoptic-bronchoscopic (FOB) examination planned after an initial oral antibiotic regimen revealed no endobronchial lesions, while bronchial lavage contained no evidence of acid-resistant bacilli (ARB). Cytological findings of bronchial lavage were non-diagnostic. After being discharged, the patient was rehospitalized some weeks later for further investigation since the pulmonary symptoms had persisted, and miliary tuberculosis and occupational exposure were initially considered as a pre-diagnosis based on the imaging results and the patient's occupational history. A physical examination at admission revealed bilateral rales on auscultation, and a pulse oximeter recorded an oxygen saturation level of 95%. The significant laboratory results at the time of admission were Leukocyte: 13400 and C-reactive protein (CRP): 24 mg/L (normal range: 0–5), while all other results were insignificant. Intravenous ampicillin/sulbactam and oral clarithromycin were administered initially. Bacteriological and serological tests revealed no pathogenic bacteria in the sputum culture and no ARB was detected in the sputum sample. Serological tests for HBsAg, anti-HCV and anti-HIV produced negative results, and it was subsequently decided to take a surgical biopsy specimen given the lack of any significant pathological-microbiological results and no response to antibiotic treatment. The patient was transferred to the thoracic surgery clinic of our hospital and, after a pre-operative evaluation, underwent video-thoracoscopic surgery (VATS), during which a lung wedge biopsy specimen was taken. The macroscopic structure of the specimen in the operating theater was reported as "nodulary and palpated as hepatized" by the surgeon. The pathological result of the biopsy specimen supported an LCH diagnosis and immunohistochemistry staining for CD1a, S-100 provided a positive result.

After the cessation of smoking, a prominent regression of pulmonary infiltration was seen on a chest radiograph (Figure 2). During follow-up, the patient reported right inguinal pain and swelling that had not existed at the time of the initial admission. The patient was referred for an ultrasonographic examination for further assessment and bilateral inguinal lymphadenopathy (LAP) which right-sided LAP dominated was detected. An excisional biopsy was taken for the investigation of LAP in another surgery clinic, and the pathology of the excisional biopsy indicated a diagnosis of LCH. A follow-up thorax CT scan revealed bilateral multiple parenchymal lung nodules, the largest of which was 20 mm, and radiology specialist reported the imaging as lung metastases (Figure 3). Consequently, a whole-body positron emission tomography (PET) scan was planned, revealing increased Fluorodeoxyglucose (18F-FDG) uptake in the bilateral lung parenchymal nodules, iliac lymph nodes and inguinal regions.

The patient was referred to hematology clinic for the investigation of lymphoproliferative diseases, where bone marrow biopsy was administered with normocellular results. The hematology clinic decided to start administration of cytotoxic drug regimen and to monitor progress at follow-up.

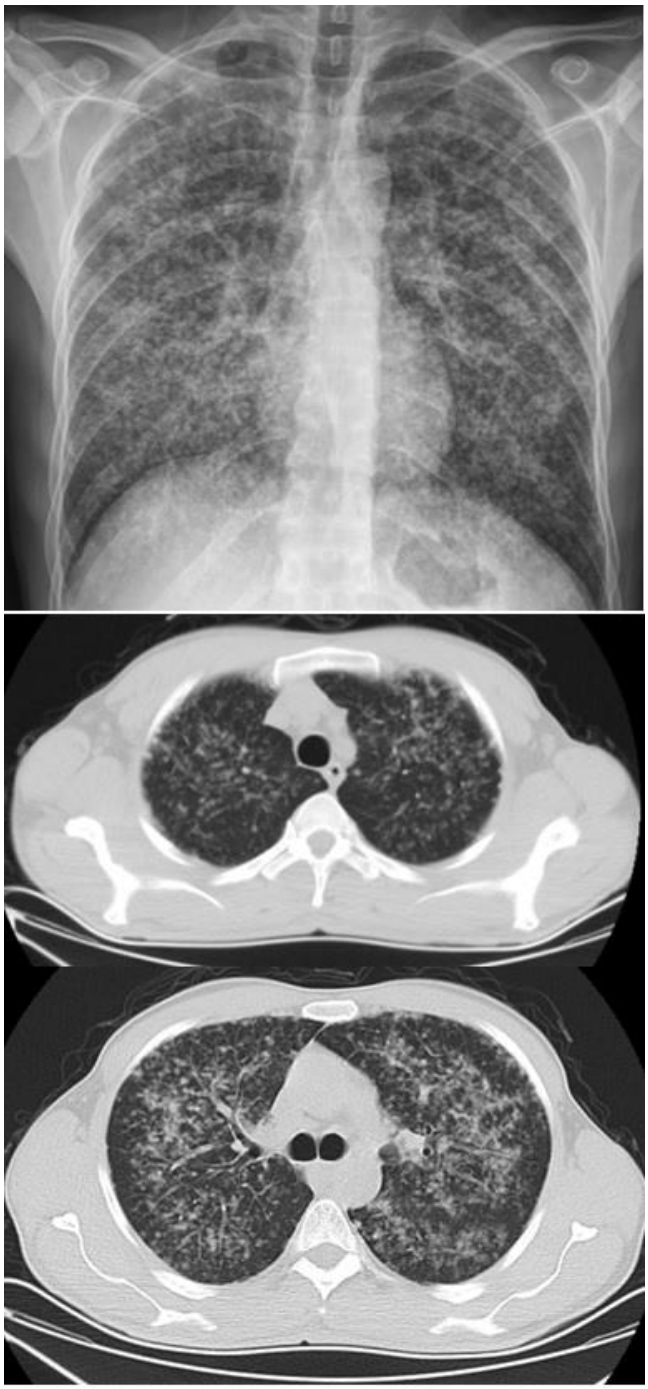

Figure 1: Chest X-ray and Thorax CT at Admission

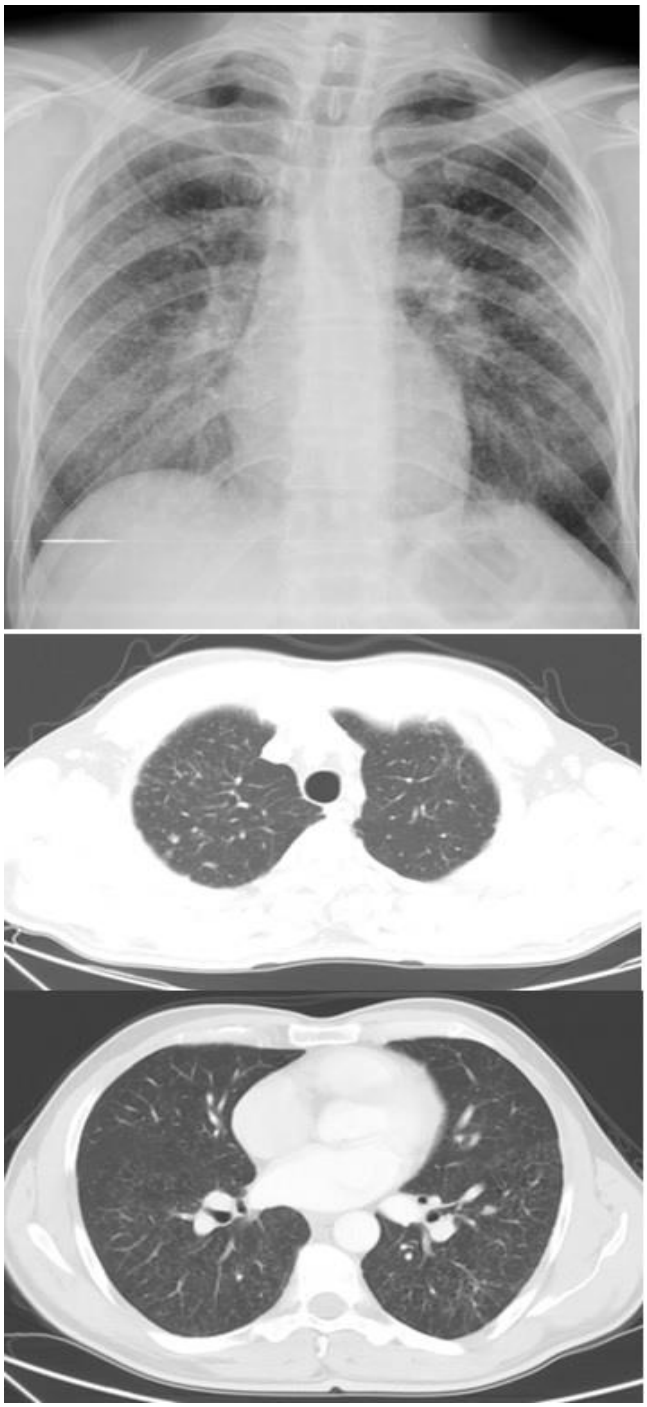

Figure 2: Chest X-ray and Thorax CT After Cessation of Smoking

DISCUSSION

LCH is a prominent disease in pulmonary medicine given its prevalence among young adults with a history of smoking and its presentation with isolated pulmonary involvement. The incidence of the disease is very rare, and its co-existence with various malignancies has been reported. Retrospective studies have suggested that the risk of acute myeloid leukemia is increased in cases with LCH (9). Thus, the risk of secondary malignancies should be considered during follow-up.

In a study reporting on a 42-year-old male patient with an asymptomatic skin lesion on the left arm, a biopsy specimen revealed a diagnosis of LCH. On follow-up, the patient was admitted to hospital with gastrointestinal symptoms such as vomiting and diarrhea. An esophagogastroduodenoscopic evaluation revealed LCH involvement of the duodenum and esophagus with features of Langerhans cell sarcoma, and a cytotoxic drug regimen of cytarabine was administered. During treatment, the patient was diagnosed with acute monoblastic leukemia that progressed aggressively and resulted in the death of the patient (10).

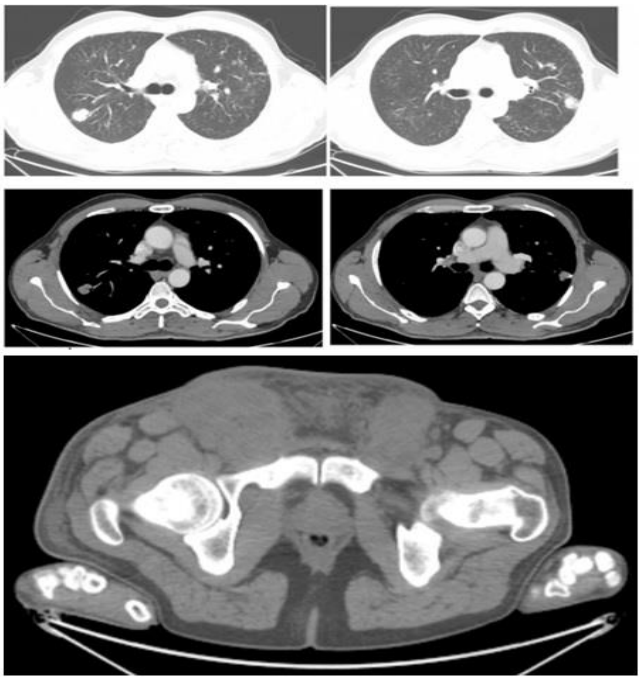

Figure 3: Parenchymal Lung Nodules and Inguinal Lymph Node on CT

The main symptoms of LCH are non-productive cough and shortness of breath (7); 25% of patients have no symptoms; 20% with chest pain are identified with spontaneous pneumothorax; and around 10% of the cases have extrapulmonary organ involvement (11).

Physical examinations and chest radiographs are primary approaches to the assessment of respiratory symptoms. Around 10% of patients have normal chest X-ray findings, while radiological findings may alter during different stages of the disease. Reticulomicronodular infiltration is the most common finding, and cystic lesions may be found in the upper and middle lung zones, whereas costophrenic sinuses are not involved (12).

High-resolution computed tomography (HRCT) imaging is the main approach to the detailed investigation of lung parenchyma, potentially revealing small nodules, cavitary nodules, and thick and thin-walled cystic changes. Nodules are generally found to have a centrilobular distribution, and as the disease progresses, cystic lesions tend to predominate. Nodules transform gradually into cavitary nodules, and then into thick-walled and thin-walled cysts (13). Pleural effusion and mediastinal LAP are not seen (11).

While transbronchial lung biopsy is diagnostic, with a success rate of 15–40%, thoracoscopic biopsy is usually recommended for diagnosis (14).

Studies of patients with PLCH published in Türkiye have reported on the clinical course of the disease. One case series followed six cases over the course of 6 years, five of whom were smokers, and the common finding from HRCT imaging was cystic lesions. The main approaches to the management of the disease were cessation of cigarette smoking and the administration of methylprednisolone 0.5 mg/kg daily. Diabetes insipidus developed in two of the cases, who were treated with desmopressin 0.1 mg/d leading to clinical improvement 1 month later (15).

Another case series from Türkiye followed four cases for 8 years, all of whom were smokers and two had a history of spontaneous pneumothorax. The cessation of cigarette smoking, and the administration of methylprednisolone 0.5 mg/kg daily were the main treatment approaches. One patient in his 20s declined the treatment and developed respiratory failure 3 years later. Echocardiographic evaluation revealed a pulmonary artery pressure of 80 mmHg. The patient was hypoxemic, and so long-term oxygen therapy was planned, and he was referred to a lung transplantation center (16).

Mutations in the MAP kinase pathway (RAS-RAF-MEK-ERK signaling) resulting in disruptions in myeloid cell differentiation have been suggested as contributing to disease development. The BRAF V600E mutation leads to the excessive activation of this pathway (Figure 4) (17), and so approaches involving such pathway proteins as MEK and BRAF are thought to have therapeutic potential.

Spontaneous remissions may occur in cases with pulmonary LCH, and the disease may not progress without treatment (7). There is a lack of consensus on the optimum treatment regimen due to the rarity of the disease and the shortage of randomized controlled trials. The currently applied treatment regimens are based generally on pediatric clinical trials and experience.

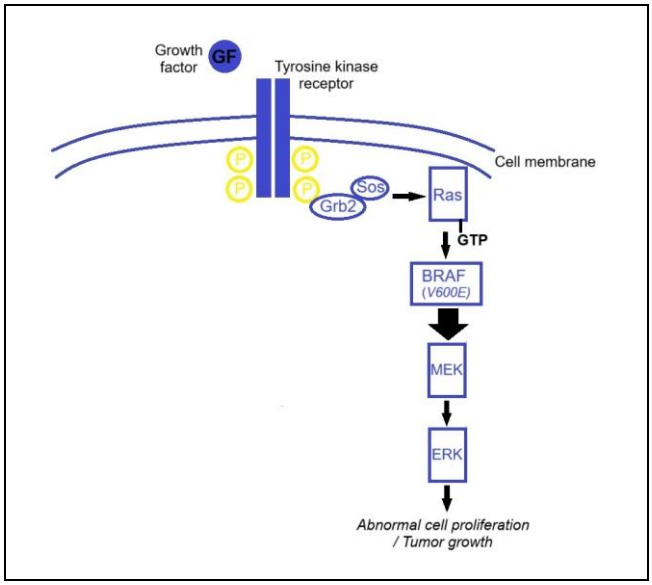

Figure 4: MAP Kinase Pathway

First-line systemic treatment regimens have been categorized by the European Consortium for Histiocytosis (ECHO), and these regimens are based primarily on case series reports and expert opinions. For cases with mild symptoms that do not have the involvement of risk organ, a regimen of methotrexate 20 mg per week po/IV or Azathioprine 2 mg/kg/d po is proposed, while for symptomatic cases, a regimen of cytarabine or etoposide 100 mg/m2 d1-5 q4w is suggested (18).

The cessation of cigarette smoking is a vital aspect of disease management. Glucocorticoid and cytotoxic treatment regimens are used empirically (11).

In another case report detailing a 31-year-old female patient with a suspected left femur lesion, an excisional biopsy revealed a diagnosis of LCH. Chemotherapy involving vinblastin and prednisolone was administered. Aside from her bone involvement, the case had multiple cystic lung infiltrations and involvement of the pituitary stalk. Recurrent pneumonia and pneumothorax developed during follow-up that led to septicemia and the death of the patient (19).

Some 25% of pulmonary LCH patients may progress aggressively and undergo diffuse cystic/destructive changes that result in end-stage fibrotic lung disease (7). The identification, investigation and reporting of new cases is vital due to the severity and lack of clinical data on adult patients, and would contribute significantly to medical literature.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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A Case of Behcet's Disease with Bilateral Pulmonary Artery Aneurysm

Bilateral Pulmoner Arter Anevrizmasi ile Seyreden Behçet Olgusu

Şehmus Işık, Tarık Kılıç, Hadice Selimoğlu Şen

Abstract

Behçet's disease is an autoinflammatory disease characterized by recurrent painful oral ulcers with small, medium and large diameter vessel involvement. Although the pathogenesis is not clearly understood, the hypersensitivity of T-cells to antigens is known to play an important role. The hyperactivation of T-cells leads to an increase in such proinflammatory cytokines as IFN-gamma and TNF-alpha, which are responsible for the symptoms of Behçet's disease. The primary clinical concerns are mucosa, skin and ocular lesions, while minor concerns are joint, neurological, gastrointestinal, vascular and pulmonary anomalies. Vascular involvement and pulmonary involvement, while rare, are the prominent clinical presentations. We present this case to literature as a rare example of bilateral pulmonary artery aneurysms.

Keywords: *Behcet's disease, vasculitis, clinical manifestations, pulmonary artery aneurysm.*

Öz

Behçet Hastalığı, tekrarlayan ağrılı oral ülserler ile karakterize ve küçük, orta, büyük çaplı damarları tutan otoinflamatuar bir hastalıktır. Patogenezi net olarak bilinmemekle birlikte, T hücrelerin antijenlere karşı aşırı duyarlılığı patogenezde önemli rol oynamaktadır. T hücrelerinin aşırı aktivasyonu, IFN-gama ve TNF-alfa gibi proinflamatuvar sitokinlerin miktarında artışa yol açar. Bu sitokinler de Behçet Hastalığındaki semptomlardan sorumludur. Başlıca klinik tutulumlar mukozal lezyonları, cilt lezyonları ve oküler lezyonlardır. Minör tutulumlar ise eklem tutulumu, nörolojik tutulum, gastrointestinal tutulum, vasküler tutulum ve pulmoner tutulumdur. Vasküler tutulum ve pulmoner tutulum en nadir ancak en mortal seyreden klinik prezentasyonlardandır. Bilateral pulmoner arter anevrizması literatürde nadir görüldüğünden olgumuz sunulmuştur.

Anahtar Kelimeler: *Behçet hastalığı, vaskülitler, klinik belirtiler, pulmoner arter anevrizması.*

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Behçet's disease is a multisystemic disease with an unknown etiology and a unique geographical distribution (1), being referred to as "Silk Road Disease" due to its frequent observation along the route of the Silk Road between China and the Mediterranean (2). Behçet's disease is relatively rare, with a frequency of 80/100,000 in Iran, 20–420/100,000 in Turkey and 0.64/100,000 in the United Kingdom (3). A meta-analysis of 45 population-based studies revealed prevalence rates of 10.3/100,000 cases for all countries, 119.8/100,000 for Turkey and 3.3/100,000 for Europe (4). Being a multisystemic disease, clinical manifestations involve almost the entire body, although the most common presentations are skin lesions in the form of oral and genital aphthous lesions and ocular involvement in the form of uveitis (5). Pulmonary involvement in Behçet's disease may take the form of pulmonary artery aneurysm, arterial and venous thrombosis, pulmonary infarction, recurrent pneumonia, bronchiolitis obliterans organizing pneumonia and pleurisy (6). Pulmonary artery aneurysms are rare in literature, with an estimated incidence of 1 in 14,000 in autopsies (7).

Clinical knowledge is limited, and the available data are generally derived from autopsy reports. The case presented here featured a bilateral pulmonary aneurysm with oral aphthae, genital ulcers and hemoptysis, and is presented to literature due to its rarity.

CASE

A 25-year-old male patient was admitted to another hospital with a complaint of hemoptysis for 13 months, and underwent a thorax Computed Tomography (CT) Angiography revealing aneurysmatic enlargements in the pulmonary artery branches in the lower lobes of both sides, the largest of which was on the left and measured approximately 3 cm in diameter (Figure 1). The patient was admitted after presenting first to the outpatient clinic.

A detailed anamnesis revealed a history of amphetamine and marijuana use 2 years previously. The patient had contracted COVID-19 approximately 13–14 months earlier and suffered from a persistent cough afterward that did not change during the day or with posture. There was no sputum. The patient also suffered from long-term occasional hemoptysis in minimal amounts that were bright red in color. Dyspnea that increased with effort had been present for the last 5–6 months. The patient had no chest pain or chronic disease in his medical history but had previously undergone an eardrum operation and an adenoidectomy. There was no history of tuberculosis or contact with tuberculosis patients. Behçet's disease was considered as a pre-diagnosis in the patient, who was identified with bilateral pulmonary artery aneurysms on radiologic imaging. An oral examination revealed frequent healing and recurring oral aphthae. A lower extremity venous Doppler ultrasound provided no evidence of thrombophlebitis or deep vein thrombosis.

A dermatology consultation was requested revealing healed wound scarring in the scrotal region, and a pathergy test was positive, and a diagnosis of Behçet's disease was made based on the sum of the findings. The patient was started on Cyclophosphamide 500 mg, with a total of four cures planned every 15 days. The patient was also started on Mesna for the treatment of hemorrhagic cystitis. The first dose of Cyclophosphamide led to a remarkable decrease in the patient's symptoms. The patient was transferred to the Rheumatology Clinic, preventing any further post-treatment control examinations as the patient was no longer part of our follow-up.

DISCUSSION

Behçet's disease is characterized by periods of exacerbation and remission that diminish in time. Vascular involvement is most commonly superficial thrombosis and deep vein occlusions, and more rarely, arterial aneurysms (8). Pulmonary artery involvement, although rare, is the main cause of morbidity and mortality in Behçet's disease and takes two forms: pulmonary artery aneurysms and pulmonary artery thrombosis.

The case presented here had developed a bilateral pulmonary artery aneurysm.

Patients with pulmonary artery involvement account for a small percentage of those with Behçet's disease. Aneurysms are usually accompanied by venous thrombosis; however, the use of anticoagulants may cause aneurysm ruptures and massive hemoptysis. Behçet's disease treatments prioritize the prevention of relapses and the rapid suppression of inflammation in vital organs through the use of immunosuppressants. Cases with pulmonary artery involvement are generally treated with a combination of steroids and cyclophosphamide, while vascular interventional methods can be applied in an emergency, such as in cases with massive hemoptysis due to aneurysm rupture, although these techniques may be ineffective if the aneurysm is too large or may lead to such complications as cavity/abscess formation (9).

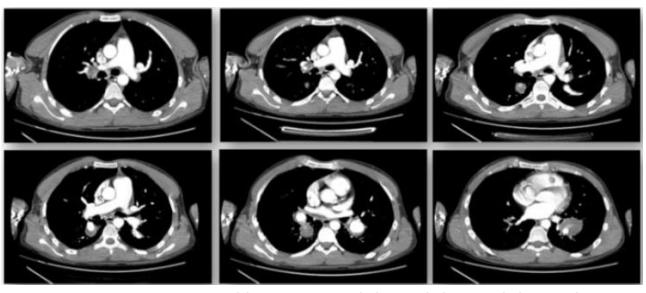

Figure 1: Aneurysmatic dilatations in bilateral lower lobe pulmonary artery branches, the largest of which was approximately 3 cm in diameter on the left

CONCLUSION

The case of Behçet's disease presented here, diagnosed with bilateral pulmonary artery aneurysm, oral aphthae and genital ulcerated lesions, responded well to immunosuppressive treatment.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - Ş.I., T.K., H.S.Ş.; Planning and Design - Ş.I., T.K., H.S.Ş., D.Ö.K.; Supervision - Ş.I., T.K., H.S.Ş.; Funding - Ş.I., T.K., H.S.Ş.; Materials - Ş.I., T.K., H.S.Ş.; Data Collection and/or Processing - Ş.I., T.K., H.S.Ş.; Analysis and/or Interpretation - Ş.I., T.K., H.S.Ş.; Literature Review - Ş.I., T.K., H.S.Ş.; Writing - Ş.I., T.K., H.S.Ş.; Critical Review - Ş.I., T.K., H.S.Ş.

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Utility of POCUS in the Diagnosis of Drowning-related Noncardiogenic Pulmonary Edema: A Case Report

Boğulmaya Bağlı Kardiyojenik Olmayan Akciğer Ödeminin Tanısında POCUS'un Faydası: Olgu Sunumu

İsmail Erkan Aydın, Nalan Kozaci

Abstract

Respiratory complications such as noncardiogenic pulmonary edema, acute respiratory distress syndrome and pneumonia are frequently seen in drowning. No additional disease was noted in the history of a 37-year-old male patient who was brought to the emergency department with cardiopulmonary arrest after drowning at sea. Spontaneous circulation returned following 12 minutes of cardiopulmonary resuscitation. Bedside point-of-care ultrasound (POCUS) revealed multiple and confluent B lines, an irregularity on the pleural line, disappearance in the A-lines, and subpleural hypoechoic areas predominantly in the 2nd, 3rd, 4th and 6th zones of the right lung and the 3rd, 4th and 6th zones of the left lung. The ventilator mode and settings were adjusted according to the POCUS findings, being a safe option in emergency departments for the diagnosis of noncardiogenic pulmonary edema due to drowning and for the management of such patients.

Keywords: *Drowning, Point-of-care ultrasonography, POCUS, Pulmonary edema.*

Öz

Boğulma sonucu, nonkardiyojenik pulmoner ödem, akut solunum sıkıntısı sendromu ve pnömoni gibi solunum komplikasyonları sıklıkla görülmektedir. Denizde boğulma sonucu kardiyopulmoner arrest olarak acil servise getirilen 37 yaşındaki erkek hastanın özgeçmişinde ek hastalık yoktu. Kardiyopulmoner resüsitasyonun 12. dakikasında spontan dolaşım geri döndü. Yatak başı yapılan nokta bakım ultrasonunda (POCUS) sağ akciğer 2. 3. 4. 5. 6 zonda ve sol akciğerde 3. 4. 5. 6. zonda ağırlıklı olmak üzere multiple ve confluent B çizgileri, plevral çizgide düzensizlik, A çizgilerinde kaybolma, subplevral hypoecoik alan görüldü. POCUS bulgularına göre ventilatör modu ve ayarları düzenlendi. POCUS acil servislerde, boğulmaya bağlı nonkardiyojenik pulmoner ödemin tanısında ve bu hastaların yönetiminde güvenle kullanılabilir.

Anahtar Kelimeler: *Boğulma, Nokta bakım ultrasonu, POCUS, Pulmoner ödem.*

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Drowning is defined as respiratory distress resulting from immersion/submersion in liquid, and is the third most common cause of accidental death in all age groups worldwide (1). Respiratory complications such as noncardiogenic pulmonary edema, acute respiratory distress syndrome (ARDS) and pneumonia are frequently observed in drowning cases, and a chest X-ray is recommended in all such cases for diagnosis. A chest computed tomography (CT) may reveal the severity of the disease, and radiological follow-up may be required in such cases, depending on the severity of the lung damage (1,2).

Ultrasonography (US) is a widely used imaging approach in intensive care units and emergency departments as a portable radiation-free option. Studies of ultrasonography have increased with the increase in the provision of training in point-of-care ultrasound (POCUS). Lung diseases such as thoracic trauma, pulmonary edema, ARDS and pneumonia can be visualized with POCUS. Studies have reported POCUS to be a reliable diagnostic tool, accelerating the time to diagnosis in patients with respiratory distress, and to be supportive of disease management and follow-up (2–6).

This case report compares the POCUS and CT images of a patient who developed noncardiogenic pulmonary edema as a result of drowning in water.

CASES

The 37-year-old male patient in the present study, who had no medical history, developed cardiopulmonary arrest as a result of drowning at sea. It was learned that the patient had been given cardiopulmonary resuscitation (CPR) for 10 minutes at the scene, and that CPR was continued until his arrival at the emergency department. The initial examination in the emergency department revealed no spontaneous breathing, no pulse, dilated pupils and no light reaction. CPR was continued in the emergency department and the patient was monitored. Pulseless electrical activity was observed on the monitor. The location of the intubation tube was confirmed by auscultation. There were diffuse rales in either lung. The aspiration of the endotracheal tube revealed constantly clear fluid. Arterial blood gas: pH: 6.74, pCO_2: 122mmHg, pO_2: 40mmHg, lactate: 11 mmol/L and BE: -18mmol/L. Spontaneous circulation returned (ROSC) at the 12th minute of CPR. After ROSC, the patient's heart rate was 138/min and blood pressure were 90/60mmHg. In arterial blood gas, pH: 7.08, pCO_2: 46mmHg, pO2: 101mmHg, lactate: 9.4mmol/L and BE: -15mmol/L. ECG revealed sinus tachycardia and right axis deviation.

The patient was placed on positive inotropic therapy and provided with positive-pressure mechanical ventilator support. POCUS was performed for the evaluation of the lungs, revealing In POCUS, multiple and confluent B lines, irregularity on the pleural line, the disappearance of A-lines and a subpleural hypoecoic area, predominantly in the 2nd, 3rd, 4th, 5th and 6th zones of the right lung, and the 3rd, 4th, 5th and 6th zones of the left lung (Figure 1, 2, 3, 4). The zones of the findings were marked on the POCUS study form, and the ventilator mode and settings were adjusted based on the POCUS findings. The pressure-controlled mode was selected, and ventilation was started with high PEEP. CT images revealed diffuse ground glass opacities in both lungs. The patient was transferred to the intensive care unit.

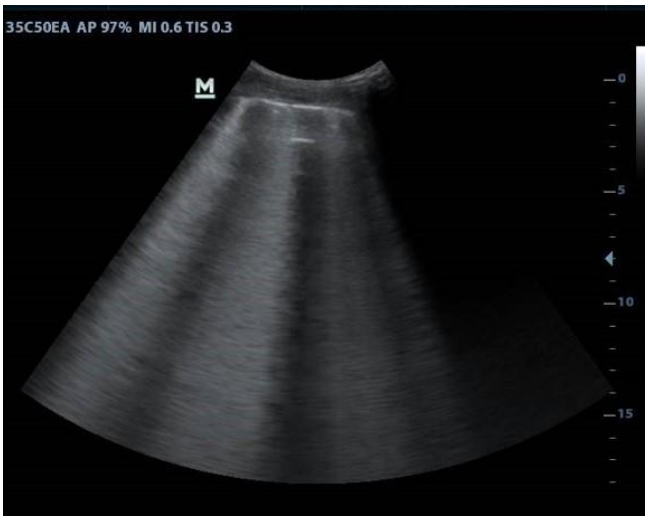

Figure 1: Confluent B lines in the 5th zone of the left lung

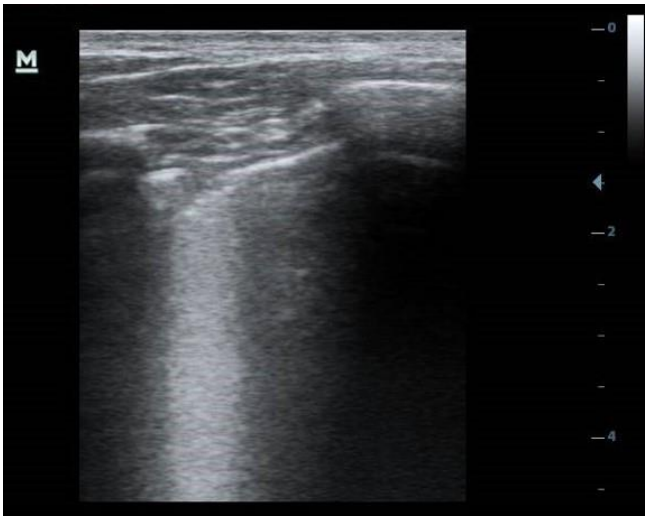

Figure 2: Irregularity on the pleural line and the disappearance of A-lines

Table 1: Point-of-care ultrasonography form

Thorax Zones				R3	R2	R1		L1	L2	L3			
	R6	R5	R4								L4	L5	L6
Normal lung signs													
A Line						+		+					
Lung sliding						+		+					
Seashore						+		+					
Lung pulse													
Pathological lung signs													
Multiple or Confluent B Line	+	+	+	+	+				+	+	+	+	+
Pleural line abnormalities	+	+	+	+	+				+	+	+	+	+
Alveolar syndrome and consolidation findings													
Subpleural hypoechoic zone	+	+		+						+		+	+
Hepatization													
Air bronchograms													
Shred sign													
Pneumothorax Signs													
Stratosphere (barcode) sign													
Lung point													
Pleural Syndrome Signs													
Quad sign													
Sinusoidal sign													

Point-of-care ultrasonography

POCUS was performed with the patient in a supine position, using 7.5 MHz linear and 3.5 MHz convex ultrasound probes (Mindray DP-30, Germany). The thorax was evaluated from the anterolateral aspect, while the hemithorax was evaluated by tracing the midsternal line and determining the right and left sides, and each hemithorax was divided into six zones on the longitudinal plane formed by the midclavicular, anterior axillary and posterior axillary lines, and the transverse plane based on a line at the nipple level. The zones were numbered from the sternum to the lateral, and each area was visualized in the longitudinal and transverse planes with linear and convex probes (4). With the linear probe, all areas were evaluated in B mode and M mode. Normal lung signs were first evaluated, followed by pathological lung signs, and the findings of each zone were noted on a POCUS form (Table 1). The POCUS was completed in 5 minutes.

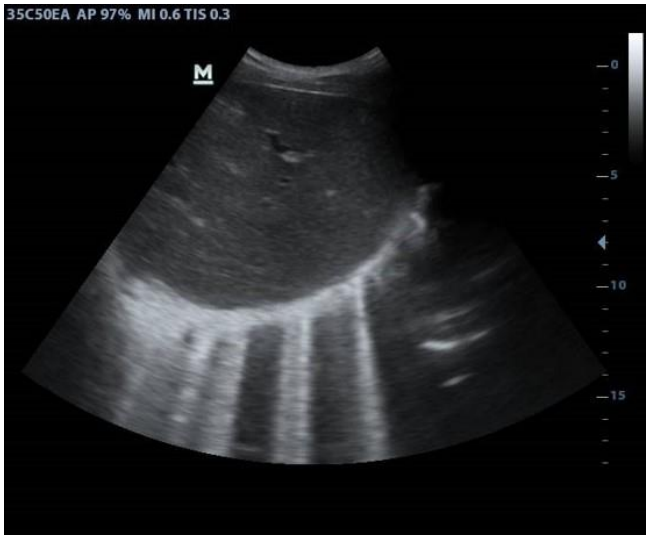

Figure 3: B lines in the 6th zone of the right lung (at the diaphragm level)

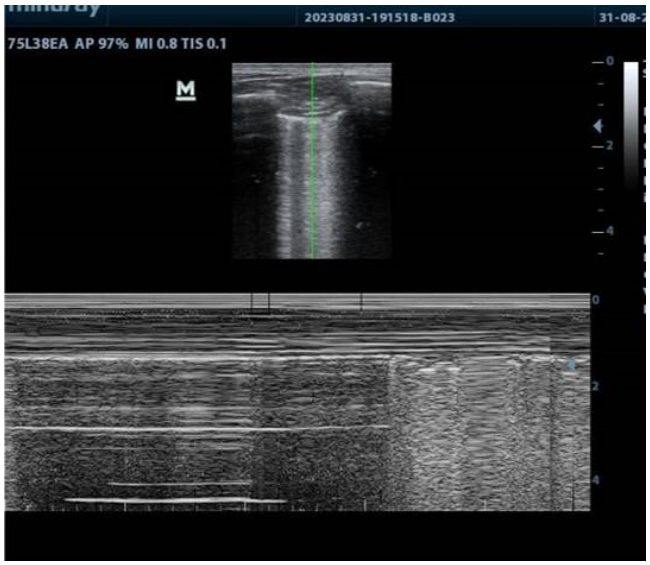

Figure 4: Viewing the zone with confluent B lines in M mode

DISCUSSION

Pulmonary edema refers to an abnormal accumulation of extravascular fluid in lung parenchyma. Pulmonary edema may occur due to both cardiogenic and non-cardiogenic causes (7), although cardiogenic and non-cardiogenic pulmonary edema may have very similar appearances in the US. B lines have been identified as a sonographic sign of interstitial-alveolar syndrome on lung US. The POCUS images of our case, who developed cardiopulmonary arrest due to drowning, were evaluated systemically for each zone, and revealed multiple and confluent B lines in the bilateral lungs, an irregularity on the pleural line, the disappearance of A-lines and a subpleural hypoecoic area. These findings are important as they indicate severe alveolar edema. The thorax CT images of the patient contained widespread ground-glass opacities in the bilateral lungs. These findings are among the most common radiographic findings seen in cases of drowning (8,9). Neither US nor CT images can distinguish between cardiogenic and noncardiogenic pulmonary edema, and so it is important to evaluate the images together with clinical findings. Clinically, the drowning cause of our patient's cardiopulmonary arrest and the continuous discharge of clear fluid upon aspiration of the endotracheal tube supported our diagnosis of non-cardiogenic pulmonary edema. Studies have reported that the number of B lines correlates well with the degree of extravascular lung water. Visualized confluent B lines are actually very close (⩽3 mm) B lines and correspond to ground glass opacities on a CT scan, and are a result of the alveoli being completely filled with fluid. For this reason, the number and profile of B lines are used in the diagnosis of pulmonary edema and for monitoring response to treatment (10,11). Confluent B lines were highly evident in the POCUS images of our case, especially in the lateral zones, and this was attributed to the increased accumulation of water in these areas due to the effect of gravity in the patient in the supine position.

In our case, the diagnosis was made rapidly based on an evaluation of the POCUS images and clinical findings together. Simultaneously, the width of the damaged area was determined by marking the pathological lung areas on the POCUS form. In our case, the extent and severity of lung damage were determined by the involvement of the 2nd, 3rd, 4th, 5th and 6th zones in the right lung, and the 3rd, 4th, 5th and 6th zones in the left lung, along with the appearance of multiple and confluent B lines in these areas. Our patient's ventilator mode and parameters were adjusted according to the POCUS findings. The pressure-controlled mode was selected, and ventilation was started with high PEEP.

CONCLUSION

The findings of non-cardiogenic pulmonary edema due to drowning noted on POCUS images are similar to those in cases with cardiogenic pulmonary edema, and it is, therefore, necessary to evaluate the POCUS findings together with clinical findings for an accurate diagnosis. POCUS can be used safely in emergency settings for the diagnosis and management of noncardiogenic pulmonary edema due to drowning.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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Rare Manifestation of Epithelioid Type Malignant Pleural Mesothelioma: Recurrent Pneumothorax

Epiteloid Tip Malign Plevral Mezotelyoma'nın Nadir Prezentasyonu: Tekrarlayan Pnömotoraks

Irmak Akarsu[1], Elgun Valiyev[1], Tuğba Körpeoğlu[2], Şevki Mustafa Demiröz[1], Nalan Akyürek[2]

Abstract

Malignant pleural mesothelioma (MPM) is a rare and aggressive tumor that leads to approximately 20,000 deaths per year. The most common symptoms are chest pain, shortness of breath, cough and weight loss. Radiologic studies usually reveal pleural thickening and pleural effusion, although the disease can also rarely present with spontaneous pneumothorax or hydropneumothorax. We present here a case of a 57-year-old male diagnosed with occult epithelioid type MPM based on video thoracoscopic (VATS) exploration and biopsy who experienced recurrent pneumothorax attacks and prolonged air leakage. Although there are few symptoms or imaging findings specific to MPM, elderly patients with recurrent pneumothorax attacks should be questioned for asbestos exposure, and MPM should be kept in mind in the differential diagnosis.

Keywords: *Pneumothorax, malignant mesothelioma, thoracic injuries.*

Öz

Malign plevral mezotelyoma (MPM), yılda yaklaşık 20.000 ölüme neden olan nadir ve agresif bir tümördür. En sık görülen semptomlar göğüs ağrısı, nefes darlığı, öksürük ve kilo kaybıdır. Radyolojik incelemeler genellikle plevral kalınlaşma ve plevral efüzyonu ortaya koyar ancak hastalık nadiren spontan pnömotoraks veya hidropnömotoraksla da ortaya çıkabilir. Bu olgu sunumunda tekrarlayan pnömotoraks atakları ve uzamış hava kaçağı olan 57 yaşındaki erkek hastada video torakoskopik (VATS) inceleme ve biyopsi ile tanı alan epiteloid tip MPM sunulmaktadır. MPM'ye özgü herhangi bir semptom veya görüntüleme bulgusu olmasa da tekrarlayan pnömotoraks atağı geçiren yaşlı hastalar asbest maruziyeti açısından sorgulanmalı ve ayırıcı tanıda MPM akılda tutulmalıdır.

Anahtar Kelimeler: *Pnömotoraks, malign mezotelyoma, göğüs yaralanmaları.*

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Mesothelioma occurs as a result of the neoplastic transformation of mesothelial cells on serosal surfaces, including the pleura, pericardium, peritoneum and tunica vaginalis. Chronic asbestos exposure is the most common cause of MPM. The average survival time is one year, and can be extended only with early diagnosis (1). The latency period following asbestos exposure can last 30–40 years. The disease usually manifests with chest pain, shortness of breath, cough and weight loss (2,3). The most common imaging findings are pleural effusion and thickening, although it may rarely present with pneumothorax and hydropneumothorax (3). Many previous studies have reported spontaneous pneumothorax accompanying malignancies (4). Here, we present a rare case with an epithelioid-type malignant mesothelioma who presented with recurrent pneumothorax as the first sign of the disease.

CASE

A 57-year-old male patient presented to the emergency room with shortness of breath and chest pain following a traffic accident. While no significant fractures were noted in the bony structures of the chest wall, a large left-sided pneumothorax was detected, and a tube thoracostomy was performed. The patient had no additional problems during follow-up and complete lung expansion was achieved, and the tube thoracostomy was subsequently terminated. The patient was discharged on the 3rd day, but was readmitted with chest pain 2 days later with recurrent pneumothorax on the left side (Figure 1), and a further tube thoracostomy was performed. Despite the chest tube treatment, the patient developed subcutaneous emphysema and massive prolonged air leakage that persisted even after autologous blood pleurodesis. The patient was transferred to our clinic on the 10th day of follow-up when a renewed thorax CT revealed subcutaneous emphysema, pleural effusion, and pneumothorax on the left hemithorax. Although not mentioned in the report, pleural thickening and hematoma-like appearances were seen on the diaphragm, pericardium, and costophrenic sinus (Figure 2). It was thought that previously performed autologous blood pleurodesis could have led to this tomography image.

The patient had no accompanying disease, although a detailed medical history revealed environmental asbestos exposure. VATS exploration was planned for the treatment of prolonged air leaks. Although no apparent bullous areas were observed on exploration, multiple nodular lesions on both the visceral and parietal pleura were accompanied by a small amount of pleural fluid (Figure 3). Multiple biopsies were taken from the nodular areas on the parietal pleura, a fistula seen on the surface of the apical visceral upon inflation was resected with a wedge resection, and pleural fluid was sampled.

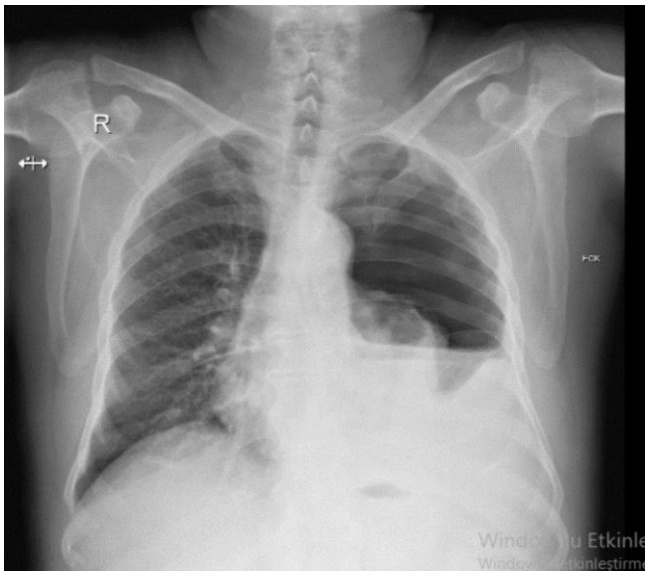

Figure 1: Preoperative left hydropneumothorax seen on chest X-ray

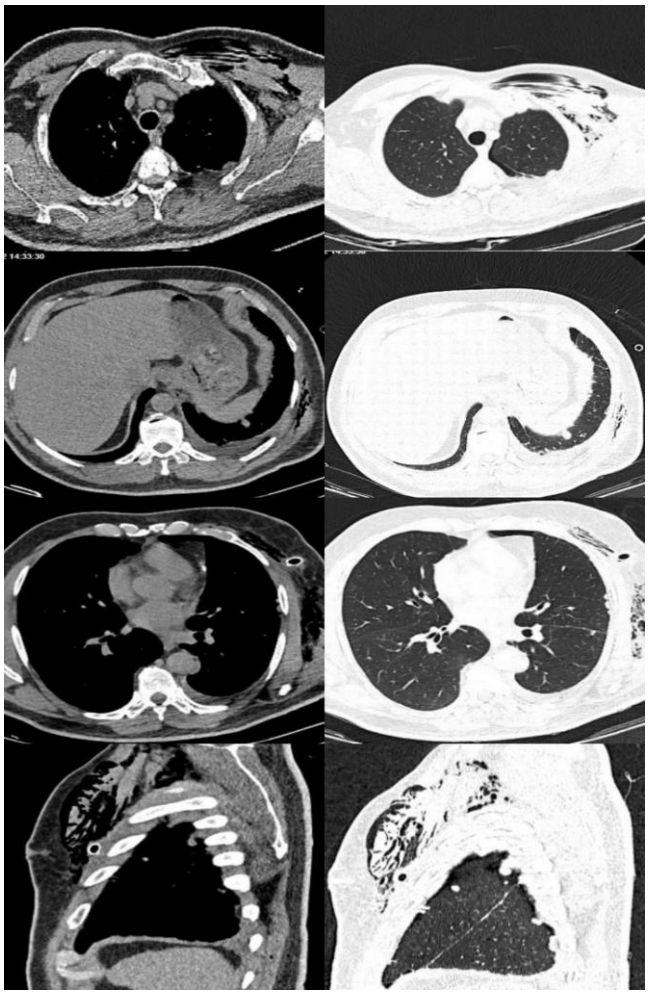

Figure 2: Thorax CT sections, showing pleural nodulation, pleural effusion, pneumothorax and subcutaneous emphysema in the left hemithorax

Table 1: Series of epitheloid MPM presenting with pneumothorax

Author	Number of patients	Age of Patients	Clinic presentation	Side	Histopathologic subtype
Nakazawa	1		Pneumothorax	Left	Mixed
Ohkado	1		Pneumothorax		UD
Tanaka	8		Hydropneumothorax (8)		Epithelioid
Gotoh	1		Pneumothorax	Right	UD
Katayam	1		Hydropneumothorax	Right	Mixed
Makidono	1	44	Pneumothorax	Right	Epithelioid
Takeuchi	1		Pneumothorax	left	UD
Mitsui	2	57 / 63	Pneumothorax (1)/ Hydropneumothorax (1)	right	Epithelioid
Sheard	5		Pneumothorax (5)	Left (3)/Right (2)	Epithelioid (2) Mixed (3)
Alkhuja	4	81/81/56/70	Pneumothorax (2)/ Hydropneumothorax(2)	Left (2)/ Right (2)	Epithelioid (3) Sarcomatoid (1)
Saleh	2	70 / 71	Pneumothorax	Right(2)	Epithelioid (2)
Fukui	1	62	Pneumothorax	Bilaterally	Biphasic
Sattar	1	79	Pneumothorax	Right	Epitheliod
Delapp	1	67	Hydropneumothorax	Right	Epithelioid
Fayed	1	69	Hydropneumothorax	Bilaterally	Epithelioid
Wu	1	69	Hydropneumothorax	Right	UD
Guha	1	73	Hydropneumothorax	Right	Epithelioid
Prasad	1	69	Pneumothorax	Right	UD (low grade)
Situnayake	1	54	Pneumothorax	Right	UD
Ema	1	61	Hydropneumothorax	Right	Epithelioid

A histopathological examination of the wedge resection material and the pleural biopsy revealed a malignant epithelial tumor. Tumor cells were positive for immunohistochemical (IHC) markers CK5/6, calretinin and WT1, and negative for TTF-1, and a loss of the BAP-1 protein was identified (Figure 4). No atypical cells were observed in pleural fluid. The final pathology was reported as "Epithelioid type MPM".

Postoperative follow-up was uneventful, and complete lung expansion was achieved on the second day, after which the chest tube was removed, and the patient was discharged on the 3rd postoperative day. Due to an unexpected diagnosis of MPM, a PET-CT was planned for staging and distant metastasis. No pathologic 18 F-FDG uptake was noted on the pleural surfaces, lymph nodes or extrathoracic regions (Figure 5). An extrapleural pneumonectomy was planned, and the patient was referred to the oncology clinic for neoadjuvant treatment.

DISCUSSION

MPM is a rare and aggressive tumor that has been linked to approximately 20,000 deaths a year (2). It can manifest with non-specific symptoms such as loss of appetite and weight, in addition to the most common symptoms associated with the pleural neoplasia itself, such as pleural thickening, effusion and pain due to thoracic wall invasion. Cases of spontaneous pneumothorax and hydropneumothorax have been rarely reported in literature (1,3). The most common symptoms of MPM and pneumothorax are chest pain and shortness of breath (3,4). In our case, the symptoms at the time of admission were chest pain and shortness of breath following a traffic accident, and recurrent pneumothorax was the manifestation type.

Mitsui et al. (3) reported male dominance and a mean age of 58 years in their study of 16 cases with MPM presenting with pneumothorax. In our case, the patient was a 57-year-old male.

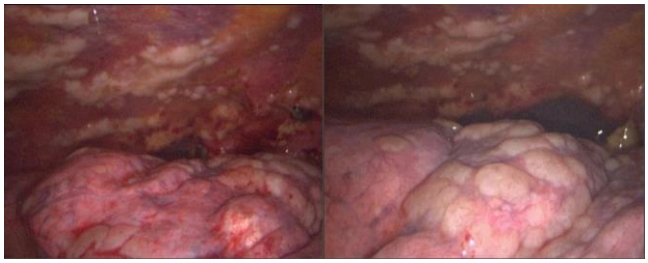

Figure 3: Nodular formation seen on video thoracoscopic imaging

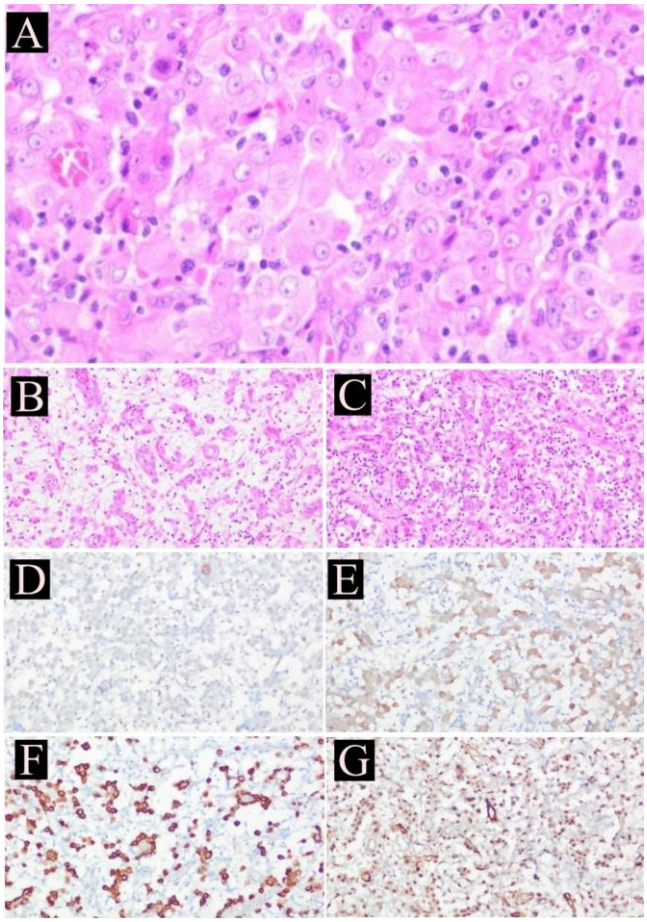

*Figure 4: Epithelioid mesothelioma. Tumor cells with eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli (H&E x400) **(A)**, Tubulopapillary pattern. Tumor cells form tubules and papillae. (H&E x200) **(B)**, Lymphohistiocytic pattern. Polygonal tumor cells in lymphocytic infiltrate with a histiocytic morphology (H&E x200) **(C)**, BAP1 loss from tumor cells x200 **(D)**, Calretinin x200 **(E)**, Ceratin 5-6 x200 **(F)**, WT-1 x200 **(G)***

The first case of spontaneous pneumothorax secondary to MPM to be reported was published by Eisenstadt in 1956. Although the etiologic mechanism of pneumothorax development in MPM patients is uncertain, three mechanisms have been suggested: (i) rupture of necrotic tumor nodules, (ii) formation and rupture of subpleural bullae, developed by peripherally located tumor nodules and (iii) pleural spread of the tumor. Included in the study by Mitsui et al. (3) were 16 MPM patients with spontaneous pneumothorax, of which nine patients had right-sided, six patients had left-sided, and one patient had bilateral pneumothorax. Of the total, 11 of the patients developed recurrent pneumothorax, and nine had an accompanying pleural effusion. Similarly, the case in the present study had recurrent pneumothorax and an accompanying pleural effusion.

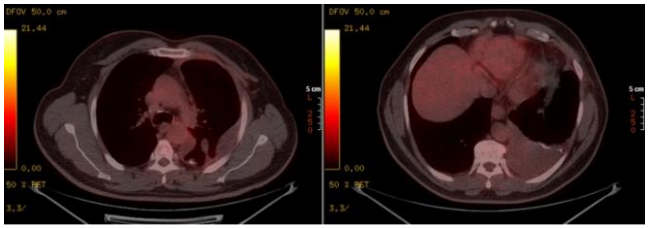

Figure 5: Pathological 18f-FDG uptake observed in areas with pleural thickening and pleural effusion on PET-CT

Thorax CT is the most common imaging approach to the diagnosis and staging of MPM, given its ability to reveal pleural effusion, thickening and nodulation, mass appearances, mediastinal shifts and invasions of the surrounding tissues (3). In their study of 84 MPM patients, Sahin et al. (2) reported unilateral pleural thickening, nodulation or mass (100%), pleural effusion (73%), mediastinal pleural involvement (93%) and volume loss (22%) as the most common CT findings. However, especially in early-stage patients, no significant findings may be seen on CT (5).

A tissue biopsy is required for the definitive diagnosis of MPM, while a pathological diagnosis of MPM is difficult as its morphological patterns can mimic many epithelial and non-epithelial malignancies. IHC studies are necessary to rule out other malignancies, but as there is not highly sensitive or specific marker for MPM, at least two carcinoma markers (e.g., pCEA BER -EP4, MOC -31, Claudin 4, HEG1) and two mesothelial markers (WT1, calretinin, CK5/6, D2- 40) are recommended (6). While the positivity of some IHCs such as pancreatin, CK5/6, calretinin and WT-1 can support a mesothelioma diagnosis, CEA, CD15 and TTF-1 are generally negative in MPM (7). Our case was positive for CK5/6, calretinin and WT-1, and negative for TTF-1, similar to previous studies in literature.

PET-CT is useful for staging MPM based on the evaluation of the pleural surface, lymph nodes, contralateral lung and distant metastases (6). In our case, the preoperative CT findings did not suggest MPM. Moreover, autologous blood pleurodesis complicated the evaluation of the pleural surfaces. Despite intraoperative explorations revealing multiple lesions on both the visceral and parietal pleura, there was no pathologic 18 F-FDG uptake on postoperative PET-CT which we attributed to the low-grade mesothelioma of our patient.

A multimodal approach is recommended for the treatment of MPM, including surgery, neoadjuvant and/or adjuvant chemotherapy, and radiotherapy. After the surgical removal of the tumor (pleurectomy/decortication,

extrapleural pneumonectomy), local recurrence can be controlled with radiotherapy, and distant metastases and micrometastases with chemotherapy (2,6). Our case is receiving neoadjuvant chemotherapy, and upon completion, extrapleural pneumonectomy is planned.

A review of literature related to cases of MPM presenting with pneumothorax suggests that all histological variants of MPM (epithelioid, sarcomatoid and mixed type) may be involved in the etiology, although it is worthy of note that most cases presenting with pneumothorax have an epithelioid-type MPM (1,3,7-11) (Table- 1). Ours is the 37th case to be presented to literature in English, in which six are undefined in terms of type, while 24 (64.86%) are the epithelioid type. Epithelioid-type MPM is the most common in all cases, with a slowly increasing prevalence (5). Some patients may present with such rare manifestations of the disease before the typical common symptoms of MPM occur.

CONCLUSION

MPM is an aggressive form of pleural neoplasia with a poor prognosis that can manifest alongside such rare conditions as spontaneous pneumothorax. A histopathological examination is necessary for the definitive diagnosis, and while thorax CT can support a diagnosis, trauma or previous autologous blood pleurodesis may mask CT findings. Patients of advanced age with recurrent pneumothorax attacks and challenging prolonged air leakage despite appropriate treatment should be questioned for risk factors of MPM, and surgical exploration should not be avoided, even if there are no apparent findings from imaging studies. Pneumothorax as the first sign is likely to point to the epithelioid subtype of the condition.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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A Case of Mesenchymal Tumor Developing on the Background of Congenital Pulmonary Airway Malformation

Konjenital Pulmoner Havayolu Malformasyonu Zemininde Gelişen Mezenkimal Tümör Olgusu

Tarık Kılıç, Şehmus Işık, Hadice Selimoğlu Şen

Abstract

Congenital pulmonary airway malformations are rare developmental lung anomalies, five types of which have been classified by Stocker. The condition is generally diagnosed prenatally during routine prenatal ultrasonography, however, some cases are asymptomatic and so may not be diagnosed until later in life. Clinically, the condition can present in newborns with shortness of breath, cyanosis and respiratory distress, and may lead to recurrent infections in later ages, and malignant transformations have been defined in literature. Here, we present a case that may be of interest to literature not only due to the diagnosis later in life, but also due to the development of a mesenchymal tumor in the background.

Keywords: *Congenital pulmonary airway malformation, Mesenchymal Tumor, Bronchopulmonary Sequestration.*

Öz

Konjenital pulmoner havayolu malformasyonu nadir görülen ve akciğerin gelişimsel bir anomalisidir. Stocker tarafından sınıflandırılmış olup beş tipe ayrılmıştır. Genellikle, prenatal rutin ultrasonografi sayesinde tanı bu dönemde konur. Ancak bazı olgular asemptomatik seyrettiği için ileri yaşa kadar tanı almayabilir. Klinik olarak, nefes darlığı, siyanoz ve yenidoğan döneminde respiratuar distress ile prezente olabilir. İleri yaşta tekrarlayan enfeksiyonların nedeni olabilir. Malign transformasyon literatürde tanımlanmış bir antitedir. Olgumuz hem ileri yaşta tanı almış olması hem de mezenkimal tümör gelişimi nedeniyle literatüre katkı sağlamak için sunuldu.

Anahtar Kelimeler: *Konjenital Pulmoner Havayolu Malformasyonu, Mezenkimal Tümör, Bronkopulmoner Sekestrasyon.*

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Congenital pulmonary airway malformations (CPAM), formerly known as congenital cystic adenomatoid malformations, are developmental lung anomalies that are generally diagnosed prenatally during routine ultrasonography scans, although diagnoses may be made incidentally or secondary to recurring infections at later ages. Bronchopulmonary sequestration, bronchogenic cyst and congenital diaphragmatic hernia should be considered in the differential diagnosis of CPAM. We consider this case to be of interest to literature due not only to the later-life diagnosis, but also the mesenchymal tumor that developed in the background of the patient's pre-existing disease.

CASE

A 52-year-old female patient with essential thrombocythemia and hyperthyroidism was referred to our clinic with clubbed fingers and shortness of breath. We were informed of a history of long-term shortness of breath and a cough for the last five months, although the patient reported no phlegm, hemoptysis or chest pain. The patient had a 30-pack/year smoking history but had quit 5 years earlier. SpO_2 was 97% in room air. A respiratory system examination revealed drastically decreased respiratory sounds in the right lung, and an analysis of the patient's medical records revealed that the results of a thoracic computed tomography (CT) performed in previous years indicated cystic adenomatoid malformation (Figure 1). A new tomography scan was carried out, and a pulmonary function test was performed due to the increase in symptoms at that time. An obvious restriction was identified in a pulmonary function test (PFT): FEV1/FVC: 75%, FEV1: 0.99 L (38% Pred), FVC: 1.33 L (40% Pred), while a thoracic CT revealed a mass lesion with calcific components on the right hemithorax (Figure 2). The patient was referred to the interventional radiology department, where a Tru-Cut biopsy was performed on the lesion revealing a spindle cell mesenchymal mass lesion. PET-CT revealed a slightly increased FDG uptake and an SUVmax value of 3 in the mass, which measured 183 × 173 × 215 mm in size with calcification to the wall and partial cystic necrotic areas in the lower lobe of the right hemithorax, but no significant FDG uptake in extrapulmonary areas. The patient underwent surgery in a different medical facility during which a mass lesion weighing approximately 3.5 kg was removed (Figure 3). The pathology results showed mesenchymal tumor proliferation with hamartomatous/teratomatous components. The tumor's diameter, the presence of necrosis and the distinct proliferation of spindle cells across larger areas indicated low-grade sarcomatous development, and the patient was recommended for follow-up. A postoperative thoracic CT revealed the right lung to be fully opened other than the tissue defects associated with surgery and postoperative changes (Figure 4). PFT revealed FEV1/FVC: 81%, FEV1: 2.42 L (94% Pred), FVC: 3.00 L (92% Pred). The patient's shortness of breath improved considerably and did not worsen during follow-up, which is continuing at our center.

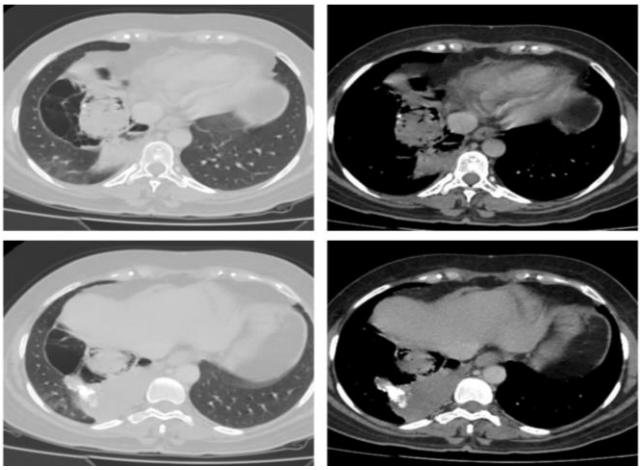

Figure 1: *Cystic adenomatoid malformation in the lower lobe of the right lung*

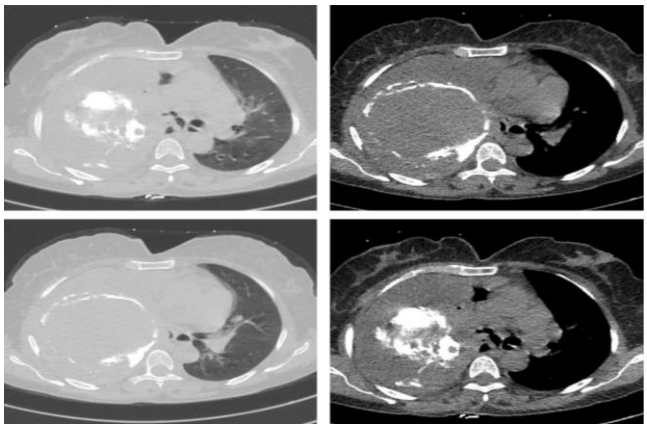

Figure 2: *Mass with calcific components in the right hemithorax*

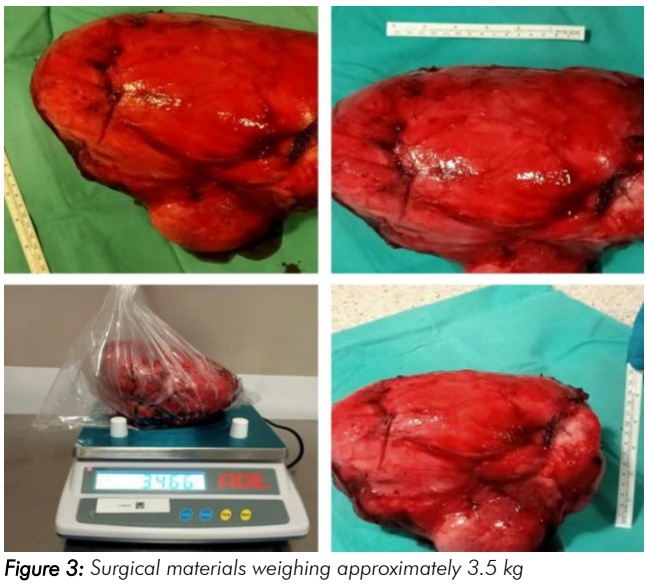

Figure 3: *Surgical materials weighing approximately 3.5 kg*

DISCUSSION

CPAM is a rare developmental lung anomaly that is seen in one in every 10,000–35,000 live births (1). It is generally diagnosed during prenatal scans in the 18th–20th weeks of pregnancy. Stocker put forward three classifications of congenital adenomatoid cystic malformations in 1977 (2) and added two further types in 2002 and updated the name of the disease to CPAM (3). It results from type 0 trachea or main bronchus. It is the most rarely observed type and is fatal. Type 1 is the most frequently encountered form, which develops in the distal and proximal bronchi, and accounts for 50–70% of all CPAM cases. Type 2 emerges from the terminal bronchioles and accounts for 15–30% of all cases, while type 3 originates in the alveoli and is considerably rare, developing as cysts that are microscopic in size and look like solid masses. Finally, type 4 also originates in the alveoli and presents multiple larger cysts.

A differential diagnosis of CPAM should consider bronchopulmonary sequestration, bronchogenic cysts and congenital diaphragmatic hernia, among which bronchopulmonary sequestration is most important, involving non-functional lung tissue fed by systemic circulation, and generally located in the lower lobes of the lung. Differentiating bronchopulmonary sequestration from CPAM can be challenging. Bronchogenic cysts occur with abnormal branching of the tracheobronchial tree. The least likely differential diagnosis, on the other hand, is congenital diaphragmatic hernia (4).

CPAM can be asymptomatic but can also present with shortness of breath, cyanosis and respiratory distress in newborns and infants, and can both be found incidentally in asymptomatic adults and as the source of recurring infections (5).

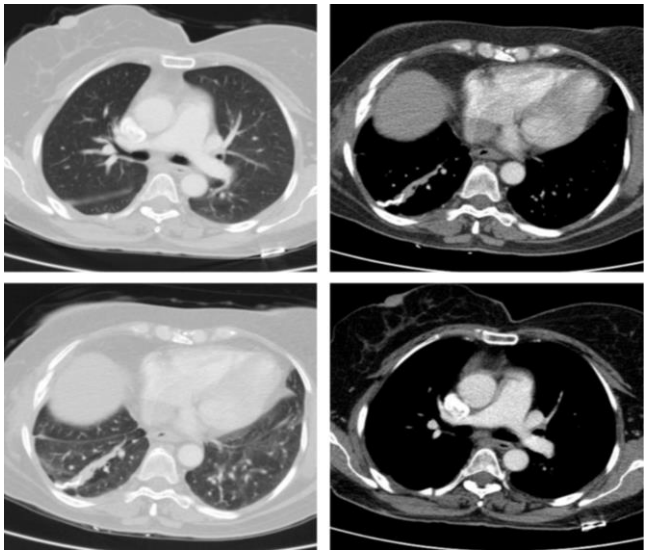

Figure 4: *Changes in sequela on postoperative thoracic CT*

The development of malignancy with CPAM has been defined in literature. Kaslovsky et al. (6) reported the development of bronchoalveolar carcinoma in a patient with type 1 CPAM who underwent an incomplete resection. Benouaich et al. (7) made a diagnosis of mixed bronchoalveolar and papillary adenocarcinoma after carrying out a surgical intervention on a 77-year-old patient with CPAM. Granata et al. (8) identified bronchoalveolar carcinoma in eight CPAM patients and rhabdomyosarcoma in five patients with CPAM. Our patient, who had long-term dyspnea and was diagnosed late, developed sarcomatous tumors, and her complaints improved significantly after surgery. Her follow-up is continuing.

We present this case to literature due to her development of a low-grade mesenchymal tumor that is rarely described in the literature.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - T.K., Ş.I., H.S.Ş.; Planning and Design - T.K., Ş.I., H.S.Ş.; Supervision - T.K., Ş.I., H.S.Ş.; Funding - T.K., Ş.I., H.S.Ş.; Materials - T.K., Ş.I., H.S.Ş.; Data Collection and/or Processing - T.K., Ş.I., H.S.Ş.; Analysis and/or Interpretation - T.K., Ş.I., H.S.Ş.; Literature Review - T.K., Ş.I., H.S.Ş.; Writing - T.K., Ş.I., H.S.Ş.; Critical Review - T.K., Ş.I., H.S.Ş.

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A Case of Primary Ciliary Dyskinesia Syndrome with Situs Ambiguous

Situs Ambigous'lu Primer Siliyer Diskinezi Olgusu

Deniz Bilici[1], Coşkun Doğan[1], Elif Yilmaz Gulec[2], Hatice İrem Uzun[1]

Abstract

Primary ciliary dyskinesia (PCD) is a rare autosomal recessive disease that develops as a result of ciliary dysfunction, and that presents with clinical findings that may vary depending on the affected system. Situs anomalies are common with PCD. Although approximately half of all cases are associated with situs inversus totalis, they may rarely be associated with situs ambiguous, which is a rare situs anomaly. We share this case of PCD with situs ambiguous due to its rarity.

Keywords: *Congenital anomalies, DNAAF3 gene mutation, primary ciliary dyskinesia, situs ambiguous.*

Öz

Primer siliyer diskinezi (PSD) nadir görülen, otozomal resesif geçişli, siliyer fonksiyon bozukluğu sonucu gelişen, etkilenen sisteme göre değişen klinik bulgular ile karşımıza çıkan bir hastalıktır. PSD ile birlikte situs anomalileri sık görülür. Olguların yaklaşık yarısı situs inversus totalis ile birlikte iken, nadir görülen bir situs anomalisi olan situs ambiguousun eşlik etmesi az rastlanılan bir durumdur. Nadir görülmesi sebebi ile situs ambiguouslu PSD olgusunu paylaşıyoruz.

Anahtar Kelimeler: *Konjenital anomali, DNAAF3 gen mutasyonu, primer siliyer diskinezi, situs ambigous.*

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Primary ciliary dyskinesia (PCD) is a rare hereditary disorder associated with impaired ciliary function. Normal ciliary function is important for respiratory host defense and sperm motility and ensures proper visceral orientation during embryogenesis (1). Congenital anomalies such as transpositions of great vessels, heterotaxia, cardiac anomalies, infertility and chronic respiratory tract infections may occur as a result of abnormal ciliary function (ciliary immotility or dyskinesia) (2).

During embryogenesis, monociliums in the embryonic nodes (9+0) cause the nodal current of the extra-embryonic fluid (to the left). The nodal current is behind the left-right body asymmetry and deteriorates in cases with abnormal ciliary structures and functions, and in the absence/inactivity of monocilia, allowing thoracoabdominal orientation to develop randomly. In this regard, derogated ciliary motility during embryogenesis leads to the transposition of thoracic and abdominal organs (3).

PCD is classified based on the accompanying situs anomaly, with situs solitus, situs inversus and situs ambiguous (SA) being the three most common situs anomalies. Organs show settlements in the body without complying with a specific order, and SA is a more serious disease than situs inversus, as 90–99% of patients with SA have cardiac anomalies (4,5).

We present here a rare case of PCD with SA diagnosed in adulthood.

CASE

A 31-year-old female patient presented to the emergency department with a recent increase in such symptoms as shortness of breath, cough and sputum, which had been present for the last 10 years. Her medical history included subaortic resection surgery due to a subaortic membrane in childhood, and frequent upper and lower respiratory tract infections since childhood, while her family history revealed her parents to be the children of two sisters. She had a 10-pack/year smoking history. An examination of her respiratory system revealed bilateral, middle and basal rhonchi and right basilary lung crepitations on auscultation, while laboratory findings were as follows: white blood cell count: 12,400/uL, hemoglobin: 12.1 gr/dL, platelet count: 234,000/uL, C-reactive protein: 80.16 mg/L and procalcitonin: 0.07 μg/L, while all other biochemical laboratory findings were unremarkable. A postero/anterior chest X-ray (PA) revealed left tracheal and mediastinal deviation, diffuse bronchiectasis in the left lung, increased air volume in the left lung and heterogeneous opacities in the right lower zone (Figure 1A). A chest computed tomography (CT) scan revealed the heart and mediastinum to be displaced to the left, diffuse atelectasis in the left lung, cystic and tubular bronchiectatic changes in both lung fields and bilateral pleural effusion (Figure 1B).

The patient was admitted to the chest diseases clinic, sputum cultures were obtained and *Haemophilus parahaemolyticus* was isolated, leading to the patient being started on broad-spectrum antibiotics and bronchodilators.

A further investigation for congenital lung diseases was planned due to the history of frequent childhood respiratory tract infections and great vessel operations, and the identification of bronchiectasis and organ location anomalies on thorax CT.

An abdominal CT also revealed left isomerism (polysplenia syndrome), inferior vena cava on the left side of the aorta, a midline position of the liver, and a direct opening of the hepatic veins to the right atrium. and a spleen location in the lower right quadrant. Also observed were appearances compatible with multiple splenosis, the largest of which was 75x40 mm in size (Figure 1C-D). The abdominal CT was reported in accordance with SA. A Waters radiograph taken for the assessment of a chronic upper respiratory tract infection revealed air-fluid levels and poor visualization of the air spaces in the right maxillary sinus, while a paranasal sinus CT revealed mucus retention cysts and mucosal thickenings in the paranasal sinuses (Figure 1E-F).

Echocardiography (ECHO) of the patient, who had a history of cardiovascular surgery, revealed stage-1 left ventricular dysfunction, left atrial dilatation, an LVOT obstruction in systole due to basal septum hypertrophy (1.6 cm) and a mitral valve obstruction (73/50 mmHg), coronary sinus dilatation, pulmonary hypertension (systolic pulmonary artery pressure [sPAP]: 55 mmHg), middle aortic valve insufficiency and mild mitral valve regurgitation.

Genetic consultation and analysis were requested, and the reported result was "consistent with PCD, a homozygous variant of NM_001256715.1:c.912+2T>A splice_donor_+2 was observed in DNAAF3 gene". The patient was discharged after her symptoms reduced significantly following treatment.

DISCUSSION

PCD almost always originates from mutations in genes related to cilia or ciliary movement, and so chronic sinopulmonary infections are usually the predominant clinical finding with this syndrome. PCD is classified according to the presence of concomitant situs anomalies, and the association of SA with DNAAF3 gene mutations is a less common condition than other situs anomalies. This rare case of PCD is presented to literature as PCD is usually diagnosed in childhood, and due to the rare gene mutation accompanying SA.

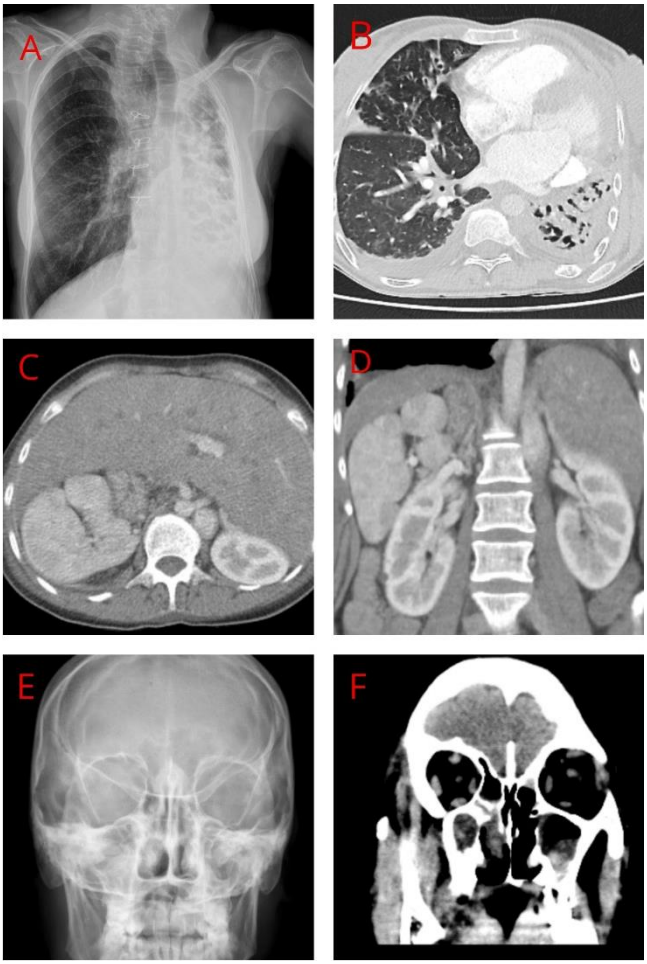

Figure 1: *Chest X-ray (PAAG) showing left tracheal and mediastinal deviations, diffuse bronchiectasis in the left lung, increased air volume in the left lung and heterogeneous opacities in the right lower zone* ***(A)****; A chest computed tomography (CT) scan revealing a displacement of the heart and mediastinum to the left, diffuse atelectasis in the left lung, cystic and tubular bronchiectatic changes in both lung fields, and bilateral pleural effusion* ***(B)****; Abdominal CT revealing the midline position of the liver and the right lower quadrant location of the spleen. Appearances compatible with multiple splenosis were also observed, the largest of which was 75x40 mm in size* ***(C, D)****; Water's radiography taken during an examination for a chronic upper respiratory tract infection showed air-fluid levels and poor visualization of air spaces in the right maxillary sinus, while paranasal sinus CT revealed mucus retention cysts and mucosal thickenings in the paranasal sinuses* ***(E, F)***

PCD is a genetically heterogeneous, typically autosomal recessive disease characterized by ciliary dysfunction and impaired mucociliary clearance. Every one of the ciliary cells that cover the apical cell surface of the upper and lower respiratory tracts contains hundreds of 9+2 microtubule cilia, creating the sweeping movement of mucus from the lower respiratory tract to the upper respiratory tract and out of the middle ear cavity. The reduced mucociliary clearance resulting from impaired ciliary movement can lead to chronic rhinosinusitis, chronic otitis media, recurrent lung infections, narrowing of the airways, chronic bronchitis and bronchiectasis, as well as infertility and sinus anomalies, and in rare cases, hydrocephalus may accompany (6). The case in the present study had bronchiectasis and recurrent rhinosinusitis. In the study by Hosie et al. (7) assessing 84 cases with PCD, 81% had chronic cough, 71% had rhinosinusitis and 49% had recurrent otitis media, while 32% had bronchiectasis at the time of admission. Based on the prevalence of SI and bronchiectasis, an incidence of PCD of around 1/16,000 births has been estimated (8). PCD can be diagnosed based on an ultrastructural examination of the nasal mucosa or bronchial brush biopsy specimens using electron microscopy, or from the detection of a mutation in one of the genes known to be associated with PCD. All abnormalities associated with PCD begin with mutations in the genes involved in cilia development or ciliary movement (9). In the early stages of embryogenesis, the position of the internal organs is determined, and asymmetry between the right and left sides of the body is normal, since the liver is on the right and the spleen is on the left. If a defect in asymmetry develops during embryogenesis, organ laterality defects called SI or SA, being mirror images of the situs, may develop (10). There are two subgroups of SA: SA with polysplenia, and SA with asplenia (11). In the presented case, SA polysplenia was identified, and an abdominal CT revealed the inferior vena cava to be located on the left side of the aorta, the midline positioning of the liver, a direct opening of the hepatic veins into the right atrium, and multiple splenosis, the largest of which was 75x40 mm in size. PCD is rarely accompanied by SA. In their study, Shapiro et al. (12) identified PCD in 12% of the 305 cases in their study, while Kennedy et al. (13) reported that 6.3% of the 337 cases with PCD in their study had SA, and of these cases, 143 (47%) had situs solitus, 125 (41%) had situs inversus totalis and 37 (12%) were in the SA group. One should keep in mind that situs anomalies like SA are commonly associated with congenital heart disease (CHD) (14). In a study by Kennedy et al. (13) reporting on 337 PCD cases, six (54.5%) of the 11 cases with left isomerism had polysplenia and cardiac/vascular anomalies, 12 (57.1%) of the 21 heterotaxia cases had cardiovascular malformations, four cases had only vascular abnormalities and eight had complicated cardiac anomalies requiring surgery. Our case had undergone surgery for a subaortic membrane. In cases with PCD, the risk of congenital heart disease due to heterotaxia has been reported to be 200 times greater than in the general population. It has been suggested that PCD is missing in many patients with heterotaxia and CHD (13,15).

Advances in DNA sequencing, genomics and proteomics in recent years have led to the identification of mutations in approximately 30 genes responsible for PCD cilia motility defects. DNAI1 and DNAH5 mutations are observed in more than 30% of cases, while mutations in the DNAAF1 and DNAAF3 genes have also been shown to

be associated with external dynein arm defects in cases with PCD (16,17). Furthermore, mutations in such genes as ZIC3, LEFTY, CRYPTIC and ACVR2B have been shown to play a role in cases of heart disease accompanying human heterotaxia syndrome (18). A genetic analysis of the case presented here revealed a mutation in the DNAAF3 (dynein axonemal assembly factor 3) gene that was first reported by Mitchison et al. (19), who suggested that this mutation caused immotile cilia as a result of the defects in both the inner and outer dynein arms, noting also left-right laterite defects in the DNAAF3 morphant embryo that were similar to the human situs inversus, thus showing the importance of the DNAAF3 gene in the movement of the cilia. DNAAF3 mutations in PCD patients were first reported by Guo et al. (20), identifying that condition in four cases with PCD, all of which had situs inversus, while our case had rare left isomerism with SA. The respiratory symptoms of Guo et al.'s cases were cough and sputum, as in the case presented here, although a computed tomography of the four cases revealed bronchiectasis in one case, localized consolidation in another, and no pathology in the lung parenchyma in the other two.

CONCLUSION

Based on the presented case of SA polysplenia accompanied by a rare PCD and an even rarer DNAAF3 gene mutation, we recommend that a diagnosis of PCD should be kept in mind in adults with frequent recurrent rhinopulmonary infections, even in the absence of situs inversus totalis.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - D.B., C.D., E.Y.G., H.İ.U.; Planning and Design - D.B., C.D., E.Y.G., H.İ.U.; Supervision - D.B., C.D., E.Y.G., H.İ.U.; Funding - H.İ.U., D.B.; Materials - H.İ.U., E.Y.G.; Data Collection and/or Processing - H.İ.U., E.Y.G.; Analysis and/or Interpretation - D.B., C.D.; Literature Review - D.B., C.D.; Writing - D.B., C.D.; Critical Review - C.D.

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