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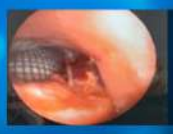

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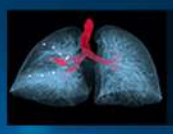

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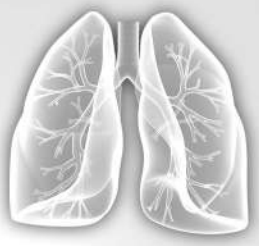

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Viewing from both Sides: Tracheoesophageal Fistula

İki Taraftan Bakış: Trakeoözafegeal Fistül

Oğuz Karcıoğlu[1], Serkan Uysal[2], Ulaş Kumbasar[2], Fuad Mustafayev[3], Ziya Toros Selçuk[1]

Abstract

Non-malignant tracheoesophageal fistulas in adults often occur due to complications after intubation. We present an 80-year-old female patient who was consulted because of fever and increased thicky secretions that need frequent aspiration. An intracranial hemorrhage 3 months earlier led to her undergoing a tracheostomy and gastrostomy due to the resulting prolonged intubation and nutritional issues. Both bronchoscopy and endoscopy confirmed the presence of a tracheoesophageal fistula (TEF) detected on computed thorax tomography. In bronchoscopy, TEF, which was opened and closed by both overinflated cuff and esophageal contractions, was observed. She was not a candidate for surgery, and her relatives declined an esophageal stent placement. We managed the case by sending a jejunostomy catheter through the gastrostomy tube and positioning at least 45 degrees to minimize the reflux.

Key words: *Tracheoesophageal Fistula, Cuff, Overinflation, Pneumonia, tracheostomy.*

Öz

Erişkinlerde malign olmayan trakeoözofageal fistüller genellikle entübasyon sonrası komplikasyonlar nedeniyle ortaya çıkar. Üç ay önce kafa içi kanama sonrası uzamış entübasyon nedeniyle trakeostomi ve beslenme sorunları nedeniyle gastrostomi öyküleri olan 80 yaşında kadın hasta tekrarlayan ateş ve yoğun kıvamlı sekresyon artışı nedeniyle başvurdu. Bilgisayarlı toraks tomografisinde saptanan şüpheli trakeoözofageal fistül (TÖF) bronkoskopi ve endoskopi ile doğrulandı. Bronkoskopide hem fazla şişirilmiş cuff hem de özefagus kasılmalarıyla açılıp kapanan TÖF izlendi. Ameliyata uygun bulunmayan hastaya stent yerleştirilmesi hasta yakınların tarafından kabul edilmedi. Hasta gastrostomi hattından jejunostomi kateteri gönderilerek ve reflüyü engellemek için en az 45 derece dik konumda tutulması önerileriyle taburcu edildi.

Anahtar Sözcükler: *Trakeoözefageal Fistül, Cuff, Overinflasyon, Pnömoni, Trakeostomi.*

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A tracheoesophageal fistula (TEF) is an abnormal connection between the trachea and esophagus that links the respiratory and gastrointestinal systems, which are physiologically blocked by a properly functioning epiglottis in normal situations. There are both malignant and benign conditions that can cause TEF, and the most common causes are prolonged intubation followed by iatrogenic injuries, traumas and infections. The timely diagnosis and management of TEF is vital due to such potentially grave complications as recurrent lower respiratory tract infections (LTRI), malnutrition, weight loss and dyspnea (1). We present here a case who developed TEF after a tracheostomy.

CASE

An 80-year-old female patient was referred with increased purulent and thicky secretions from the tracheostomy cannula. Her previous medical history included hypertension, coronary artery disease, atrial fibrillation and chronic obstructive lung disease. She had fallen and hit her head after experiencing dizziness three months earlier and was admitted to the emergency room with left hemiparesis, confusion and sleepiness. A cranial tomography revealed a 43x70mm hematoma and surrounding edema at the left temporal lobe, a 5 mm subdural hemorrhage and an 8 mm shift to the right. A craniotomy was performed to remove the hematoma, and a tracheostomy due to prolonged intubation in the intensive care unit. A percutaneous gastrostomy (PEG) was also performed to provide adequate nutrition. After a while, the patient complained of copious secretions from the tracheostomy cannula and fever, suggesting aspiration.

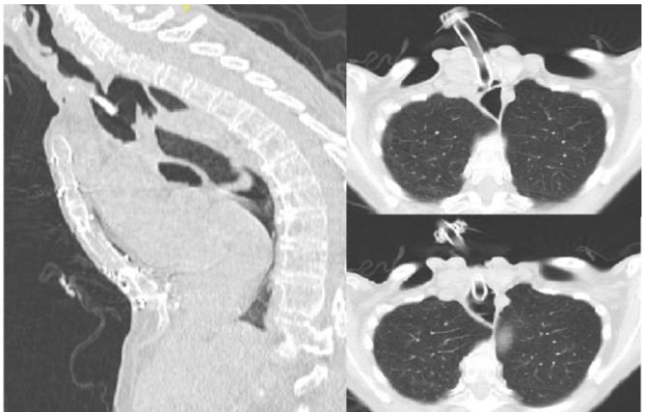

Figure 1: Computed tomography section showing tracheoesophageal fistula

Computed chest tomography revealed a TEF approximately 18 mm in length and 16 mm in width at the upper esophagus, above the tracheostomy cannula (Figure 1). Since her tracheostomy cannula was too narrow for a bronchoscope, we approached via the nasal route, which allowed us to view the aforementioned TEF above the right side of the overinflated cuff that was opening and closing with the esophagus muscle contractions (Video 1▶). An endoscopy revealed the fistula and the tracheostomy cuff (Video 2▶). The fistula was oval-shaped, and there was no stenosis in either the trachea or esophagus. Surgery was not considered due to multiple comorbidities, and we opted not to place a tracheal stent as there was no stenosis and the tracheostomy cannula was providing adequate ventilation. The patient declined an esophageal stent placement. A jejunostomy catheter was passed through the PEG and was advanced to the jejunum (PEG-J) to minimize the reflux. We recommended that the patient be positioned at least 45 degrees, anti-reflux medication and frequent suctioning of the tracheostomy cannula.

DISCUSSION

TEF is a rare complication of percutaneous tracheostomy that may be associated with an injury to the posterior tracheal wall adjacent to the esophagus during the procedure, chronic irritation of the tracheal wall by the tracheostomy tube or an overinflated cuff (2). A concomitant nasogastric tube in patients unable to feed orally increases the risk of complications (3). Co-existing diseases such as diabetes mellitus, acute infections, malnutrition and radiation, and drugs including steroids and bevacizumab may facilitate the development of a TEF (1,4).

The determination of a TEF is crucial since spontaneous closure is rare except for small fistulas. The inspection of fistula by bronchoscopy and/or endoscopy is required when imaging techniques such as barium esophagography and computed tomography suggest the presence of a TEF in suspected patients. Although the majority can be detected by direct visualization, the diagnosis of small fistulas may be challenging due to the accompanying local erythema, edema and musculature of the esophagus. They are typically round in shape, and open between the posterior wall of the trachea and the esophagus, and may appear and disappear with swallowing.

The main purposes of the treatment are ensuring the patency of the airways and protecting the lungs from aspiration, while allowing swallow of at least saliva. It is essential to view the defect from both sides, as in the present case, since treatment options can be performed via both tubes. Direct visualization will allow the size, shape and localization of the fistula to be determined, and the identification of tracheal or esophageal obstructions, thus guiding management. The treatment approach should be decided upon based on the cause, size and location of the TEF, whether the patient's surgical treatment is appropriate and survival expectancy (5). Curative surgery aims the treatment of benign TEF in suitable patients. In patients who are not candidates for surgery, stent placement, occlusive treatments (fibrin glue, silicon rings), and endoscopic clips may be considered, depending on the location and size of the lesion (1,6). When none of these methods are appropriate for the patient, PEG-J should be kept in mind for the minimization of reflux. Regardless of the chosen treatment modality, respiratory failure requiring positive pressure ventilation is the worst possible scenario, as this will hinder the healing of the treatment site, and will also result in the distention of the stomach by air, resulting in further respiratory deterioration.

General measures including bed elevation, anti-reflux treatment, aspiration of secretions, adequate nutrition and the effective treatment of possible infections are also crucial for the management of patients.

CONCLUSION

TEF is a rare but severe complication of tracheostomy in which the key symptoms are cough during feeding, dyspnea, gastric distension, increased airway secretions, recurrent LTRI and weight loss. Although they are unlikely to be curative, PEG and PEG-J can prevent the progression of the lesion.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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RESPIRATORY CASE REPORTS

Tracheoesophageal Fistula Associated with Nivolumab

Nivolumab İlişkili Trakeaözefagial Fistül

Ayşe Bahadır, Sibel Yurt, Mehmet Akif Özgül, Muhammet Atıf Karagöl, Levent Arafat

Abstract

Tracheoesophageal fistula (TEF) is a pathological connection between the trachea and the esophagus that can be congenital or can develop in older ages as a result of benign or malignant causes. It develops as a result of mediastinal invasion or after chemoradiotherapy in lung and esophageal cancers, and is associated with high mortality and morbidity. TEF has been reported in the past to be a rare side effect of immune control inhibitor (ICI) drugs used for the treatment of non-small cell lung cancer, and several cases have been reported. A 78-year-old patient who underwent a left pneumonectomy after being diagnosed with NSCLC one year earlier had a history of esophageal stenting and Nivolumab use two months previously to relieve the pressure of a mediastinum mass invading the esophagus that was causing dysphagia in the patient. The patient developed TEF in the first week of hospitalization, which was thought to be a side effect of the ICI drugs. Our case, who was thought to place a stent in the trachea, died after developing massive hemoptysis. We present this case of the development of TEF to literature due to its rarity as a side effect of ICI drugs.

Key words: *Tracheoesophageal fistula, lung cancer, immunotherapy.*

Öz

Trakea ve özafagus arasında patolojik bir bağlantı olması trakea-özafagiyal fistül (TÖF) olarak adlandırılır, doğuştan veya bening ya da maling nedenlere bağlı sonradan oluşabilmektedir. TÖF, akciğer ve özefagus kanserlerinde kemoradyoterapi sonrası veya mediastinal invazyon nedeni ile gelişen, yüksek morbidite ve mortaliteye neden olan bir komplikasyondur. Son yıllarda Non-small cell akciğer kanseri (NSCLC) tedavisinde immun kontrol inhibitör (ICI) ilaçların kullanımının artışına bağlı nadir görülen yan etkiler ortaya çıkmakta ve olgu bazında bildirilmektedir. Yetmiş sekiz yaşında bir yıl önce NSCLC tansı ile sol pnömonektomi olan olgumuzda mediastene invaze kitlenin özafagusa basısına bağlı disfaji nedeni ile iki ay önce özafagusa stent uygulama ve nivolumab kullanım öyküsü vardı. Yatışının ilk haftasında hastada TÖF gelişti. Trakeaya stent yerleştirilmesi düşünülen olgumuz, masif hemoptizi gelişmesi nedeni ile eksitus oldu. Ayırıcı tanı sonrası ICI ilaça bağlı yan etki olarak TÖF geliştiği düşünüldü. Nadir bir yan etki olarak görülmesi nedeni ile olgumuzu literatür bilgileri ile sunmak istedik.

Anahtar Sözcükler: *Trakeaözefagial fistül, akciğer kanseri, immunoterapi.*

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Tracheoesophageal fistula (TEF) refers to a pathological connection between the trachea and the esophagus that can occur congenitally or later in life, and to have benign or malignant causes (1). TEF, which develops due mediastinal invasion or chemoradiotherapy in lung and esophageal cancers, is associated with high mortality and morbidity. In recent years, immunotherapy has been the standard treatment for melanoma, renal cell carcinoma, Hodgkin lymphoma, bladder, head and neck cancers and lung cancer (2,3), and the use of immunocontrol drugs such as nivolumab has become widespread. In addition to the pulmonary toxicities associated with drugs, rare side effects such as TEF can also be seen. The identification of such life-threatening side effects as TEF in the future will be possible through awareness-raising activities.

CASE

A 78-year-old male patient presented to the emergency department with a complaint of increasing dyspnea for two months. The patient had been a 50 pack-year smoker, but had quit one year earlier. The patient's diabetes was under control, but underwent a left pneumonectomy operation one year earlier for the treatment of non-small cell lung cancer, followed by chemoradiotherapy in the postoperative period. Two months before presenting to our facility the patient had been fitted with a stent in the esophagus to ease his dysphagia and he had been treated with nivolumab since. Five days after hospitalization, the patient's complaints of cough, sputum and shortness of breath increased. A thorax CT, revealed air-fluid level on the left. A tracheoesophageal fistula was observed on the esophageal stent at the level of the carina (Figure 1). The patient was operated with FOB, during which it was found that the stent in the middle 1/3 of the esophagus had eroded the tracheal wall and caused a complete opening into the trachea. Stent placement in the trachea was planned with rigid bronchoscopy (Figure 2), however, the patient died due to the sudden onset of hemoptysis.

DISCUSSION

We present here to literature a rare case of a tracheoesophageal fistula (TEF) caused by Nivolumab – an ICI drug used for the treatment of non-small cell lung cancer. TEF associated with malignancies is a complication with high mortality and morbidity, and generally develops as a side effect of lung cancer, cancer invasion into the mediastinum, or as a side effect of chemoradiotherapy during the treatment of cancer of the esophagus (1).

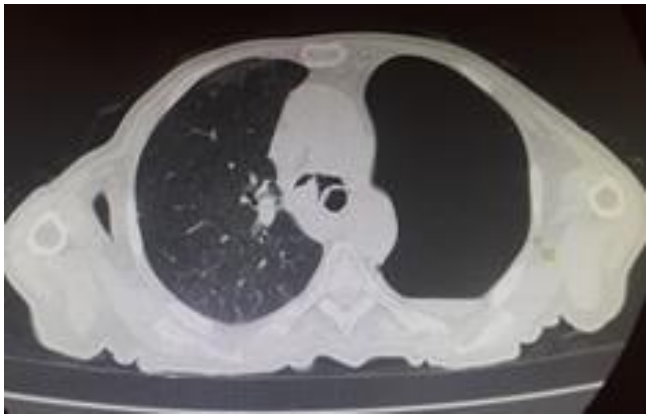

Figure 1: *Thorax CT*

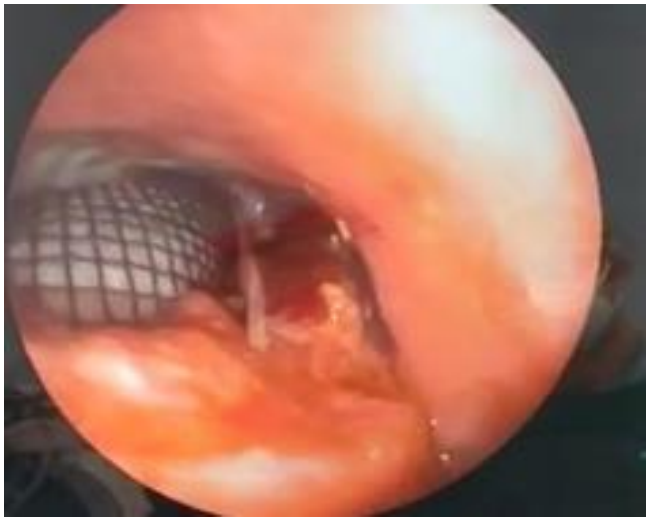

Figure 2: *FOB imaging*

TEF has been reported in 4.5% of esophageal cancers and in 0.3% of lung cancers (4). The male/female ratio is 3/1, and the most common symptoms are cough, aspiration, fever and dysphagia. The fistula localization site is most often in the trachea 53%, left main bronchus 22% and right main bronchus 16%. (5) The European Society of Gastrointestinal Endoscopy recommends the use of metallic coated stents for the treatment of dysphagia due to lung cancer. (1)

In our case, a metal-covered stent had been fitted 2 months earlier due to dysphagia, and nivolumab treatment was started due to tumor progression. Nivolumab is a PD-1 monoclonal inhibitor that was one of the first immune control drugs to be approved for the treatment of small- and non-small cell lung cancer, and it has been widely used in recent years. (3)

Although pulmonary toxicity due to immunocontrol drugs (ICI) is frequently reported in literature, the development of TEF is rare and is reported as a case report (2). The development of a bronchomediastinal fistula was reported in a patient receiving durvalumab following chemora-

diotherapy in stage-3 NSCLC, while the development of TEF due to pseudoprogression and metastatic mediastinal LAM was reported in a patient diagnosed with lung adeno carcinoma who was undergoing nivolumab therapy (6,7).

Pseudoprogression is defined as tumor growth or the development of new foci when the general situation of the patient is stable, with an incidence rate of 3.4–6.9% reported in patients using PD-1 inhibitors for the treatment of non-small cell lung cancer. (8)

Pseudoprogression was not considered in the present case since the patient's general situation did not improve with stent placement and immunotherapy, and there was no growth in the mass invading the mediastinum.

In a retrospective study of stent placement failures in patients with esophageal stents due to benign or malignant reasons, stent over 12 cm in length, stent placement in the 1/3 mid-esophageal area, and dilation before stent placement were reported as risk factors. In the same study, the risk of perforation was 3.3%, the development of fistula was reported to be 2.5–7.9% and the stent failure time was reported to be an average of 75 days after placement (9).

Our case, who had DM, had a 4 cm fistula located in the center of the lateral wall trachea middle part of trachea. The presence of DM, the stent placement in the middle esophagus and presence of a mass invading the mediastinum were risk factors for fistula development in the present case. The length of the stent was shorter than 12 cm and had been fitted approximately 2 months earlier, and no ICI-related pseudoprogression was detected. After excluding differential diagnoses, it was concluded that the TEF may have developed as a side effect of the ICI treatment.

The development of ICI-induced fistula is thought to be a result of avascular necrosis or small vessel vasculitis developing into ischemia. It has been reported that the stent itself can cause tissue hyperplasia and inflammatory cell infiltration in patients with an esophageal stent, and that these factors in combination may lead to the development of fistula in patients with a stent undergoing ICI treatment. (6) TEF is diagnosed based on radiology and endoscopic procedures, and requires a multidisciplinary approach that includes interventional pulmonology, gastroenterology and thoracic surgery. Survival after a TEF diagnosis is usually less than 3 months. Comorbidities such as DM, airway infection, steroid use, and the presence of a nasogastric tube increase the risk of TEF. The clinical course varies depending on the size and localization of the tracheoesophageal fistula, comorbidity and immunological status of the patient. (10) Our case had diabetes mellitus and a 4 cm fistula in the lateral wall of the central third of the trachea. A bilateral stent placement in both the esophagus and the trachea is recommended for treatment (1). As our patient had an esophagus stent, it was planned to apply a stent to the trachea, however the patient died from a sudden massive hemoptysis. Survival after the placement of an esophageal stent was 2 months in the patient, which was consistent with previous studies.

It should be kept in mind that a tracheoesophageal fistula may develop in the presence of such facilitating factors as mediastinal invasion, CRT prior to ICI treatment (which has recently gained popularity for the treatment of NSCLC in recent years), comorbidities such as DM, steroid therapy and mediastinal invasion. In patients with esophageal or tracheal stents, follow up should be taken in the treatment and follow-up of ICI in terms of the risk of fistula development.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

YAZAR KATKILARI

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Rothmund Thompson Syndrome: A Case Report Presenting with Aspiration Pneumonia

Rotmund Thompson Sendromu: Aspirasyon Pnömonisi ile Prezente Olan Bir Olgu

Halil İbrahim Yakar, Handan Inonu Koseoglu, Ahmet Cemal Pazarlı, Gökhan Aykun, Mustafa Parti, Hacer Kılınç

Abstract

In the few studies of Rothmund Thompson Syndrome (RTS) to date in literature, two clinical subforms have been identified: the RTS-I form, characterized by poikiloderma, ectodermal dysplasia and juvenile cataract; and the RTS-II form, characterized by congenital bone defects, increased risk of childhood osteosarcoma and skin cancer. We present here a case with the RTS-II form with bone deformities, history of skin cancer and growth retardation. The patient was admitted to our hospital with complaints of dyspnea for two days. Total atelectasis in the right lung and severe dilatation and obstruction in the distal esophagus were observed on a posteroanterior chest X-ray and thorax computed tomography, and antibiotherapy, oxygen therapy and supportive treatments were initiated after a diagnosis of aspiration pneumonia was made. Alveolar hemorrhage and hematuria developed during follow up due to bleeding disorder. Despite supportive treatment, the patient developed multiple organ failure (respiratory failure, renal failure, pancytopenia), and died on the 8th day of hospitalization. We present this case study to draw attention to the risk of bleeding tendency and aspiration pneumonia in RTS patients.

Key words: *Rothmund Thompson Syndrome, Aspiration Pneumonia, Esophageal Dilatation, Hemorrhage.*

Öz

Rothmund Thompson Sendromu (RTS) oldukça nadir görülen bir sendromdur. İki klinik alt formu tanımlanmıştır: poikiloderma, ektodermal displazi ve jüvenil katarakt ile karakterize RTS-I formu ve konjenital kemik defektleri, çocuklukta artmış osteosarkom ve cilt kanseri riski ile karakterize RTS-II formudur. Burada sunulan hasta, kemik deformiteleri, cilt kanseri öyküsü ve gelişme geriliği nedeniyle RTS-II formu idi. Hasta, iki gündür başlayan nefes darlığı ve hırıltı şikayeti ile hastanemize başvurdu. Posteroanterior akciğer grafisinde ve toraks bilgisayarlı tomografide sağ akciğerde total atelektazi, özefagusda ileri düzeyde dilatasyon ve özefagus distalinde obstrüksiyon izlendi. Aspirasyon pnömonisi tanısıyla, antibiyoterapi, oksijen tedavisi ve destek tedavi başlandı. Tedavi altında iken, kanama bozukluğu nedeniyle alveolar hemoraji ve hematüri gelişti. Destek tedaviye rağmen çoklu organ yetmezliği (solunum yetmezliği, böbrek yetmezliği, pansitopeni) gelişen hasta 8. günde exitus oldu. Olgu RTS hastalarında kanamaya eğilim ve aspirasyon pnömonisi gelişimine dikkat çekmek adına sunulmuştur.

Anahtar Sözcükler: *Rotmund Thompson Sendromu, Aspi¸rasyon Pnömonisi¸, Özefagus Dilatasyonu, Hemoraji.*

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Rothmund Thompson Syndrome is a very rare disease that has been reported on in 300 patients in literature (1). It was first described in 1868 by ophthalmologist Rothmund who observed growth retardation and rapidly progressive bilateral juvenile cataracts and poikiloderma in 10 children in a Bavarian village. In 1936, British dermatologist Thomson reported poikiloderma, skeletal defects, growth retardation in three children, but no cataracts. We present here as case of RTS with bleeding tendency who was diagnosed with aspiration pneumonia.

CASE

A 29-year-old female patient was admitted to our hospital with complaints of dyspnea after food intake. The patient had diagnosed hypothyroidism, esophageal dilatation and RTS, and a history of surgery to the right ankle due to skin cancer in childhood, and had undergone splenectomy and femoral fracture surgery three years earlier. A physical examination revealed mental confusion, decreased respiratory sounds in the right lung and sonor crackles in the left lung. Pulse 02 saturation was 70% and heart rate was 120/min. Radiopacity was observed due to total atelectasis in the right lung on a chest X-ray (Figure 1). Total atelectasis was observed in the right lung, the esophagus was noted to be severely dilated and the distal esophagus to be obstructed on thorax CT (Figure 2). Piperacillin tazobactam antibiotherapy, prophylactic dose anticoagulant, deep tracheal aspiration and respiratory physiotherapy were initiated with a diagnosis of aspiration pneumonia. Hematuria developed following the insertion of a catheter. The hemoglobin blood level was followed up and continuous irrigation was applied upon the recommendation of urology. The patient was intubated due to the lack of clinical or radiological improvement despite antibiotherapy and supportive treatment. After intubation, regression of the right atelectasis was noted on a control chest X-Ray (Figure 3), however, diffuse alveolar hemorrhage developed due to mechanical cleaning due to bleeding tendency (Figure 4). The patient received two units of fresh frozen plasma and three units of erythrocyte suspension due to pancytopenia and alveolar hemorrhage. Despite supportive treatment, multiple organ failure (respiratory failure, renal failure, pancytopenia) occurred and the patient died on the 8th day of hospitalization.

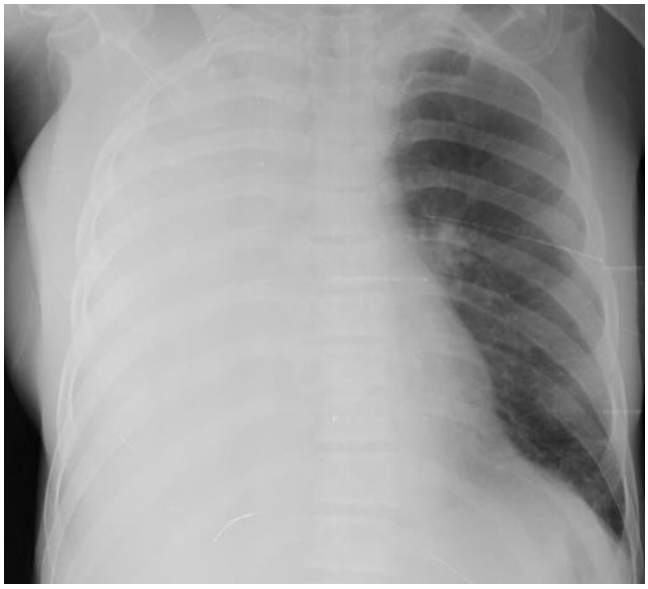

Figure 1: Total atelectasis of the right lung revealed on the initial chest X-Ray upon hospital admission

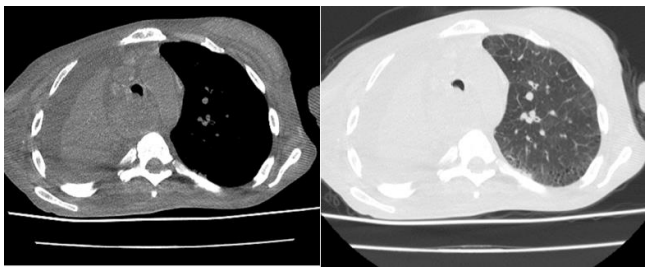

Figure 2: Atelectasis in the right lung and dilatation of the esophagus seen on Thorax CT

DISCUSSION

Two clinical subforms of RTS have been described in literature: the RTS-I form, characterized by poikiloderma, ectodermal dysplasia and juvenile cataracts; and the RTS-II form, characterized by congenital bone defects, an increased risk of osteosarcoma in childhood and skin cancer in adult life. While the RTS-II form is caused by homozygous or compound heterozygous mutations in the RECQL4 helicase gene, detected in 60–65% of RTS patients, the etiology of RTS-I is unknown (2). RECQ proteins are conserved DNA strands that act as helicases, and the RECQ helicase family plays a role in the regulation of aging while also acting as tumor suppressors. Mutations in RECQ4, one of the RECQ family proteins, therefore, not only result in developmental abnormalities and cancer predispositions, but also potentially premature aging. Patients with RTS-II are thus at risk of both advanced age cancer and signs of premature aging in the skin (3).

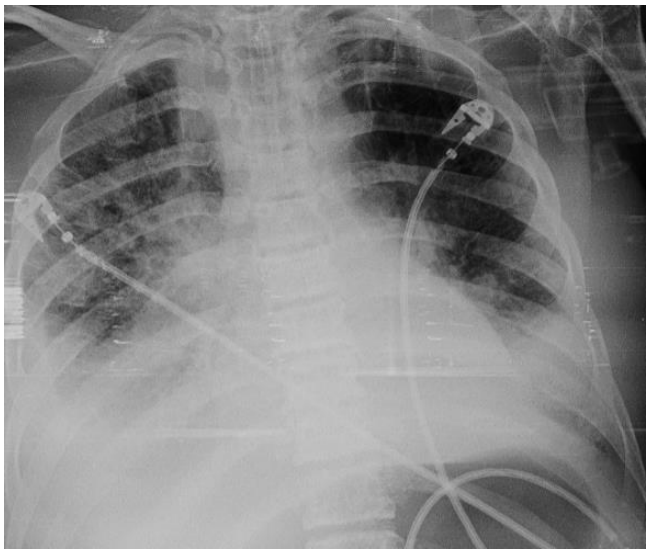

Figure 3: Recovery of atelectasis seen in the right lung one day after deep tracheal aspiration

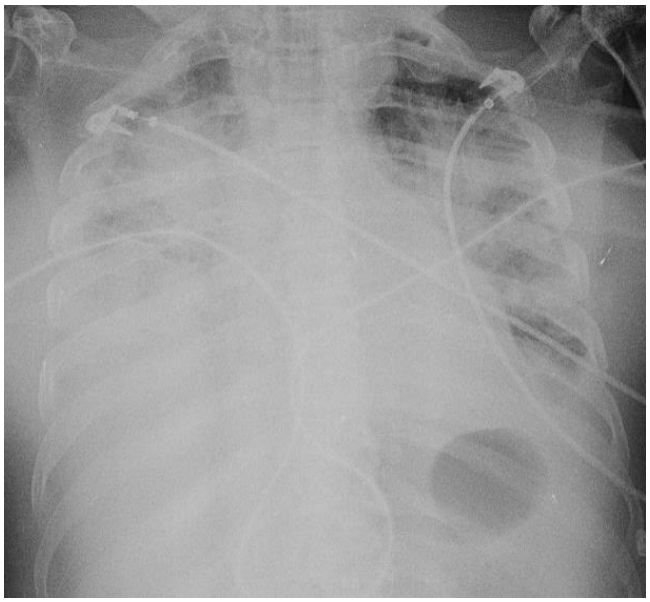

Figure 4: Alveolar hemorrhage seen on chest X-Ray after massive hemoptysis on day 2 following intubation

The case we present here had the RTS-II form of the condition. Concurring with previous studies in literature, the patient was mentally normal, had sparse thin hair, a dysmorphic jaw and tooth structure, microdontia, short stature and low weight, keratosis and sclerosis of the skin, saddle nose and esophageal dilatation due to pyloric stenosis, as detected on physical examination.

Previous studies have described progressive leukopenia requiring transfusion, chronic microcytic hypochromic anemia, malignant hematological abnormalities ranging from myelodysplasia to aplastic anemia and leukemia in RTS cases (4,5). In our patient, erythrocyte suspension and fresh frozen plasma replacement were applied to the treatment protocol due to microcytic anemia, leukopenia and low platelet. Subcutaneous vasodilation (telangiectasia) and hematological abnormalities are common in RTS patients, making them prone to bleeding during interventional procedures. In our patient, a bleeding tendency was observed after all kinds of interventional procedures, such as catheter insertion and deep tracheal aspiration.

Bronchiectasis and recurrent pneumonia have been described only rarely in patients with RTS (4,6,7). Although bronchiectasis was not observed in our case, there was total atelectasis due to aspiration pneumonia in the right lung.

CONCLUSION

This case emphasizes that gastrointestinal pathologies are common in RTS patients, and that aspiration pneumonia may develop after esophageal dilatation. The study further draws attention to the occurrence of hemoptysis and hematuria due to the likelihood of bleeding from mucosal tissue.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

YAZAR KATKILARI

Fikir - H.İ.Y., H.I.K., G.A., A.C.P., H.K., M.P.; Tasarım ve Dizayn - H.I.K., H.İ.Y., M.P., A.C.P., H.K., G.A.; Denetleme - A.C.P., G.A., H.K., M.P., H.İ.Y., H.I.K.; Kaynaklar - M.P., H.K., H.İ.Y., G.A., A.C.P.,H.I.K.; Malzemeler - H.İ.Y., H.I.K., A.C.P., G.A., H.K., M.P.; Veri Toplama ve/veya İşleme - M.P., H.K., H.İ.Y., H.I.K., A.C.P., G.A.; Analiz ve/veya Yorum - A.C.P., G.A., H.İ.Y., H.I.K., M.P., H.K.; Literatür Taraması - M.P., H.İ.Y., H.K., H.I.K., A.C.P., G.A.; Yazıyı Yazan - H.İ.Y., H.I.K., A.C.P., G.A., M.P., H.K.; Eleştirel İnceleme - A.C.P., G.A., H.K., H.İ.Y., H.I.K., M.P.

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A Case of Incidental Bronchial Atresia

İnsidental Bir Bronşiyal Atrezi Olgusu

Ayşe Baha[1], Ugurcan Balyemez[2]

Abstract

Bronchial atresia (BA) is a rare condition that appears radiologically as a perihilar mass lesion and increased peripheral aeration. A 29-year-old asymptomatic male patient was identified with a right perihilar mass during a routine medical examination linked to a job application. Before applying to our clinic, the patient had had undergone non-contrast thoracic CT and PET-CT. Physical examination was normal, while contrast-enhanced thorax tomography revealed a right central mass and signs of air trapped in its periphery. A pulmonary function test was normal. All bronchi were open on bronchoscopy, however a small blunt orifice was observed at the right upper lobe posterior segment entrance. We present this case due to it being a rare condition and the potential for confusion with cancer radiologically. BA with mass image and increased peripheral aeration on thorax CT can be diagnosed based on clinical and radiological findings, allowing unnecessary invasive interventions to be avoided.

Key words: *Mass, air trapping, bronchial atresia.*

Öz

Bronşiyal atrezi nadir görülen bir durumdur. Radyolojik olarak genellikle perihiler kitle lezyonu ve periferal havalanma artışı şeklinde karşımıza çıkar. Yirmi dokuz yaşında asemptomatik erkek hastanın iş başvurusu sırasında yapılan sağlık taramasında çekilen akciğer grafisinde sağ perihiler kitle saptanmış. Kliniğimize başvuru öncesinde hastaya kontrastsız toraks tomografisi (BT) ve PET-CT çekilmiş. Fizik muayenesi normal olan hastaya kontrastlı toraks BT çektik, sağ santral kitle ve periferinde hava hapsi saptadık. Solunum fonksiyon testi normaldi. Bronkoskopide tüm bronşlar açıktı, sağ üst lob posterior segment girişinde küçük kör sonlanan orifis görüldü. Bu olguyu, radyolojik olarak kanser le karışabilmesi ve nadir görülmesi nedeniyle sunmak istedik. Kitle imajı ve periferik hava hapsi ile karakterize olan bronşiyal atreziye klinik ve radyolojik olarak tanı koyulabilir ve gereksiz invazif girişimlerden kaçınılabilir.

Anahtar Sözcükler: *Kitle, hava hapsi, bronşiyal atrezi.*

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Bronchial atresia (BA) is a rare condition caused by focal interruptions of the bronchus that may be lobar, segmental or subsegmental, and usually related to mucus impaction (1). Radiologically, it presents with a central mass and peripheral air trapping (1). The central mass-like image may lead to malignancy being investigated, with potential for exposure to unnecessary invasive procedures. BA is more common in men than women, with an estimated prevalence of 1.2 cases in 100,000. Around two-thirds of patients are asymptomatic (2). We share here a case of bronchial atresia that was detected incidentally from a chest X-ray and investigated with a suspicion of malignancy.

CASE

The posteroanterior chest X-ray taken at another health facility during the routine health screening of a 29-year-old male patient with no smoking history, occupational exposure, comorbidity or symptoms revealed a right perihilar, well-defined, homogeneous opacity approximately 3 cm in size. A subsequent non-contrast thorax computed tomography (CT) scan taken at another health center revealed a 3.5 cm mass and led to him being directed to a 3rd-level health institution. The patient applied to another 3rd-level health institution where a PET-CT was made due to suspicions of cancer, and a SUV-max of 0 was recorded. The patient who had undergone a non-contrast thorax CT scan and a PET-CT then applied to out center for further examination and treatment.

The patient had no cough, sputum, weight loss, night sweats or loss of appetite, but described mild dyspnea occurring with heavy exertion. The patient had a history of frequent bronchitis as a child, but his family history was unremarkable. Upon physical examination, his general condition was good, oxygen saturation was 98% in room air, heart rate was 78/min, body temperature was 36.8 °C, respiratory rate was 13/min and respiratory sounds were normal.

Thorax CT scan and PET-CT images taken in previous health centers were re-examined, and it was decided to perform a thorax CT scan with contrast to rule out any vascular pathology. Following the injection of a contrast material into the left brachial vein to allow the examination of both the arterial and venous phases, a 64-channel multidetector CT was used to obtain arterial phase images (0.6 mm cross-sectional axial plane, coronal and sagittal MIP images, and 3D volume images).

In the central part of the right upper lobe, a 33x25 mm well-defined hypodense lesion was observed that did not show contrast in the obtained pulmonary arterial or late venous phase images. Wide air trapping covering primarily the posterior segment and lateral of the right lung upper lobe, beginning in the area of the lesion, and a mosaic attenuation pattern in the right lung upper lobe apical segment, were noted, (Figure 1 and 2). The 3D volume images are presented in Figure 3. Based on these findings, we made a preliminary diagnosis of bronchial atresia.

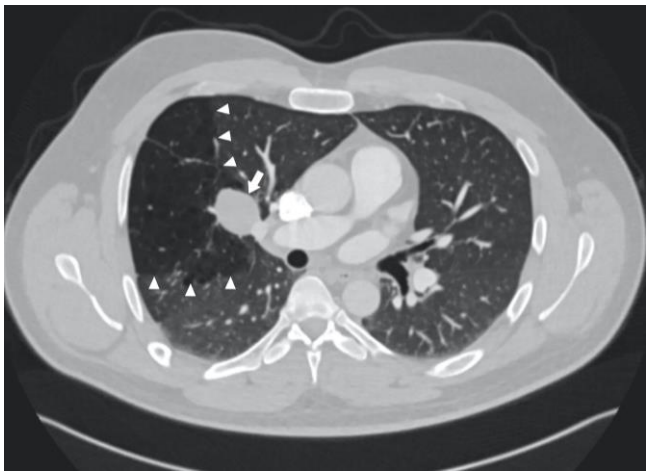

Figure 1: Axial CT image in parenchymal window showing the dilated atretic bronchus plugged with mucus (Arrow) and a radiolucent area due to air trapping and oligemia in the adjacent lung parenchyma (arrowheads)

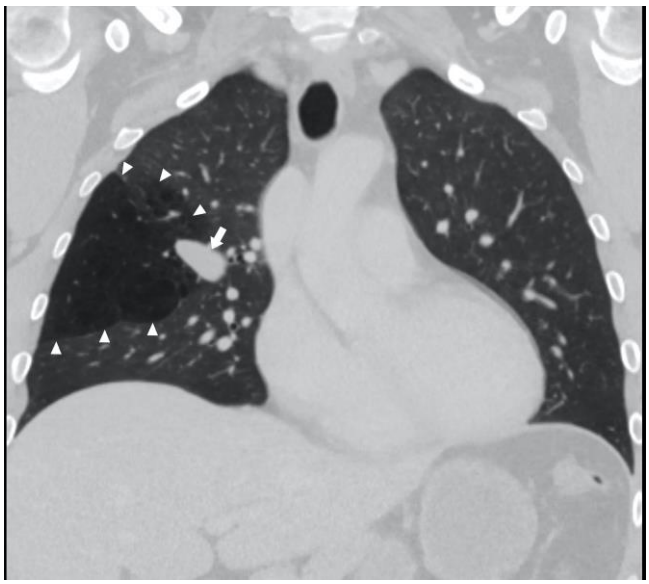

Figure 2: Coronal CT image in a parenchymal window showing the dilated atretic bronchus plugged with mucus (arrow) and a radiolucent area due to air trapping and oligemia in the adjacent lung parenchyma (arrowheads)

A bronchoscopy was performed to support our preliminary diagnosis and to rule out other possible pathologies. The bronchoscopy revealed the mucous membranes to be regular and the right upper lobe segments to be open, however, a narrowed and blind orifice was observed at the posterior segment entrance (Figure 4). The other lobes and segments were noted to have a clear and normal anatomical structure, and a pulmonary function test (PFT) was normal (FEV1/FVC: 83%, FEV1: 3450 ml 112%, FVC: 4100 ml 115%, reversibility test is negative). The patient was diagnosed with BA, and was followed up accordingly.

DISCUSSION

Bronchial atresia (BA) is an uncommon congenital anomaly characterized by focal obliteration of the proximal lumen of a lobar, segmental or subsegmental bronchus, and is related to peripheral mucus accumulation and the related hyperinflation of the obstructed lung segment (1). The most commonly affected areas are the apicoposterior segment of the left upper lobe, followed by the right upper lobe and middle lobe segments (3). Congenital BA was first described in 1953 by Ramsay and Byron (4).

The precise etiology of bronchial atresia is unknown. In a healthy person, during embryonic airway development, lobar bronchi, subsegmental bronchi and distal bronchioles emerge in the 5th, 6th and 16th weeks, respectively. In BA, it is assumed that it occurs as a focal bronchial obstruction before delivery (1). One theory suggests that BA occurs after the 16th week of the embryonic period due to intrauterine ischemia (5,6), while another theory claims that BA develops earlier than the 4th–6th week of intrauterin development, which is a period in which many congenital pulmonary anomalies occur (5-8). Raynor et al. (9), on the other hand, report secondary BA cases caused by the mucosal flap, bronchial mucosal hypertrophy, bronchial wandering related to herniation, or external compression of the bronchi through abnormal vascularization.

BA is usually diagnosed incidentally as patients are generally asymptomatic (1). Some patients may develop such asthma-like symptoms as dyspnea, wheezing and coughing. The most common clinical situation is recurrent lower respiratory tract infection (4,10). BA may be associated with pectus excavatus (11). It has been detected together with spontaneous pneumothorax in a few cases (12). BA, however, is usually an isolated anomaly. Pulmonary function tests (PFTs) are generally normal, but obstructive-type pulmonary dysfunction has been described (13). Our patient's PTF results were normal.

The optimum and most sensitive imaging technique for diagnosis is computed tomography. Mucocele, segmental hyperinflation and hypovascularity are typical features of bronchial atresia, and a combination of these findings on thorax CT is diagnostic (14,15). Radiographic findings include mass-like images and increased peripheral aeration due to collateral air trapping. Hyperlucency is seen in 90% of cases, perihilar masses in 8%, and both in 70% (12,15). Mass like images are caused by mucocele. In our patient's CT, diffuse air trapping in the lateral and posterior segments of the right upper lobe and a well-defined hypodense appearance of 33x25 mm in the central region of the right upper lobe were observed.

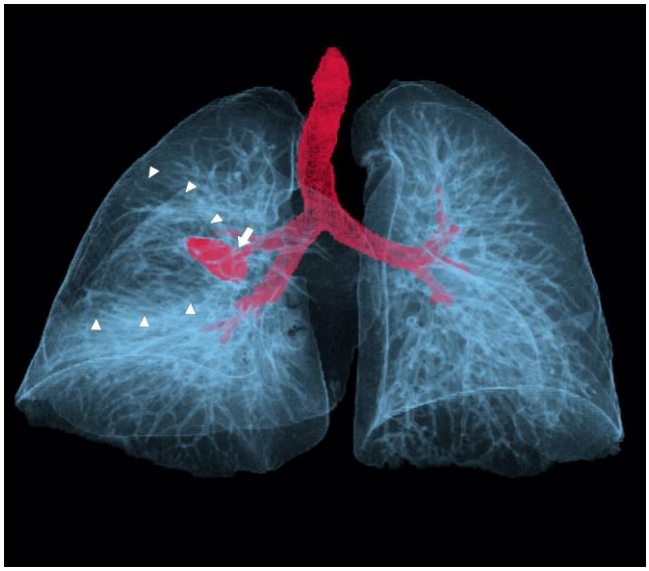

Figure 3: Coronal Colorized Volume Rendered image showing the atretic bronchus (arrow) and air trapped lung parenchyma (arrowheads)

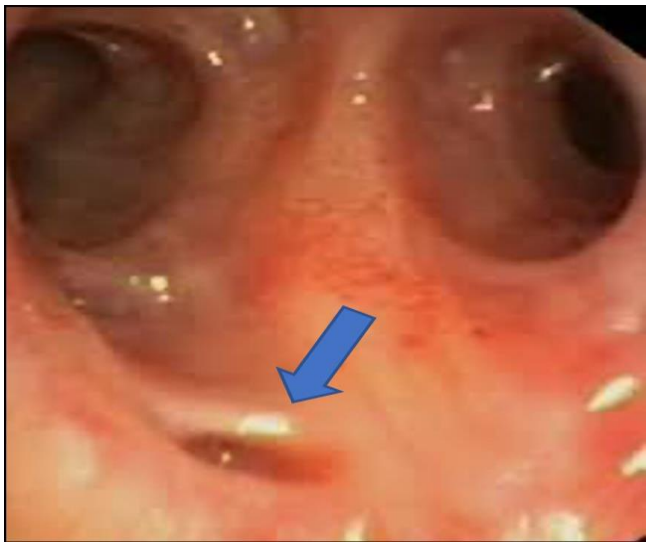

Figure 4: Narrowed blind orifice (blue arrow) at the right upper lobe posterior segment entrance

In patients with BA, generally the main bronchi are open upon bronchoscopy, and no intraluminal occlusive lesion is apparent (14). A bronchoscopic examination in our patient revealed no endobronchial lesion, while a small segment orifice was noted in the upper lobe of the right lung that was not suitable for the normal anatomical structure.

In a differential diagnosis, malignancies, benign neoplasms, allergic bronchopulmonary aspergillosis, arteriovenous malformations, abnormal pulmonary venous return, intralobar pulmonary sequestration, bronchogenic cyst and foreign body aspiration should be considered (13).

The treatment of asymptomatic BA is usually conservative and follow-up should include a chest X-ray. If the patient has severe and recurrent infections, surgical treatment may be considered (16).

There are some limitations related to this case. First of all, thorax CT with contrast should have been performed when a mass-like image was detected on the patient's chest X-ray, as there may have been no need for a PET-CT or a new CT-scan. It should not be forgotten, however, that recognizing BA, which is a rare disease, radiologically requires experience. We were lucky in this regard as the patient had applied to us after being examined by two other health institutions, and so we were able to make a diagnosis without the need for a more invasive procedure than bronchoscopy.

Our patient was diagnosed with BA based on the rudimentary segment orifices observed in bronchoscopy and typical radiological appearances observed in thorax CT. Radiological masses on images should not be assumed to be cancer. BA should be kept in mind in differential diagnosis. Considering BA in cases with mass-like radiological images, but accompanied by increased peripheral aeration and bullae, will save the patient from unnecessary invasive procedures.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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

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Rhodococcus equi Related Bacteremia and Cavitary Lung Lesion in a Patient Receiving Renal Transplant: A Rare Case Report

Böbrek Nakil Alıcısı Olan Bir Hastada Rhodococcus equi İlişkili Bakteriyemi ve Kaviter Akciğer Lezyonu: Nadir Bir Olgu Sunumu

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Abstract

Rhodococcus equi is a rare cause of cavitary lung infection that is often mistaken for tuberculosis in immunosuppressed patients who are HIV positive and in organ transplant recipients. A 69-year-old male kidney transplant patient was admitted to an external healthcare center with complaints of weight loss, cough and hemoptysis that had started 6 months earlier. A computed tomography revealed a cavity in the upper segment of the left lung lower lobe, and a PET-CT revealed a high SUV-max uptake. Upon application to our hospital, the same symptoms were identified, along with R. *equi* growth observed in Bronchoalveolar Lavage and blood cultures. The patient was followed up with mechanical ventilator as intubated. *Acinetobacter baumannii* grew in the control ETA (endotracheal aspirate) culture on the 6th day of hospitalization, and he died subsequently on the 23rd day of hospitalization from colistin-induced nephrotoxicity. To the best of our knowledge this is the first case in which *R. equi* cavitary pneumonia has been seen together with *R. equi* bacteremia in our country.

Key words: *Rhodococcus equi, Immunocompromised host, Cavitary lung lesion.*

Öz

Rhodococcus equi is HIV pozitif ve organ nakil alıcısı olan immunsüpresif hastalarda özellikle tüberküloz ile sıklıkla karışan kaviter akciğer infeksiyonuna neden olan nadir bir etkendir. Altmış dokuz yaşında böbrek transplant alıcısı ve immünsüpresif tedavi alan erkek hasta 6 aydır devam eden kilo kaybı, öksürük ve hemoptizi semptomları olması üzerine dış merkeze başvurmuş. Çekilen bilgisayarlı tomografide sol akciğer alt lob üst segmentte kavite saptanmış. Malignite düşünülmesi üzerine PET-CT çekilmiş ve yüksek SUV-max tutulumu tespit edilmiş. Hasta hastanemize başvurduğunda mevcut şikayetleri devam etmekteydi. Alınan Bronkoalveolar Lavaj kültüründe ve kan kültürlerinde *R. equi* üremesi oldu. Hasta entübe edilerek mekanik ventilatör ile takip edildi. Kontrol ETA (endotrakeal aspirat) kültüründe *A. baumannii* üremesi oldu. Bunun üzerine tedaviye kolistin de eklendi. Hasta tedavisinin 23. gününde kolistine bağlı nefrotoksisite nedeniyle exitus oldu. Bildiğimiz kadarıyla bu olgu ülkemizde *R. equi* kaviter pnömonisinin *R. equi* bakteriyemisi ile birlikte görüldüğü ilk olgudur.

Anahtar Sözcükler: *Rhodococcus equi, Bağışıklığı baskılanmış konak, Kaviter akciğer lezyonu.*

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Rhodococcus equi is a facultative aerobic, non-motile, non-spore-forming, intracellular gram-positive, weak acid-resistant *coccobacillus* belonging to the nocardioform actinomycetes group (1), and is a rare zoonotic organism that affects predominantly the immunocompromised (2). *R. equi* can cause various infections in humans, primarily cavitary pneumonia, bacteremia, infective endocarditis and meningitis (1,3-5).

Here, we present a case of bacteremia and cavitary pneumonia due to *R. equi* in a 69-year-old male renal transplant recipient. *R. equi* is often difficult to identify, being similar to other bacterial pathogens such as diphtheroids, mycobacterium and nocardia species (6). The identification of *R. equi* is made with MALDI-TOF MS (Bruker Daltonics), being more reliable and accurate than Vitek MS (7). The aim with the present study is to increase awareness of *R. equi* among physicians as one of the rare causes of cavitary pneumonia in immunosuppressed patients, especially in transplant recipients.

CASE

A 69-year-old male patient who had undergone a kidney transplant 7 years earlier due to diabetic nephropathy, and who had been in contact with such animals as cattle, was admitted to an another hospital with complaints of weight loss, cough and hemoptysis that had started 6 months earlier. A computed tomography of the thorax revealed a cavitary lesion in the lower lobe superior segment of the left lung (Figure 1). BAL EZN (Ehrlich-Ziehl-Neelsen) staining was negative for AFB (acid fast basil). To investigate whether the cavitation was due to malignancy, a PET-CT (positron emission tomography-computed tomography) was performed, and in the cavity was intensely FDG avid (SUVmax 5.6), while no FDG uptake was present elsewhere. A transthoracic biopsy was then performed but was non-diagnostic, and the patient refused a repeat biopsy.

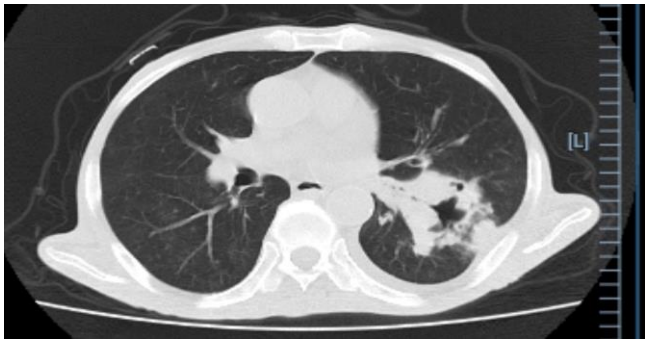

Figure 1: *Cavitary lesion in the lower lobe superior segment of the left lung*

The patient applied to our hospital in January 2021 with complaints of cough, shortness of breath, weight loss and anorexia. A physical examination revealed no abnormality in lung auscultation except tachypnea (22/min). Oxygen saturation at room air was 89%. The patient was using mycophenolate mofetil (500mg/day) and tacrolimus (0.5 mg/day). His past medical history included diabetes mellitus, while there was no previous history of tuberculosis. He had been smoking for 30 pack years. Laboratory parameters at the time of admission were: Glucose 343.9 mg/dL (74-106), Urea 84.1 mg/dl (17-43), Creatinine 1.41 mg/dl (0.67-1.17), CRP 20.52 mg/dl (0 -0.5), WBC count 5740 /mm^3 (3700-10100), Hb 8.8 g/dl (12.9-14.2), HCT 25.9% (37.7-53.7) and PLT 164.106/ml. (155.106-366.106).

The patient was admitted to the chest diseases intensive care unit to investigate the cause of the cavitary lung lesions. Tuberculosis infection was primarily investigated. A FOB (Fiberoptic bronchoscopy) was planned, during which purulent secretions were seen in the main bronchus of the left lung. BAL (Bronchoalveolar Lavage) was taken from the patient and sent to the tuberculosis and bacteriology laboratory for BAL culture, tuberculosis culture, gram and EZN staining. Partial acid-resistant *coccobacillus* was revealed by the EZN staining (Figure 2). The specimen was inoculated on 5% sheep blood agar, chocolate agar and MacConkey's agar plates incubated for 48 h at 37°C. Soft mucoid pink bacterial colonies were identified on the 5% sheep blood agar and the chocolate agar, but not on MacConkey's agar, and these were identified as *R. equi* based on a matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) Bruker Daltonics ® mass spectrometry (MS) with >2 score (Figure 3). In addition to the MALDI-TOF MS identification, traditional tests were also performed for verification purposes. Catalase, CAMP (Figure 4), and urease tests applied to the microorganism were positive, the oxidase test was negative and was found to be non-motile. The high success of the Matrix-Assisted Laser Desorption to Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) method in literature, together with the clinical and radiological appearance of the patient being compatible with the agent, and the biochemical properties of the agent was being compatible with *R. equi*. There was no need for identification via a molecular method. The mycobacterial culture was negative, and gram-positive coccobacillus was seen on the Gram stain (Figure 5). The antibiotic MIC values of the isolate were determined by E-test method (Table 1).

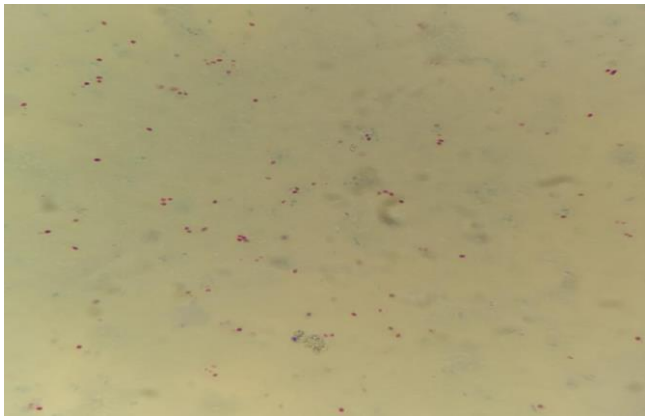

Figure 2: Partial acid-resistant coccobacillus in the EZN staining

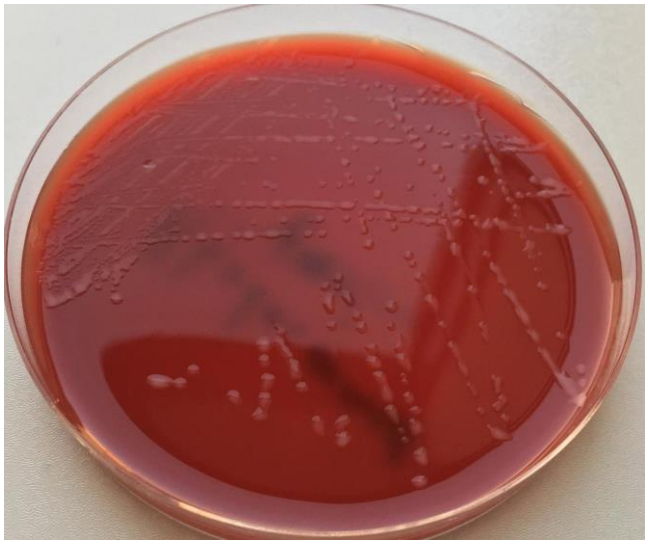

Figure 3: Soft mucoid pink bacterial colonies on 5_ sheep blood agar

The patient was treated with meropenem 500 mg IV (intravenous) (3 x 1) + vancomycin 1 g IV (2 x 1) and levofloxacin 500 mg IV (2 x 1) for cavitary pneumonia caused by *Rhodococcus equi*. For deep vein thrombosis prophylaxis, 40 mg enoxaparin was started. A computed tomography of the brain was made given that there may have been an association of *Rhodococus equi* with brain abscess, but the CT revealed no evidence of abscess in the brain. Subsequently, with the development of thrombocytopenia, heparin-induced thrombocytopenia (HIT) was considered, and enoxaparin prophylaxis was discontinued. HIT was excluded due to the persistence of thrombocytopenia, which was attributed to meropenem, and treatment with ampicillin-sulbactam was continued in place of meropenem. The Tacrolimus was stopped and treatment continued with mycophenolate mofetil due to the high tacrolimus blood level. Respiratory failure and confusion developed on the third day of antibiotic treatment. The patient was followed up with a mechanical ventilator as intubated. *Acinetobacter baumannii* grew in the control ETA (endotracheal aspirate) culture on the 6th day of the patient's hospitalization. Imipenem IV 4 x 500 mg + colistin IV 300 mg maximal tolerable dose and a 2 x 150 mg maintenance dose were added to the antibiotic treatment. The ampicillin-sulbactam treatment was discontinued. The patient had high inflammatory biomarkers and was followed up intubated. Acute renal damage developed due to colistin nephrotoxicity, and *Rhodococcus equi* also grew in the blood cultures of the patient in their septic condition. The patient died from septic shock on the 23rd day of hospitalization.

DISCUSSION

R. equi is a gram-positive, nonmotile, facultative intracellular, weak acid resistant, catalase, and urease positive, obligate aerobic microorganism. Its microscopic appearance can change from cocci to bacillus, depending on the stage of the growth cycle and growth conditions, and so can be considered a component of normal flora or as bacteria from *Diphtheroid Bacillus*, *Micrococcus* or *Bacillus* species and delay diagnosis. *Rhodococcus equi* can be confused with mycobacterium clinically (insidious beginning and chronic course) in terms of the lung region in which it is located (usually upper lobes), as well as CT findings, granuloma formation and acid-resistant properties (1,3,4,6). In the present case, the cavitary consolidation observed in the lower lobe superior segment of the lungs initially suggested tuberculosis granuloma, and so a BAL sample was collected from the patient and investigated for tuberculosis. Bacteria with the morphology of *coccoccobacilli* that were partially resistant to acid were detected in EZN staining, but upon further examination the agent growing in BAL was identified as *R. equi*. Nocardia, which can cause pulmonary infection in immunosuppressed humans opportunistically, can be clinically mistaken for *R. equi* pulmonary infection, and it is also a Gram-positive aerobic bacterium that stains acid-fast, and that can be mistaken microbiologically for *R. equi* (6,8). Failure to identify the pathogen and the insidious course of the clinic in human *R. equi* infections may delay diagnosis and treatment. *R. equi* easily grows on non-selective media and under aerobic conditions, and often forms mucoid, large and irregular colonies on the medium. The red-pigmented colonies that form become characteristic salmon-colored colonies after 48 hours of incubation (6). When we defined the pathogen isolated from this case based on traditional methods, it was identified as catalase and urease positive, nonmotile, CAMP-test positive and oxidase negative gram-positive *coccoccobacillus*. In previous studies, Matrix-Assisted Laser De-

sorption Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) has been found to be successful in defining *R. equi* at a species level, in which the 16S rRNA gene sequencing method was used as a reference method (7). The agent defined as *R. equi* in both BAL and blood culture with a > 2 scoring on the automated system was found to be compatible with *R. equi* when using conventional methods.

The patient's clinical and radiological findings were consistent with *R. equi* infection. The colony appearance on the medium was specific for *R. equi*, as were its biochemical properties, and MALDI-TOF MS was also successful in identifying *R. equi*. As such, there was no need to carry out a molecular identification of the pathogen. *Rhodococcus equi* is a bacterium found in water and soil that can infect animals and humans through respiration and nutrition. Bacteria can also enter the body through wounds or the mucosa and cause an infection, while no human-to-human transmission has been detected to date (9). In our case, the source of infection could not be determined precisely, although it was learned that the patient had been in contact with cattle for feeding. While it rarely infects humans, *R. equi* is the most common *Rhodococcus* species behind human infections (10). Only 10--15% of the patients in whom *R. equi* is detected as a pathogen is immunocompetent, while immunosuppressive patients are frequently infected. The majority of patients identified with an *R. equi* infection were found to be HIV-positive. *R. equi* has been identified in more than 100 cases of infection to date, and most (approximately 50%) were localized infections. Respiratory infections account for 80% of all cases. Lung infections (mostly necrotizing pneumonia) have been detected in 84% of immunosuppressed patients and 42% of immunocompetent patients. Chronic cavitary pneumonia infection caused by *R. equi* often results in relapse, despite long-term antibiotic treatment, and the mortality rate is high. *R. equi* infections result in death in 50% of HIV-infected patients, 20–25% of patients with immunosuppressive diseases due to non-HIV causes, and approximately 11% of immunocompromised patients (8,9,11-14). *R. equi* is a facultative intracellular pathogen that has the ability to survive and destroy human macrophages, which is the basis of the pathogenesis of the infection and its resistance to antibiotics. It is also thought to be effective in the development of severe and/or recurrent infections (15,16). Extrapulmonary spread is generally thought to occur as a late manifestation of pulmonary infection, occurring through the bloodstream, and extrapulmonary relapse is usually seen in the central nervous system in the form of brain abscess or meningitis. It can also cause extrapulmonary infections such as wound infections, subcutaneous abscesses, pericarditis, osteomyelitis, cervical adenopathy, endophthalmitis, lymphangitis and mastoiditis (17). The medical history of the presented case included a diagnosis of diabetes mellitus, being a disease that suppresses the immune system, and the use of immunosuppressive drugs following a kidney transplantation. The patient had both cavitary pneumonia and extrapulmonary bacteremia. The microorganism is phagocytosed by alveolar macrophages, and macrophages continue to grow in it, leading to a granulomatous inflammatory reaction and the subsequent development of necrosis. Pneumonia can start without symptoms and may be overlooked, especially in immunosuppressed patients. Often, symptoms such as weight loss, cachexia, pleuritic chest and pain accompanied by fatigue, fever and cough are observed (9). *R. equi* can also be isolated in blood cultures due to the bacteremia in pulmonary infections. Bacteremia has been observed at a rate of 10% in immunocompetent patients and 25% in HIV-infected solid organ transplant recipients (15,17).

Figure 4: *CAMP test of the microorganism*

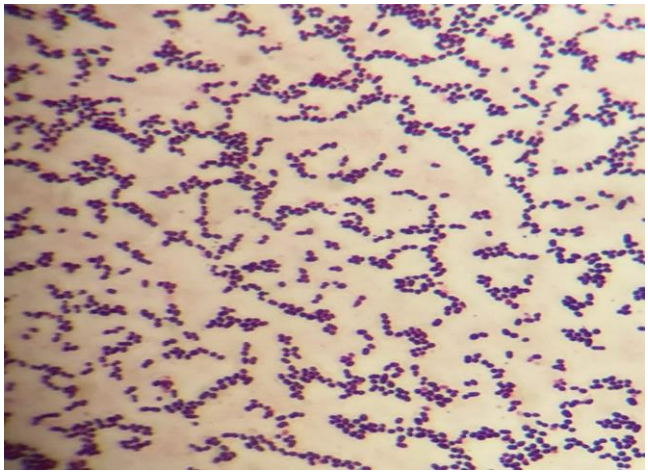

Figure 5: Gram-positive coccobacillus on the Gram stain

Table 1: Antibiotic mic values of the isolate

ANTIBIOTIC	MIC(mg/L)
Cefotaxim	0,094
Ceftriaxon	0,25
Cefoxitin	8
Imipenem	0,047
Meropenem	0,125
Doripenem	0,064
Daptomycin	>256
Tigecyclin	0,25
Vancomycin	0,19
Linezolid	2

In the presented case, the patient had experienced shortness of breath, cough and severe weight loss within the last year, consistent with previous studies. He had developed cavitation in the lung, and the radiological appearance was compatible with pneumonia. The agent that was first isolated from the respiratory tract showed systemic spread a few days later, and was isolated from both right and left peripheral blood cultures.

Menon et al. (18) identified 40 cases of *R. equi* in organ transplant patients prior to 2012, the majority of which were male (82.5%) and kidney transplant recipients (58.5%). It has been determined that infections can develops over a period ranging from 3 months to 19 years after transplantation. In the presented case, *R. equi* cavitary pneumonia and bacteremia developed in a kidney transplant recipient 7 years after transplantation, consistent with literature.

The most appropriate protocol and duration of treatment for *R. equi* infections have yet to be determined, and it is currently recommended that each patient be evaluated individually. The duration of treatment should be determined according to the infection site, immunity and clinical response (14).

Azap et al. (19) published a similar article in our country, but bacteremia was also present in our case. As such, this is the first case of *R. equi* cavitary pneumonia together with *R. equi* bacteremia to be reported on in our country.

Based on both in vitro studies and clinical experience, it has been suggested that two or three drugs, including imipenem, vancomycin, ciprofloxacin, aminoglycoside, rifampin and/or erythromycin, can be administered intravenously in combination, with vancomycin in particular, can be recommended in combination (20,14).

In the presented case, since the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has set no limit value as a reference for the *R. equi* antibiotic susceptibility test, the MIC values of the antibiotics were determined using the E-test method. The treatment was subsequently planned as meropenem 500 mg IV (3x1) + vancomycin 1 g IV (2x1) + levofloxacin 500 mg IV (2x1), in accordance with the findings of previous studies. The response of *R. equi* to treatment could not be fully evaluated. While the patient's treatment was continuing, colistin was added to the protocol with the development of pneumonia due to *A. baumannii*, and the patient died of renal toxicity, being a side effect of colistin. In conclusion, the *R. equi* pathogen should be considered in cases of cavitary pneumonia, especially in immunosuppressed patients with a history of solid organ transplantation. Rare bacteria can be identified using automated systems in routine laboratory services, allowing infectious diseases to be diagnosed early, and facilitating the immediate start of treatment.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

YAZAR KATKILARI

Fikir - F.K., H.K., H.S.Ş., S.Y., N.U.; Tasarım ve Dizayn - F.K., H.K., H.S.Ş., S.Y., N.U.; Denetleme - F.K., H.K.,

H.S.Ş., S.Y., N.U.; Kaynaklar - F.K.; Malzemeler - F.K., H.K., N.U.; Veri Toplama ve/veya İşleme - F.K., H.K., N.U.; Analiz ve/veya Yorum - F.K., H.K., S.Y.; Literatür Taraması - F.K., H.K.; Yazıyı Yazan - F.K., H.K.; Eleştirel İnceleme - H.S.Ş., S.Y.

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RESPIRATORY CASE REPORTS

Development of ARDS due to COVID-19 in a Pregnant Woman in the Third Trimester and Successful Multidisciplinary Case Management

Üçüncü Trimester Gebede COVİD-19' a Bağlı ARDS Gelişimi ve Başarılı Multidisipliner Olgu Yönetimi

İlker Yılmam[1], Pervin Hancı[2]

Abstract

The course of COVID-19 disease may be more severe in pregnant patients due to the physiologic changes induced by pregnancy. Although most pregnant patients with COVID-19 are followed up as outpatients, requiring no hospitalization, COVID-19 infection, especially in the presence of risk factors such as increased immunosuppression in the third trimester and lack of vaccination, can progress rapidly and lead to respiratory failure, as in our case. Our patient was in the third trimester of her pregnancy, and required intensive care due to COVID-19 pneumonia on the third day of hospitalization, and an emergency delivery was performed initially with a multidisciplinary approach. The patient was then followed up in the respiratory intensive care unit under mechanical ventilation. Our patient is a remarkable example of severe COVID-19 disease in the third trimester of pregnancy.

Key words: *COVID-19, pregnancy, intensive care unit, multidisciplinary management.*

Öz

Gebe hastalarda COVID-19 hastalığı, gebeliğin getirmiş olduğu fizyolojik değişiklikler nedeni ile daha ciddi seyredebilmektedir. Çoğu COVİD-19'lu gebe hastamız, hastane yatışına gerek duyulmadan ayaktan takip edilmekle birlikte, özellikle 3. trimesterde artan immünsupresyon, hastanın aşısız olması gibi risk faktörleri varlığında, olgumuzda olduğu gibi COVİD-19 enfeksiyonu hızlı progresyon gösterip solunum yetmezliğine neden olabilir. Gebeliğinin 3. trimesterinde olan hastamızın yatışının 3. gününde COVİD-19 pnömonisine bağlı yoğun bakım ihtiyacı göstermesi üzerine multidisipliner bir yaklaşım ile önce acil doğum operasyonu gerçekleştirildi ve hasta postop yoğun bakım ünitesinde mekanik ventilasyonda takip edildi. Hastamızı, gebeliğinin 3. trimesterinde ciddi seyreden COVİD-19 hastalığına bir örnek teşkil etmesi nedeni ile sunmak istedik.

Anahtar Sözcükler: *COVİD-19, gebelik, yoğun bakım ünitesi, multidisipliner yönetim.*

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Since December 2019, when the health facilities of Wuhan city in Hubei province, China, and the Chinese Center for Disease Control and Prevention reported an outbreak of pneumonia of unknown cause, the subsequently named coronavirus disease (COVID-19) has spread rapidly and has come to affect the entire world. The World Health Organization (WHO) declared COVID-19 caused by SARS-CoV-2 a global epidemic (pandemic) on March 11, 2020.

Although all members of society are susceptible to COVID-19, health care workers are the occupational group at the highest risk, with those of the male sex, people older than 50 years, people with comorbidities and people living in community shelters being among the higher risk groups (1).

Pregnancy is a condition that can be difficult to manage in the presence of viral infections. Although coronaviruses are no more virulent in pregnant women than in the normal population, it can complicate clinical management by prolonging and complicating the disease (2). Symptoms in COVID-19-positive pregnant women can take the form of fever, weakness, cough, sore throat, and loss of smell and taste, and patients tend to endure the disease isolated at home.

Our case was admitted to our hospital with radiological findings of viral pneumonia and respiratory failure, unlike in the cases we usually see in pregnant women. We present our case to literature to highlight the importance of the accurate and timely treatment of pregnant COVID-19 patients, as the case became critical in a short time and was intervened with a multidisciplinary approach due to the life-threatening situation of the mother and child.

CASE

A 31-weeks non-smoking pregnant woman with no known chronic disease history and who had not been vaccinated against COVID-19 complained of cough, shortness of breath and back pain on the 5th day of COVID-19 PCR positivity on 26/11/2021, and was referred to our hospital after extensive COVID-19 pneumonia was detected in a thorax CT at the State District Hospital (Figure 1).

Upon admission to our facility, SpO_2 was 91% (3-4 L/min O_2 mask support), and laboratory tests revealed Wbc: 7400 /mm^3, CRP: 98 mg/l, Lym: 570 /mm^3 and D-dimer: 1.7 mg/l. No obstetric pathology was detected during the ultrasonography (USG) or in the non-stress test (NST) examination performed by the Department of Obstetrics and Gynecology. The patient was admitted to the pandemic ward for further treatment where she was treated with 40 mg of methylprednisolone and a prophylactic dose of low molecular weight heparin (LMWH). After the onset of tachypnea, an increase in oxygen demand (SpO_2: 88 under 8-10 L/min O_2 support with face mask) and progression on a posteroanterior (PA) chest X-ray (Figure 2), the patient was given a 250 mg methylprednisolone infusion and treated with a broad-spectrum antibiotic on day 3 of follow-up. During follow-up, the patient was taken for an emergency cesarean section by the Gynecology and Obstetrics department due to a worsening of the respiratory symptoms and oxygenation, and the resulting threat to life.

The patient was intubated and monitored in the Respiratory intensive care unit (ICU) in the postoperative period. Upon admission to the ICU, the patient was ventilated with a tidal volume of 6 ml/kg (ideal weight) in assisted volume-controlled mode at 14 cmH2O positive end-expiratory pressure after the recruitment maneuver, as part of a lung-sparing ventilation strategy, under sedation and analgesia. The ratio of partial arterial oxygen pressure to oxygen fraction (PaO_2/FiO_2) was 135 at blood gas measurement 30 minutes after current settings. The patient could not tolerate the prone position due to recent abdominal surgery. Upon admission to the ICU, her SOFA score was 4, APACHE II score was 19, CRP level was 84.8 mg/L, procalcitonin level was 0.19 ng/mL and ferritin level was 326 ng/mL. The treatment with 1x250 mg methylprednisolone the was started in the ward was completed over 3 days during follow-up, with 2x40 mg methylprednisolone then continued as a maintenance dose. The tidal volume was adjusted so that the plateau pressure was less than 30 cmH_2O and the driving pressure was less than 15 cmH_2O. After a blood gas analysis, the value of PEEP was gradually decreased taking into account the FiO_2 requirement (Table 1). When the patient's FiO_2 requirement was 45%, sedation analgesia was discontinued, and the value of PEEP was decreased to 8 cmH_2O on the 6th day of ICU stay. Regression was revealed on PA chest X-ray, and the patient was extubated on postoperative day 8 when her vital signs had stabilized and successful spontaneous breathing was achieved. After extubation, oxygen therapy was continued with nasal high-flow therapy (flow: 50 L/min, FiO_2: 35%). During follow-up, the patient, whose oxygenation and other vital signs were stable under low-flow oxygen therapy (4 L/min nasal cannula), was transferred to the chest diseases ward on the 10th day of her intensive care stay. The methylprednisolone dose was reduced but continued. The

patient required no oxygen at follow-up and showed clinical and radiological regression (Figure 3), and was discharged on postoperative day 15 with a recommendation to taper and discontinue the methylprednisolone treatment.

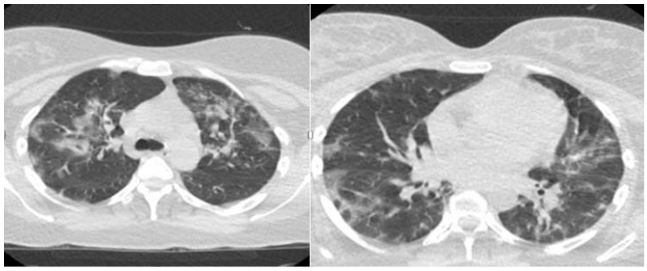

Figure 1: Computed tomography showed bilateral consolidation in the lung

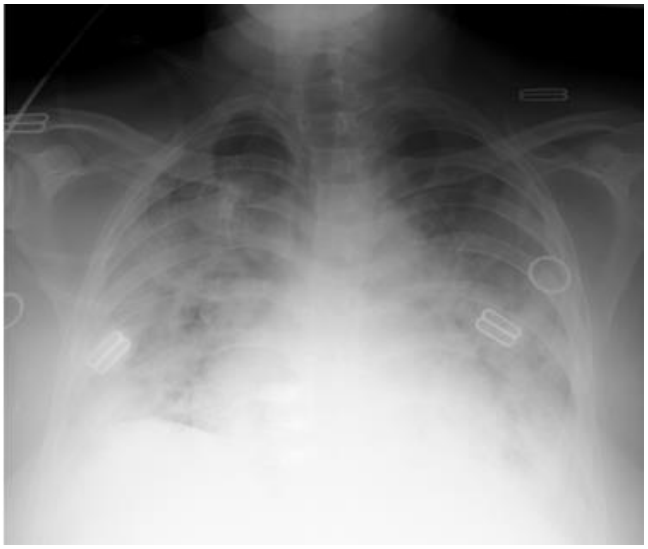

Figure 2: Chest X-ray showed radiological progression on the 3rd day of hospitalization

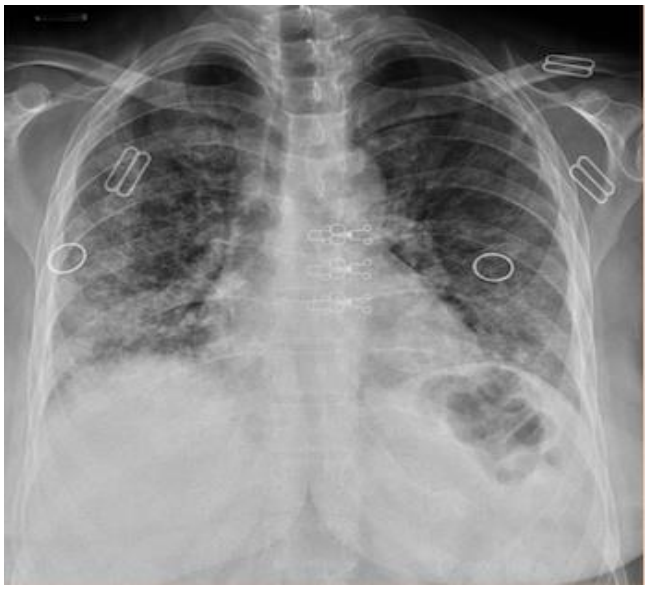

Figure 3: Chest X-ray showed radiological regression on postoperative day 15

Table 1: Daily PO_2/FiO_2 ratio and ventilator settings during ICU follow-up

	PO_2/FiO_2 (mmHg)	TV/IBW (ml/kg)	PEEP (cmH_2O)	FiO_2
1. 1st Day	135	6	14	0.60
2. 2nd Day	147	6	12	0.55
3. 3rd Day	146	6.5	10	0.55
4. 4th Day	205	7.6	10	0.50
5. 5th Day	195	7.6	8	0.45
6. 6th Day	278	8.0	8	0.40

Abbreviations: PO_2: partial arterial oxygen pressure, FiO_2: oxygen fraction, TV/IBW: tidal volume/ideal weight, PEEP: positive end-expiratory pressure

DISCUSSION

At the outset of the COVID-19 outbreak, many questions arose about its effects on pregnant women. These included whether pregnancy increased susceptibility to COVID-19 infection, whether pregnant women were more susceptible to severe disease, whether SARS-Cov-2 infection increased the risk of adverse pregnancy and neonatal outcomes, as well as the effects of COVID-19 vaccinations on pregnancy and lactation.

To the best of our knowledge, pregnant women are affected by COVID-19 infection to the same extent as non-pregnant women (3-5), although pregnant women are known to be at increased risk of morbidity and mortality from such respiratory infections as influenza and SARS-CoV-2 (6), placing them among the populations considered at risk of COVID-19 infection. SARS-Cov-2 infections are more common in pregnant women living in socially and economically disadvantaged areas than in non-pregnant women. A report from New York City reported that pregnant women living in buildings with lower incomes, higher unemployment and more households are more likely to develop a SARS-Cov-2 infection (7).

There have been many studies reporting the prevalence of SARS-Cov-2 infection in pregnant women at rates ranging from 3-20% (8,9). In cases of pregnancy, the COVID-19 diagnostic algorithm is the same as for non-pregnant women.

There have been several studies reporting an increase severity of COVID-19 during pregnancy. Some of the best-informed information comes from the COVID-19 tracking system of the U.S. Centers for Disease Control and Prevention (CDC), which includes the data of 400,000 reproductively competent people with symptomatic COVID-19, ranked by age, race, ethnicity and underlying medical conditions. Compared to non-pregnant women, pregnant women are three times more

likely to be admitted to the ICU, 2.9 times more likely to require invasive ventilation, 2.4 times more likely to require extracorporeal membrane oxygenation and 1.7 times more likely to die (10). Other studies from the United States and from Europe have reached similar conclusions. For example, in a study of four European hospitals, pregnant and non-pregnant women were compared for age, body mass index and comorbidities, and an increased risk of developing severe disease during pregnancy was identified, including increased risk of ICU admission (11). An increased risk of hospitalization, need for oxygen therapy and need for endotracheal intubation in infected pregnant women was identified also in the present study. The increased risk of severe disease during pregnancy may be attributable to such mechanical factors as decreased lung volume, immunologic changes and increased risk of thromboembolic disease during fetal growth (10).

A cohort study of 5,183 pregnant and 175,905 non-pregnant women identified pregnancy as a risk factor for death, pneumonia and ICU hospitalization in women of reproductive age (12).

Studies of corticosteroids in patients with viral pneumonia and ARDS have yielded mixed results (13,14). In the Randomized Evaluation of COVID-19 Therapy (RECOVERY) study, in which 2,104 patients with COVID-19 were randomized to receive 6 mg of dexamethasone daily for up to 10 days, showed that dexamethasone reduced 28-day all-cause mortality (15), and the greatest benefit was noted in patients who had been symptomatic for more than 7 days and required mechanical ventilation. Conversely, there was no benefit to patients who were symptomatic for a shorter period and that did not require any supplemental oxygen. A cohort study of 201 patients with COVID-19 pneumonia and ARDS in Wuhan, China, reported that treatment with methylprednisolone was associated with a lower risk of death (16). In our patient, the administration of a corticosteroid dose of 250 mg methylprednisolone/3 days contributed to the positive evolution of the patient's critical condition due to the deepening of respiratory failure.

CONCLUSION

Pregnant women can be considered a special healthcare population in whom a multidisciplinary team approach involving chest diseases, gynecology and obstetrics, infectious diseases and intensive care physicians is critical for the management of viral infections with potential for a progressive course, such as COVID-19. Such an approach can support the timely administration of appropriate treatments for maternal and child health, the appropriate follow-up care, the identification of a need for mechanical ventilation in the event of progressive respiratory failure, and the development of an individualized delivery plan. The importance of high-dose corticosteroid therapy and vaccination to prevent severe disease development in the event of severe disease due to COVID-19 is particularly evident.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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YAZAR KATKILARI

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

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Ground Glass Opacities Differential Diagnosis in COVID-19 Pandemic: A Case Report

COVID-19 Pandemisinde Buzlu Cam Ayırıcı Tanısı: Bir Olgu Sunumu

Ceren Degirmenci

Abstract

The pandemic has predisposed all healthcare professionals to assess all viral pneumonia cases preliminarily as COVID-19, with a definitive diagnosis of COVID-19 made on the basis of a positive RT-PCR result. Occasionally, however, there are cases with negative RT-PCR test results both with thoracic CT findings indicative of COVID-19. It is thus very important to consider immunosuppressive conditions and other viral types of pneumonia in the differential diagnosis in patients who do not seem to respond to COVID-19 treatments. We present her a case of HIV infection identified in a differential diagnosis of ground glass opacities.

Key words: *COVID-19, pneumonia, HIV, AIDS, CMV, PCP.*

Öz

Pandemi, doktorların tüm viral pnömonileri birinci ön tanı olarak COVID-19 olarak değerlendirmeye yatkın hale getirmiştir. COVID-19'un kesin tanısı, pozitif bir RT-PCR testi ile konur, ancak bazen RT-PCR test sonuçları negatif olan, fakat COVID-19'u gösteren toraks BT bulguları olan olgular da vardır. Bu nedenle, COVID-19 tedavilerinden fayda görmeyen hastalarda ayırıcı tanıda immünsupresif sebeplerin ve diğer viral pnömonilerin araştırılması çok önemlidir. Buzlu cam opasiteleri ayırıcı tanısında HIV enfeksiyonu saptanan bir olgu sunulmuştur.

Anahtar Sözcükler: *COVID-19, pnömoni, HIV, AIDS, CMV, PCP.*

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**This case report was presented as an e-poster at the Turkish Thoracic Society 24th Annual National Congress, which was held between November 17-22, 2021.*

Millions of people have been infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since the disease caused by the virus – COVID-19 – emerged in the city of Wuhan in China in December 2019. A definitive diagnosis of COVID-19 is based on the detection of a reverse transcription polymerase chain reaction (RT-PCR) of SARS-CoV-2-specific ribonucleic acid (RNA) in the secretions of the patient suspected of having COVID-19 in samples obtained via such methods as throat-nose swab and tracheal aspirate (1,2). The specificity of RT-PCR for the diagnosis of COVID-19 is high, while its sensitivity is relatively low (3). COVID-19 patients may be asymptomatic or present with non-specific symptoms such as cough, malaise, fever and shortness of breath. Imaging methods are frequently used for the examination of patients with suspected COVID-19 due to the moderate to severe respiratory complaints, as they provide significant benefits in the diagnosis of pneumonia, for evaluations of the degree of spread, the investigation of possible complications such as pulmonary embolism or pneumothorax, the follow-up of patients and the guidance of differential diagnosis. The most common thoracic CT findings in COVID-19 pneumonia are ground-glass opacification and areas of consolidation areas that are indicative of bilateral, peripheral and basal dominant distribution (4). That said, these findings are common to many other infectious or inflammatory diseases, and so it is of great importance to know the differential diagnoses and the clinical and radiological differences between COVID-19 pneumonia and other causes, and to not overlook other viral infections in the differential diagnosis of ground-glass opacity during the pandemic.

CASE

A 41-year-old patient with a previous diagnosis of Crohn's Disease presented to the emergency service with shortness of breath, cough and fever. The patient reported shortness of breath and cough for about a month, despite no history of smoking, and stated that the shortness of breath and cough had exacerbated in the last few days, and that a fever had developed. The patient also complained of hematochezia in the last two months, and a loss of 10 kg in weight in the same timeframe. The patient had been diagnosed with Crohn's disease based on a colonoscopy performed 1 month earlier and had been started on oral budesonide treatment. Upon admission, the patient's body temperature was 38.3°C, pulse 105/min, systolic/diastolic blood pressure 120 and 75 mmHg, respectively, and oxygen saturation (SpO_2) 85%. An examination of his respiratory system indicated bilateral rhonchi. His laboratory results were as follows; white blood cell count (WBC): 6910/mm^3, lymphocyte count: 1220/mm^3, neutrophil count: 5430/mm^3, Hemoglobin (Hb): 11.5g/dL, C-reactive protein (CRP): 126 mg/L, D-dimer: 1.59mg/L, ferritin: > 1675 ng/mL and troponin: 6.6 mg/L. The results of liver and kidney function tests were within normal limits. A postero-anterior (PA) chest X-ray revealed clear bilateral sinuses, and no cardiomegaly or clear ground-glass opacification or areas of consolidation (Figure 1). Thorax computed tomography (CT) revealed diffuse ground-glass infiltrates in both lungs that were determined to be more prominent in the right upper lobe; focal aeration increases and parenchymal density differences in both lungs that were more prominent in the left lower zone; and air cysts and paraseptal emphysema areas in the upper zones that were more prominent on the right side (Figure 2). While the patient's imaging findings were compatible with COVID-19 pneumonia, the result of a PCR test was negative and so a second PCR test was performed that also yielded a negative result. The patient was hospitalized with suspicion of COVID-19 and started on nasal oxygen therapy, favipiravir, low molecular weight heparin, prednisolone and levofloxacin treatments. His hepatitis and HIV markers were sent out on the first day of hospitalization as per routine. The anti-HIV test yielded a positive result on the 4th day of hospitalization. The patient's fever could not be alleviated, and so he was started on trimethoprim-sulfamethoxazole treatment with a suspicion of pneumocystis pneumonia (PCP) by the infectious diseases department. The patient was then referred to a health center with an infectious diseases clinic. The result of the cytomegalovirus immunoglobulin G (CMV IgG) antibodies test was positive and his CMV DNA level was 119432 genomes/ml. The patient has since been undergoing treatment as a newly diagnosed HIV-positive and CMV-positive patient.

DISCUSSION

The pandemic has predisposed all healthcare professionals to assess all viral pneumonia cases preliminarily as COVID-19. All patients, who deemed to be suspicious based on their clinical and radiological findings, and that have an indication for hospitalization during the pandemic are hospitalized with a preliminary diagnosis of COVID-19. The case presented here was pre-diagnosed with COVID-19 based on his high CRP, ferritin and D-dimer levels, as well as bilateral ground-glass opacifica-

tion on CT. A definitive diagnosis of COVID-19 is made on the basis of a positive RT-PCR result, although occasionally cases arise with negative RT-PCR test results yet with thoracic CT findings indicative of COVID-19 (5). It is thus very important to consider immunosuppressive conditions and other viral pneumonias in the differential diagnosis of patients who do not seem to benefit from COVID-19 treatments and who do not respond to attempts to alleviate fever.

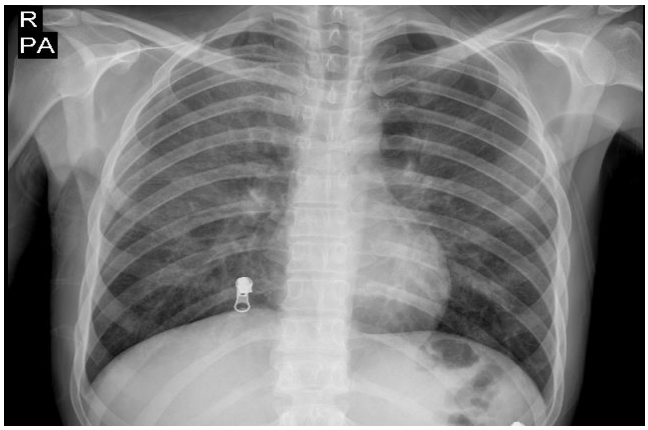

Figure 1: Chest X-Ray

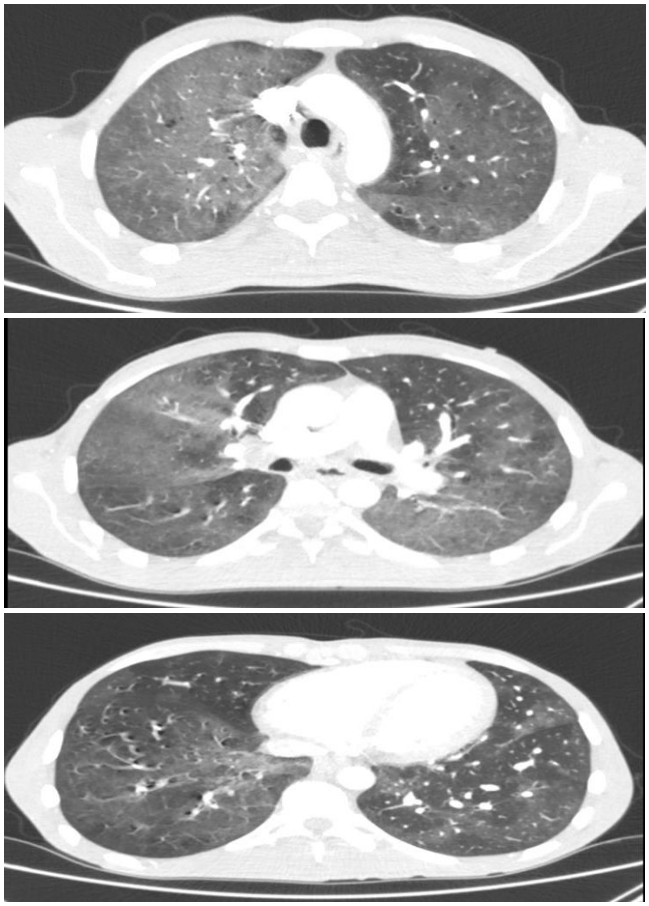

Figure 2: Thorax computed tomography revealing diffuse ground-glass infiltrates in both lungs (determined to be more prominent in the right upper lobe), increased focal aeration and parenchymal density differences in both lungs

There are generally overlaps in the imaging findings of viral pneumonias and those of non-viral infections and inflammatory pathologies, and so it is often difficult to isolate and identify viral pneumonia agents (6-9). A number of imaging findings that may be associated with the pathogenesis of viral infections have been identified, and members of the same virus family have similar pneumonia pathogenesis and radiological findings. CMV pneumonia, as in the case presented here, is frequently seen in immunosuppressed patients and is characterized by irregular ground-glass opacification areas that are scattered or diffusely located in both lungs on thorax CT (6), while COVID-19 pneumonia, in contrast, tends to be more heterogeneous and focal-peripheral (7).

In cases of influenza virus pneumonia, chest radiography and thorax CT findings are generally normal in the vast majority of cases, while the most common findings are more dominant nodules in the mid-upper zones, and areas of focal consolidation and ground-glass opacification around the nodules (6,8). In COVID-19 pneumonia, on the other hand, patchy ground-glass opacification areas with peripheral and multilobar distribution can often be detected in the middle-lower lung zones. Unlike in pneumonia associated with swine flu (hemagglutinin-1 neurominidase-1 [H1N1]), or with the highly pathogenic Asian avian influenza A (H5N1), nodules and consolidation, and areas of ground-glass opacification around the nodules, are not among the findings seen in connection with COVID-19 pneumonia (9). Nasal discharge and flu symptoms are very common in rhinovirus pneumonia, but are seen only rarely in connection with COVID-19 (6). Moreover, fungal infections can also lead to various involvements in the lungs, for example, the PCP caused by the Pneumocystis jirovecii fungus is one of the most common opportunistic infections with serious consequences for immunocompromised patients (10). The epidemiology of PCP has increased dramatically with the emergence of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) (11). HIV-associated PCP mostly presents with fever, dry cough, and shortness of breath (12). The clinical symptoms and physical examination findings of PCP and COVID-19 are similar, with diffuse ground-glass opacification areas and accompanying air cysts seen typically in the bilateral upper lobes of the lung in both conditions (7). Both diseases can coexist, and there is potential for a PCP patient to be misdiagnosed with COVID-19, or vice-versa (13). Aside from the infections, cryptogenic organizing pneumonia (COP) and acute interstitial pneumonias should also be

included in the differential diagnosis of ground-glass opacity. Radiological and histopathological findings of COP largely overlap with those of COVID-19. In both cases ground-glass opacification and consolidation areas with peripheral and peribronchovascular distribution are the most common radiological findings, and the reversed halo sign (RHS), also called the atoll sign, are seen in approximately one-fifth of both COP and COVID-19 cases. Furthermore, in both cases lesions in the lung can relocate over time (migratory opacities) (14).

In short, the radiological findings of COVID-19 can be confused with those of many viral pneumonias, and so it would be useful to make a careful differential diagnosis considering the comorbidities and the immune suppressed status of the patient.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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

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

Ayşegül Pehlivanlar, Tevfik Özlü

Abstract

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

Key words: *IPF, COVID, fibrosis.*

Öz

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

Anahtar Sözcükler: *IPF, COVİD, fibrozis.*

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

CASE

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

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

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

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

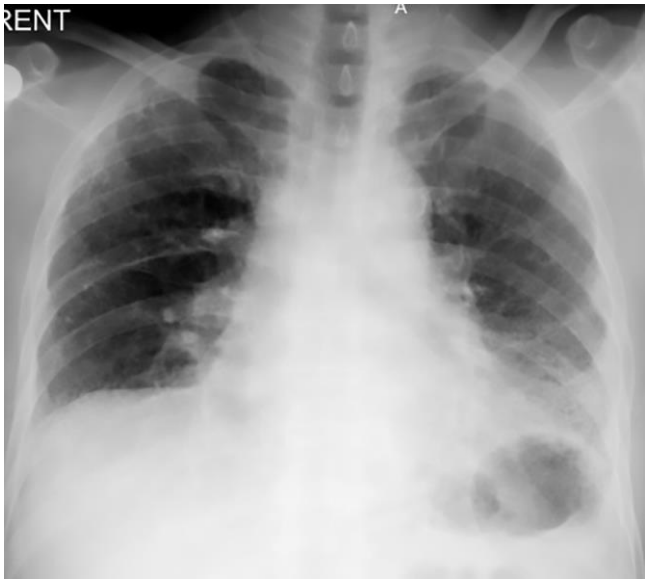

Figure 1: Admission Posteroanterior Chest Radiography

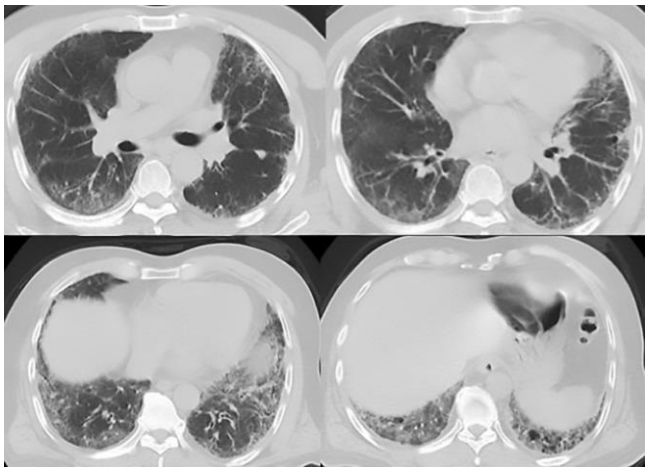

Figure 2: Admission thorax CT scan

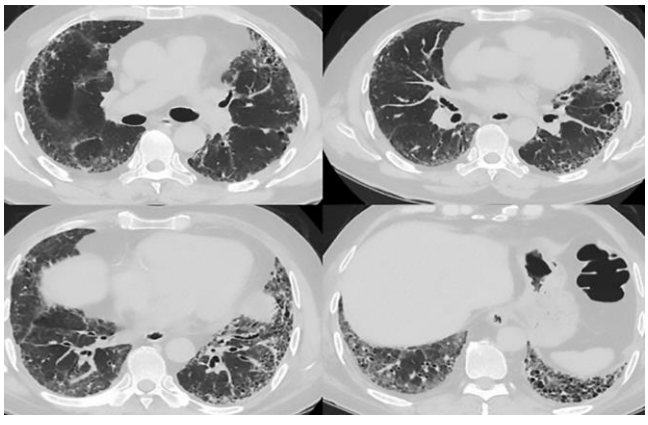

Figure 3: Thorax CT scan after medication revision

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

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

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

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

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

DISCUSSION

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

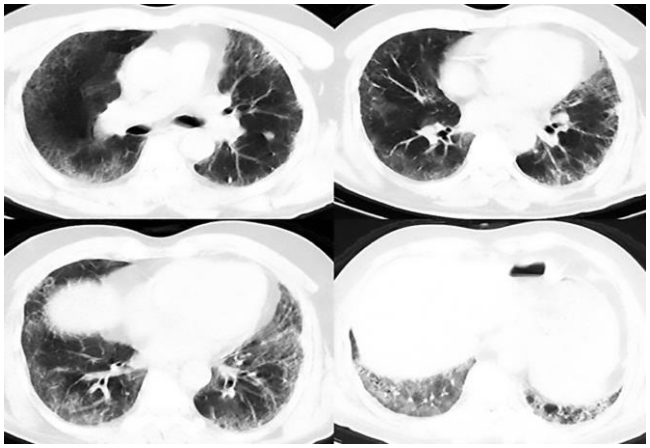

Figure 4: COVID period thorax CT scan

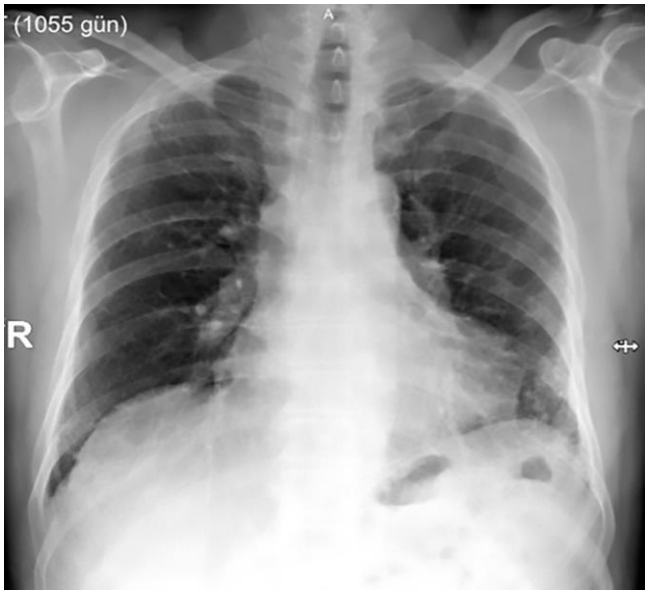

Figure 5: Pre-COVID posteroanterior roentgenogram

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

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

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

CONCLUSION

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

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

YAZAR KATKILARI

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

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Methanol Intoxication in the Differential Diagnosis of COVID-19

COVID- 19 Ayırıcı Tanısında Metanol İntoksikasyonu

Emine Afşin[1], Furkan Küçük[1], Melike Elif Kalfaoğlu[2]

Abstract

Although central nervous system findings are prominent in methanol intoxication, the lungs are also affected. There have been several studies in literature describing autopsy-based lung findings, while there have been no clinical cases reported on to date. We present here a case identified radiologically as pulmonary edema that was included in the differential diagnosis of COVID-19.

Key words: *Methanol intoxication, pulmonary edema, COVID-19.*

Öz

Metanol intoksikasyonunda merkezi sinir sistemi bulguları ön planda olsa da akciğerler de etkilenmektedir. Literatürde otopsi olgularında akciğer bulguları tariflenmekte olup klinik olgulara rastlanmamıştır. Olgumuz, radyolojik olarak akciğer ödemi varlığı olması ve COVID-19 ayırıcı tanısında yer alması nedeniyle sunulmaktadır.

Anahtar Sözcükler: *Metanol intoksikasyonu, pulmoner ödem, COVID-19.*

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Acute methanol intoxication occurs as a result of the accidental or suicidal consumption of fraudulently produced alcoholic beverages (1). During the latent 12–24 hour period, methyl alcohol is metabolized into formaldehyde and formic acid, which are more toxic than methanol, and multiorgan failure develops due to the inhibition of cellular respiration and cytochrome oxidase (2). The clinical findings can include visual impairment, headache, dizziness, nausea, vomiting, dyspnea, weakness, seizure, stupor, coma, respiratory failure and sometimes death.

Diagnosed is based on the presence of high anion gap metabolic acidosis and high serum methanol or formic acid levels (3). To prevent the conversion of methanol into toxic metabolites, ethanol or fomepizole, which has a 10–20 times higher affinity for alcohol dehydrogenase enzyme than methanol, is administered as a treatment (4). Gastric lavage, and the correction of acidosis with sodium bicarbonate, folic acid or hemodialysis may also be required, although mortality is as high as 44% (5). The characteristic magnetic resonance (MR) finding in methanol toxicity is bilateral putaminal necrosis, and while central nervous system findings are prominent, pulmonary involvement may rarely occur. Previous studies of the issue in literature are based on autopsies with focus on lung findings, in which edema, hemorrhage, atelectasis, acute bronchitis and tracheobronchitis have been reported to develop in the lungs in the first 4–36 hours postmortem (6,7). The case presented here is of particular interest as a clinical example of methanol intoxication with lung involvement.

CASE

A 34-year-old male patient was brought to the emergency room with confusion and headache, nausea, and vomiting after imbibing methyl alcohol the previous day. The patient, who had bilateral mydriatic eyes, had a Glasgow coma score of <8 and so he was intubated and followed on a mechanical ventilator. The patient's methyl alcohol level could not be measured with decompensated metabolic acidosis due to the lack of the necessary facilities in our hospital. The pathological laboratory results were as follows: C-reactive protein of 37.7 mg/L (normal range: 0-5 mg/L), leukocytes of 20.300 K/uL, lymphocyte of 0.92 K/uL, and potassium of 5.8 mmol/L. A cranial MRI revealed symmetric diffusion restriction in the bilateral putamen (Figure 1). A chest computed tomography (CT) of the patient who underwent hemodialysis and bicarbonate replacement revealed bilateral diffuse ground glass and consolidated areas (Figure 2). The patient's nasopharyngeal swab was negative for SARS-CoV2 PCR, and there was radiological regression after two days of intensive care follow-up (Figure 3). The symptoms subsequently regressed entirely, and the patient was discharged. Written approval was obtained from the patient to publish his case report and images.

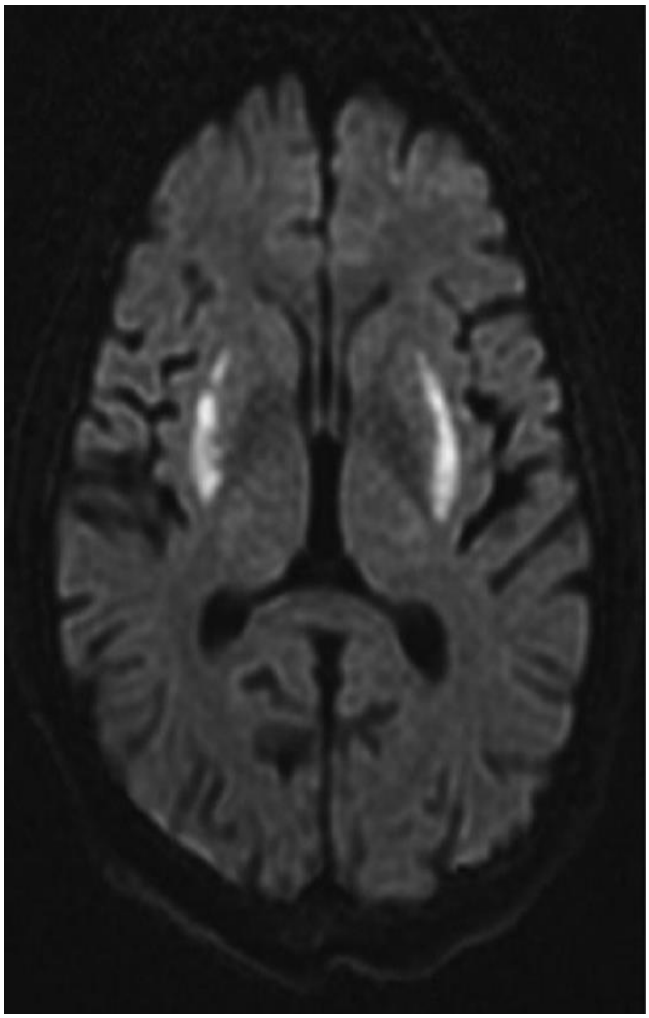

Figure 1: Diffusion restriction in bilateral putamen on cranial MR

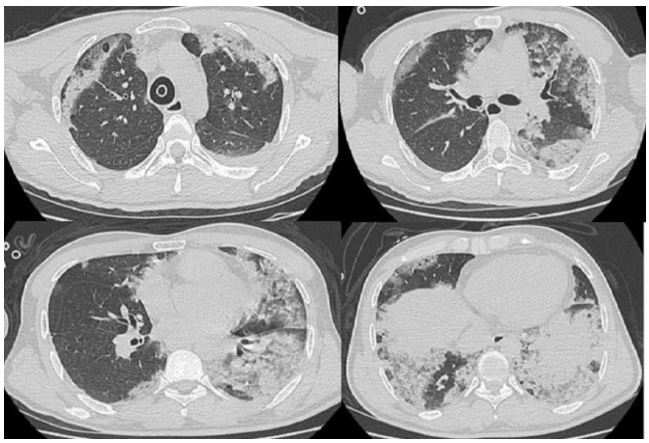

Figure 2: Bilateral diffuse ground glass and consolidated areas on thorax CT

DISCUSSION

The clinical presentation of methanol intoxication can vary greatly from patient to patient, from agitation, tetanic convulsions, seizures and hypothermia to coma accompanied by acute pulmonary edema (8). Cough and shortness of breath due to aspiration pneumonia may occur following the loss of consciousness that usually develops in the late stages of methanol poisoning. Most drug addicts live in environments with poor hygiene and crowded places where comorbidities are rife, and so the risk of contracting COVID-19 is also high. There can be overlaps in the laboratory findings of drug addicts and COVID-19 patients, and so the risk of contracting and transmitting the virus is higher, and the risk of a late and challenging diagnosis of COVID-19 symptoms is greater. COVID-19 should be suspected in cases of substance abuse (9). Despite the widespread parenchymal involvement in the chest CT in our case, and the ongoing pandemic and the suggestion of COVID-19 pneumonia, a SARS-CoV2 PCR was negative, and pulmonary edema was diagnosed due to the rapid recovery of the clinic, the absence of hypoxemic course and the radiological response.

If metabolic acidosis becomes evident, respiratory failure may develop (10) and the risk of mortality increases. Dyspnea has been reported in 61.1% of cases of methanol intoxication and the need for mechanical ventilation in 44.4% (11). The clinical findings of the present case regressed significantly after extubation following the second day of intubation.

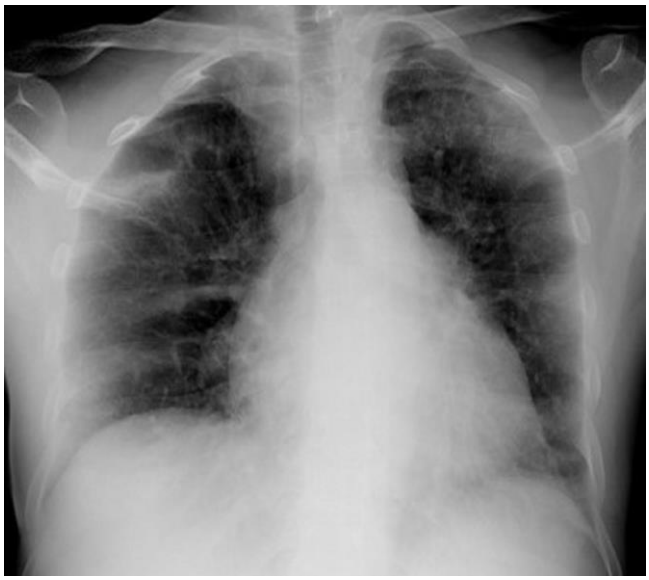

Figure 3: Chest X-ray after two days of intensive care follow-up

The most characteristic MRI finding in methanol toxicity is bilateral putaminal necrosis, which may present with various degrees of hemorrhage. This finding is not specific to methanol toxicity, as it can also be determined in Wilson's and Leigh's diseases (12). Our diagnosis was supported as putaminal necrosis was also observed in our patient with compatible clinical and laboratory findings.

The pulmonary findings of methanol intoxication are based mainly on autopsy data. Buhas et al. (7) defined autopsy findings as acute edema or hemorrhage in the lungs. In our case, the identified radiological bilateral extensive involvement and the exclusion of COVID-19 were beneficial in indicating the pulmonary effect of methanol intoxication.

CONCLUSION

Although methanol intoxication is better known for its neurological, ocular and gastrointestinal effects, it can also present in the lungs. In the presence of bilateral lung involvement and confusion in the pandemic period, methanol intoxication should be included in the differential diagnosis.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

YAZAR KATKILARI

Fikir - E.A., F.K., M.E.K.; Tasarım ve Dizayn - E.A., M.E.K., F.K.; Denetleme - E.A., F.K., M.E.K.; Kaynaklar - E.A., F.K.; Malzemeler - E.A., F.K.; Veri Toplama ve/veya İşleme - E.A., M.E.K.; Analiz ve/veya Yorum - E.A.; Literatür Taraması - E.A., F.K.; Yazıyı Yazan – E.A.; Eleştirel İnceleme E.A., M.E.K.

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

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

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Abstract

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

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

Öz

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

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

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

CASE

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

DISCUSSION

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

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

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

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

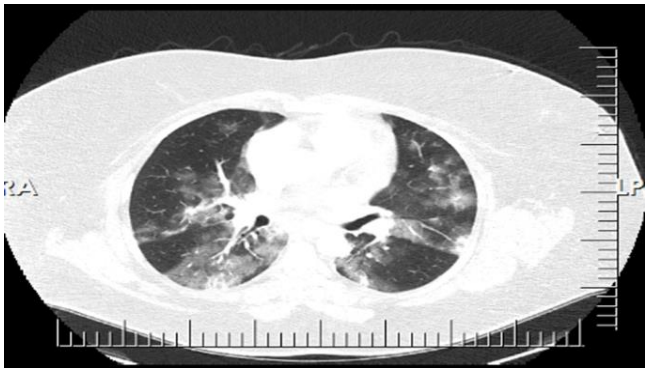

Figure 1: *The patient's Computed Tomography image*

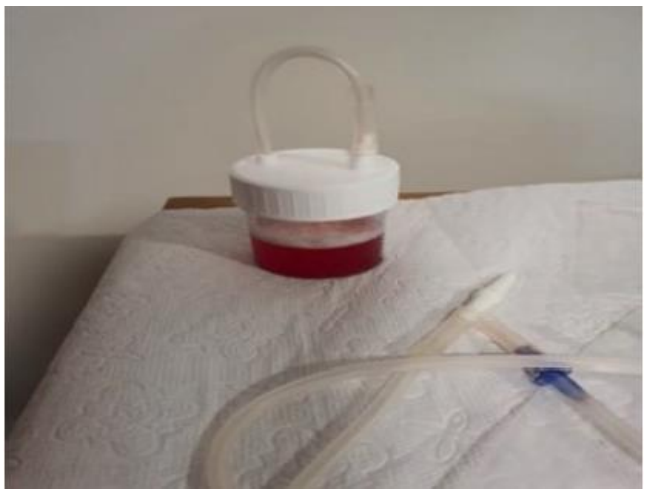

Figure 2: *The patient's bronchial lavage fluid sample obtained through fiberoptic bronchoscopy*

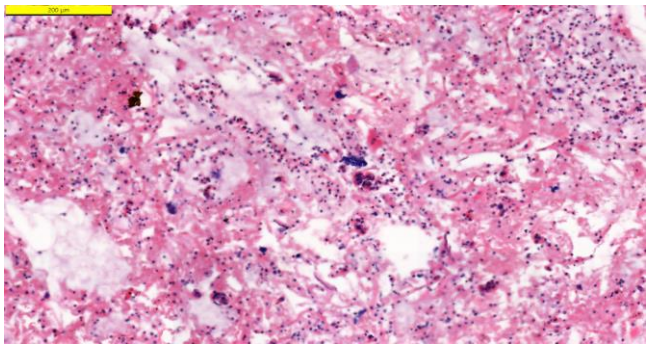

Figure 3: *Reactive bronchial epithelial cells, alveolar macrophages, lymphocytes and erythrocytes seen in the bronchial lavage cytology (H&E, x40)*

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

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

CONCLUSION

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

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

YAZAR KATKILARI

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Management of COVID-19-Associated Pleural Empyema

COVID-19 ile İlişkili Plevral Ampiyemin Yönetimi

Sevinc Citak[1], Mustafa Vayvada[1], Murat Ersin Çardak[1], Gonca Geçmen[2], Erdal Tasci[1], Kaan Kirali[3]

Abstract

The highly contagious and rapidly spreading coronavirus 2 (SARS-CoV 2) has been associated with the development of severe acute respiratory syndrome, a potentially fatal disease. A patient who underwent coronary artery bypass surgery for an acute myocardial infarction developed acute respiratory failure due to coronavirus 2 (SARS-CoV-2) pneumonia in the early postoperative period. The patient was placed on mechanical ventilation (MV) and V-V (veno-venous) ECMO (Extracorporeal Membrane Oxygenation) support. Here we discuss the application of decortication in the patient due to the development of pneumothorax and prolonged air leak empyema in the follow-up, and the subsequent development of pleural thickening.

Key words: Lung Decortication, COVID-19, Empyema.

Öz

Son derece bulaşıcı ve hızla yayılan koronavirüs 2 (SARS-CoV 2) hastalığı, potansiyel olarak ölümcül bir hastalık olan şiddetli akut solunum sendromuna neden oldu. Akut miyokard enfarktüsü nedeniyle koroner arter baypas ameliyatı olan hastada ameliyat sonrası erken dönemde koronavirüs 2 (SARS-CoV-2) pnömonisine bağlı akut solunum yetmezliği gelişti. Hastaya mekanik ventilatör (MV) ve V-V (veno-venöz) ECMO (Ekstrakorporeal Membran Oksijenasyonu) desteği verildi. Takipte pnömotoraks, uzamış hava kaçağını takiben ampiyem ve plevral kalınlaşma gelişmesi nedeniyle dekortikasyon uygulanan olguyu sunduk.

Anahtar Sözcükler: *Akciğer Dekortikasyonu, COVID-19, Ampiyem.*

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Coronavirus disease 2019 (COVID-19) was first identified in December 2019 after an outbreak of pneumonia epidemic in Wuhan, China and was declared a global pandemic by the World Health Organization (WHO). There have since been over 22 million cases and over 780,000 deaths worldwide (1).

The severity of COVID-19 symptoms can differ depending on the viral load and the immune response of the individual. The clinical course can range from asymptomatic or mild upper respiratory tract infection, to respiratory failure and death due to viral pneumonia. The condition is more severe in the elderly and in people with comorbidities. COVID-19 is a significant cause of morbidity and mortality (2). This study presents a case in which the patient was found to be positive for the novel coronavirus after heart surgery, and discusses the empyema and other devastating effects that developed.

CASE

A 42-year-old male patient was admitted to the cardiology outpatient clinic with complaints of atypical chest pain and shortness of breath for a year. He had a history of epilepsy, coronary artery disease, hypertension, diabetes mellitus and cerebrovascular disease. Vital signs were within normal limits and the patient's electrocardiography (ECG) revealed a normal sinus rhythm. Single-photon emission computed tomography myocardial perfusion imaging was performed on the patient who had been fitted with a stent in the right coronary artery 7 years earlier. Ischemia was reported in the lower wall, and a coronary angiography revealed stent occlusion for which coronary artery bypass grafting (CABG) was planned. The patient had an uneventful early postoperative period after three-vessel CABG surgery. He was extubated on the first postoperative day in the intensive care follow-up.

The patient complained of worsening dyspnea on the third postoperative day, even at rest and was in poor general condition, with fever, tachycardia and tachypnea. The vital signs were: blood pressure 105/62 mm Hg, heart rate 128 beats/min, respiratory rate 26 breaths/min and oxygen saturation 91% in room air. The laboratory results were: platelet count 160000 μL, hemoglobin 10 g/dl, leukocyte 17200/mm^3, lymphopenia 0.06 $\times$ 103/μL (5%), ferritin 944 μg/L, C-reactive protein (CRP) 167 mg/L, d-dimer 80 Ng/ml, a cytokine 300 pg/ml, alanine aminotransferase (ALT) 90 U/L, total bilirubin 1.2 mg/dl, albumin 2.6 gr/dl and pro-calcitonin 1.06 ng/mL. The patient's nasopharyngeal swab test produced a positive COVID-19 result. Diffuse opacity was seen on a chest X-ray, and a thorax computed tomography scan confirmed bilateral ground-glass opacities (Figure 1).

The patient was started on favipiravir, hydroxychloroquine and supportive treatment. The patient was intubated on the eighth postoperative day after experiencing a decrease in saturation and dyspnea, providing mechanical ventilator support. On the second day of mechanical ventilator support, the patient's blood oxygen saturation decreased upon high positive pressure ventilation (Peak Inspiratory Pressure 38 H_2O, Positive End-Expiratory Pressure 10 cm H2O, Inspired Oxygen Fraction 100%). An arterial blood gas analysis revealed pH, PaO_2 and PaCO2 to be 7.28, 61mmHg and 115 mmHg, respectively. We established V-V ECMO as the patient had developed hypoxia and hypercarbia, despite optimal treatment (Figure 2). A 19 Fr heparin-coated cannula was used for the cannulation of the right internal jugular vein, and a 23 Fr heparin-coated cannula was used for the right femoral vein. The ventilator settings were set to rest lung mode with a 2 ml/kg tidal volume, PEEP 10 cmH_2O and a respiratory rate of 10 bpm. On day the 13th of V-V ECMO, a chest X-ray revealed a large pneumothorax on the right and a chest drain was inserted. At the patient with persistent air leak, exudative pleural effusion was detected. *Acinetobacter baumannii* complex was grown in the culture from the pleural fluid, and antibiotic treatment was started based on the antibiogram. On the 39th day, V-V ECMO was weaned and the patient was followed up with mechanical ventilator support. The patient weaned from ventilatory support 15 days later and followed with nasal oxygen. A computed tomography of the thorax due to continued air leakage revealed a thickening of the visceral pleura of the right lung that had resulted in a trapped lung. Total decortication was planned (Figure 3). A thoracotomy was performed through the 5th intercostal space in the left lateral decubitus position, and air leakage was observed at the lung's apex, where the pleura had become thickened, preventing the expansion of the lung parenchyma tissue. The thickened visceral pleura was stripped, allowing lung expansion, and a wedge resection was performed in the area with air leakage at the apex. Pleural pathology revealed chronic nonspecific inflammation, interstitial fibrosis and organized granulation tissue fibrosis (Figure 4).

The need for nasal oxygen decreased in the postoperative follow-up and the air leakage reduced. The patient began to complain of abdominal pain on the 7th postoperative day, and an abdominal examination revealed rebound and defense. The patient underwent emergency

surgery during which bowel perforation was detected. He was placed on mechanical ventilation support due to a deterioration in general condition and respiratory depression and the air leaks increased due to the high pressure of the mechanical ventilation. As the air leak could not be controlled, the patient was evaluated surgically, and it was observed that his lung had been destroyed during the operation. A right pneumonectomy was performed, but after the first surgery the patient died of septic shock on the 193rd day.

DISCUSSION

COVID-19 infection has in rare cases been found to cause spontaneous pneumothorax, and usually in patients with barotrauma due to mechanical ventilation treatment or a pre-existing cardiopulmonary comorbidity (3). An alveolar-pleural fistula may develop causing persistent air leak, leading to prolonged hospital stay and high morbidity (4). Complications of persistent air leaks include pleural space infection, hypoxia and incomplete lung expansion.

The optimum approach to the treatment of prolonged air leaks and pleural thickening in COVID-19 disease remains controversial, and Current publications are limited to a number of case reports. A wide spectrum of treatments are suggested, from bleb resection to salvage lobectomy (5,6). While major surgeries, such as decortication and lobectomy, are not recommended as the first choice in treatment, successful results can be obtained in selected and necessary situations.

Pneumothorax is defined as a rare (1%) finding in patients diagnosed with COVID-19 (7). Although iatrogenic pneumothorax resulting from mechanical ventilation is rare, a fatal complication of high mortality of 15% (8). Previous studies have reported this rare complication to be associated with underlying lung disease (chronic obstructive pulmonary disease, acute respiratory distress syndrome) (9) On the other hand, pneumothorax may be the only reason for hospitalization during the medical treatment of COVID-19 (10).

As in cases of acute respiratory distress syndrome, the lungs of COVID-19 patients with significant interstitial involvement appear small due to low compliance and low elasticity (11) which may explain the prolonged air leaks and the reason for lung failure to fill the thorax. Excessive swelling and high PEEP in fibrotic and hypoelastic lungs can cause alveolar or pre-existing bleb rupture. Iatrogenic pneumothorax is seen only with disease progression in intubated COVID-19 patients, but is rare (12). Although the first-line treatment is chest tube placement, prolonged air leak should be investigated with thoracoscopy performed by venting the lungs with low tidal volume (13,14). The ideal time of such a procedure is uncertain, and we believe each case should be evaluated by a multidisciplinary team, with the procedure and timing decided upon considering the patient-specific pros and cons (6).

The traditional treatment of thoracic empyema is decortication (15) given the greater risk of mortality associated with nonsurgical treatment (16). Acinetobacter baumannii complex grew in the culture sample taken from the pleural drainage of our patient with ECMO support and general condition disorder, and antibiotic treatment was started based on the culture antibiogram. A chest tube was inserted to support the healing of the patient's parenchyma, while a "wait-and-see" strategy was applied in the identification of the effectiveness of the treatment.

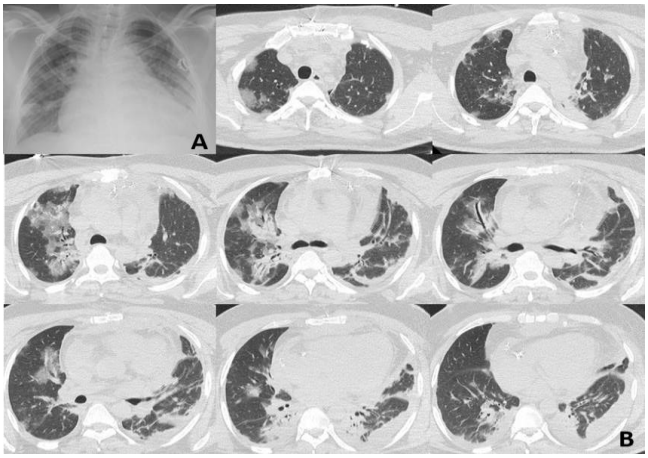

Figure 1: Bedside chest X-rays of suspected COVID-19 (A) and a chest computed tomographic scan revealed the presence of bilateral peripheral ground-glass opacities (B)

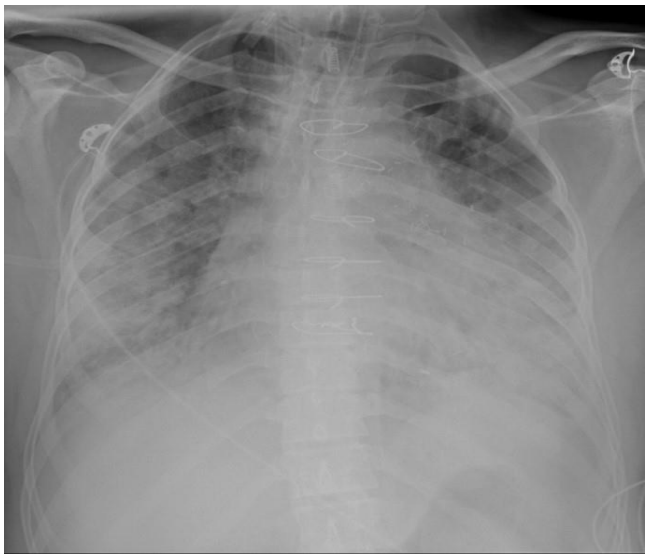

Figure 2: Chest X-ray before extracorporeal membrane oxygenation (ECMO) cannulation

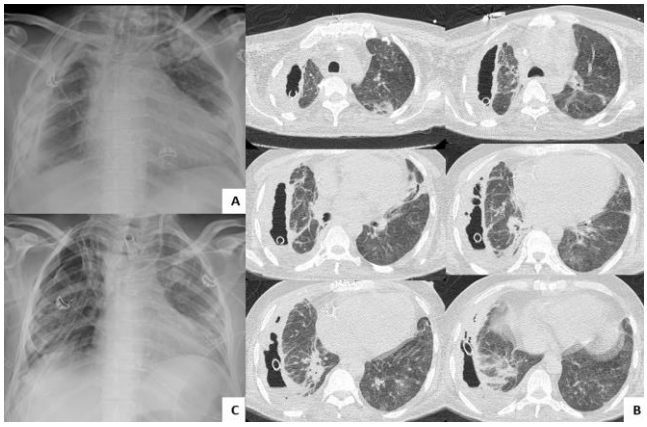

Figure 3: Chest X-ray before decortication (A), computed tomography of thick pleura before decortication (B), chest X-ray after decortication on the first day with three drains in the chest (C)

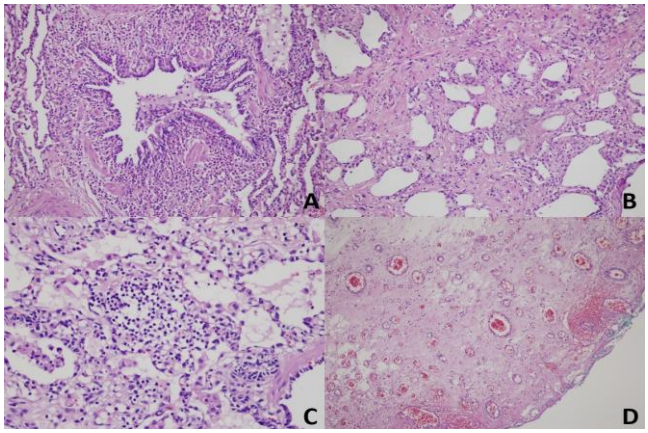

Figure 4: A. Bronchiolitis (A), fibrosis (B), lymphocytic infiltration (C), pleural edema and congestion (D)

Patient management was challenging due to an intestinal perforation that developed in the postoperative period that was one of the causes of mortality. Considering the etiology of such perforations, postoperative abdominal complications are closely related to the effect of extracorporeal circulation on gastrointestinal system blood flow. With both splanchnic hypoperfusion and impaired oxygenation in its pathogenesis, ischemia is thought to be the primary cause of most GI complications. Systemic inflammation and SIRS response occur as a result of reperfusion injury with the surgical stress response, contact with the CPB circuitry, mechanical ventilation and ischemia itself (which can activate and maintain SIRS). All these factors contribute to the improper distribution of blood flow and the disruption of mucosal oxygen delivery, and so patients with one or more of these factors should be carefully monitored for perforation (17).

CONCLUSION

Chest tube drainage is indicated as the first-choice treatment, and thoracoscopy may be necessary in persistent or recurrent pneumothorax cases. The timing of minimally invasive treatment is not certain, however, we believe early intervention with thoracoscopy should be attempted for the control of disease, and major surgery should not be avoided when deemed necessary. Early thoracoscopy ahead of complicated cases may result in better results and more effective air leak control.

COVID-19 infection has rarely been found to cause spontaneous pneumothorax, and patients usually have barotrauma as a result of mechanical ventilation treatment or a pre-existing cardiopulmonary comorbidity (3). An alveolar-pleural fistula causing persistent air leaks may develop and cause prolonged hospital stays and high morbidity (4).

Although chest tube drainage has been identified as a first-choice treatment, thoracoscopy may be necessary in persistent or recurrent pneumothorax cases. The timing of minimally invasive treatment is uncertain, although early intervention with thoracoscopy should be initiated to control the disease, and major surgery should not be avoided when deemed necessary. Early thoracoscopy ahead of complicated cases may lead to better results and more effective air leak control.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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RESPIRATORY CASE REPORTS

Lung Hernia as a Rare Complication of Thoracic Surgery: A Case Series

Göğüs Cerrahisinin Nadir Bir Komplikasyonu Olan Akciğer Hernisi: Olgu Serisi

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Abstract

The four cases presented here reveal the possibility of herniation in the lung from defects in the chest wall following surgical procedures. A review was made of four cases who developed cough and a visible swelling of the chest wall after surgery between February 2009 and June 2017. Lung hernia is a rare condition that is most commonly associated with trauma rather than thoracic surgery. In the four presented cases, the herniation occurred following thoracotomies in two cases, VATS in one case and tube thoracostomy in one case. All cases had an intercostal localization. Aside from one patient who was at risk of pneumothorax, all patients were operated after being followed up with a pressure dressing for two weeks. No postoperative complications occurred other than in one patient who was using methotrexate, and this patient was discharged without complications after myoplasty. Lung herniation is a rare complication of thoracic surgery and should always be kept in mind. Symptomatic surgery results are encouraging from the perspectives of pain and aesthetics.

Key words: *Lung herniation, iatrogenic, complication.*

Öz

Sunulan bu olgular, cerrahi işlemler sonrası göğüs duvarındaki bir defektten akciğer hernisi olabileceğini göstermeyi amaçlamıştır. Şubat 2009 ile Haziran 2017 arasında, ameliyattan sonra öksürük ve göğüs duvarında gözle görülür şişlik gelişen dört hasta incelendi. Akciğer hernisi, göğüs cerrahisinden ziyade en sık travmaya bağlı görülen nadir bir durumdur. Olgularımızda iki torakotomi, bir VATS ve bir tüp torakostomide herniasyon görüldü. Olguların tamamı interkostal yerleşimliydi. Pnömotoraks riski taşıyan bir hasta dışında tüm hastalar iki hafta baskılı pansuman ile takip edildikten sonra ameliyat edildi. Metotreksat kullanan bir hasta dışında postoperatif komplikasyon görülmedi. Bu hasta miyoplasti sonrası komplikasyonsuz olarak taburcu edildi. Akciğer hernisi göğüs cerrahisinin nadir görülen bir komplikasyonudur ve daima akılda tutulmalıdır. Semptomatik cerrahi sonuçları ağrı ve kozmetik nedenler açısından cesaret vericidir.

Anahtar Sözcükler: *Akciğer hernisi, iyatrojenik, komplikasyon.*

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Lung herniation is defined as the protrusion of the lung tissue surrounded by the pleura from a defect in the chest wall. The cases presented here show the possibility of lung herniation from a defect in the chest wall following minor or major surgical procedures such as thoracotomy, video assisted thoracoscopy (VATS) or even tube thoracostomy.

CASE

Case 1: A 66-year-old male patient was admitted to our clinic with a seroma on the incision line and a mass causing swelling outside the thoracic wall from the same location upon Valsalva maneuver after a neurogenic tumor excision with a right thoracotomy 6 months earlier (Figure 1). An image compatible with a pulmonary hernia was detected to which we applied conservative treatment with a pressure dressing for two weeks. A revision decision was made after the patient reported no regression in the complaint and that the pain and swelling were increasing. The old incision line was opened, the layers in the anatomical plan were crossed, the ribs in the area in which the defect was detected were approximated and repaired with a prolene patch, and a thorax tube was placed and closed. The drain of was terminated in the absence of complications on follow-up on the first postoperative day, and the patient was discharged with recovery on the second postoperative day.

Case 2: A 42-year-old male patient with a history of methotrexate use for the treatment of rheumatoid arthritis presented with a soft mass that expanded outwards with coughing on the old incision line and pain in the same area after an operation one month earlier. In the patient's history, empyema had developed one month after a tube thoracostomy due to a pleural effusion, for which he underwent decortication with a right thoracotomy. There was no improvement after two weeks of conservative treatment with a pressure dressing and so surgery was decided in which a polytetrafluoroethylene (PTFE) patch was used to repair the chest wall defect. In the second postoperative week, infection developed at the incision area due to steroid therapy for underlying rheumatoid arthritis, due to steroid therapy for underlying rheumatoid arthritis, due to steroid therapy for underlying rheumatoid arthritis, and myoplasty was performed using the latissimus dorsi muscle along with an appropriate antibiotherapy. The patient was discharged on the 14th day following the revision.

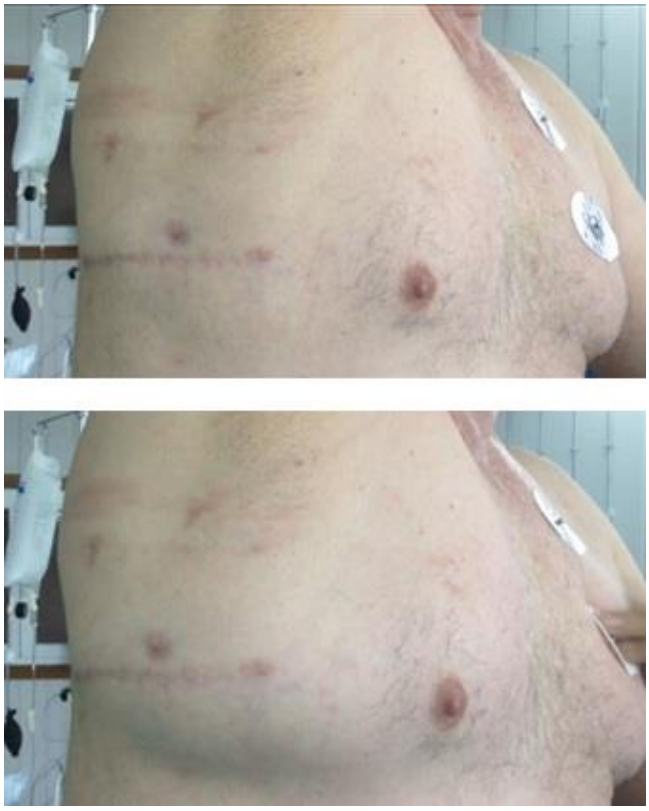

Figure 1: *Image of Case 1 before revision, normal and swelling due to lung tissue protruding out of the thorax with coughing*

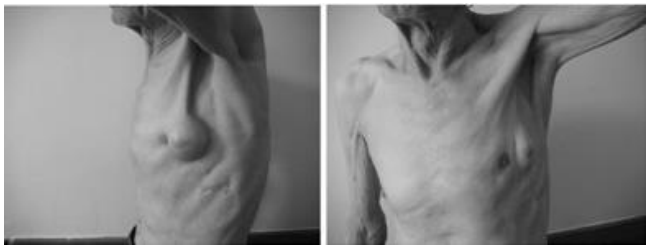

Figure 2: *Inspiratory and expiratory images of Case 3*

Case 3: A 45-year-old male patient who had been followed for chronic obstructive pulmonary disease (COPD) for many years and had undergone a left tube thoracostomy due to secondary pneumothorax developed swelling and pain two years later at the old incision that became evident with coughing (Figure 2). Direct chest radiography and thorax CT examinations were performed (Figure 3) and a bulla on the left pleural wall was detected protruding from the intercostal space in which a tube thoracostomy was performed. Surgery was preferred over conservative treatment due to the risk of pneumothorax. The defect was repaired primarily by not using a patch. A 32 F thorax tube was placed and the thorax was closed. On the second postoperative day, the drain was terminated and the patient was discharged without complications.

Case 4: A 46-year-old male patient was admitted to our clinic with complaints of pain, cough and swelling in the right chest, four years after a right VATS thymectomy. Physical examination and thorax imaging revealed a hernia of lung tissue from the auxiliary incision line to the outside of the thorax. Conservative treatment was applied for two weeks involving a pressure dressing, and surgery was subsequently planned due in the absence of the expected improvement. The herniated lung tissue was replaced with an incision made above the swelling, and the defect in the rib area was repaired with a polytetrafluoroethylene (PTFE) patch (Figure 4). The procedure was terminated without placing a drain. The patient was discharged on the second postoperative day without complications.

DISCUSSION

We analyze here four cases who applied to our clinic with complaints of external swelling and cough at the incision line on the chest wall after thoracic surgery. Of the four patients, who were aged 42–66 years, two had a thoracotomy, one had VATS and one patient had a history of tube thoracostomy. The mean operation time was 30 minutes; no preoperative complications developed in any of the cases; the mean hospital stay was four days; no complication developed in any of the cases except one during postoperative follow-up; and all four cases were discharged with full recovery after treatment.

There are few reports in the literature addressing the issue of lung herniation. The condition was first defined by Roland, and classified according to pathology and localization by Morel-Lavallee in 1847. The most common forms are iatrogenic herniations, as in the four cases presented here. The acquired form is categorized into four groups as pathological, spontaneous, traumatic and iatrogenic. Intercostal defects are prominent and can often be seen following surgical interventions such as thoracotomy, tube thoracostomy or video-thoracoscopy, less frequently as penetrating traumas, and rarely as a result of blunt trauma (1). In blunt and high-energy traumas, lung herniation from the anterior chest wall, in which strong muscle support is lacking, is more common in cases of multiple rib fractures and fractures in the sternocostal region (2-5). Lung hernias seen following penetrating traumas or after thoracotomy or video-assisted thoracoscopic surgery (VATS) develop in the long or short term, and can often be attributed to ineffective closure of the ribs or weakness in the intercostal muscle tissue (6). In symptomatic cases, the most common complaint is pain followed by aesthetic concerns and body image disorder. Dyspnea and hemoptysis are rare symptoms, and asymptomatic cases can also be encountered. The specific finding upon physical examination is palpation of a mass protruding from the thorax with coughing that expands with the cough. Although rare, complications include incarceration, hemoptysis, pneumothorax and recurrent infections. For the treatment of lung hernia, both surgical and conservative treatments are recommended, and spontaneous recovery is not possible. Symptomatic patients often require surgical treatment due to the risk of incarceration of the pulmonary parenchyma, while asymptomatic cases can be followed up with pressure dressings (1,3-7).

Our preference is to first try conservative treatment involving a pressure dressing for two weeks in cases of lung hernia, however the lack of response to conservative treatment in three of the cases we present here led to surgical treatment. Since there was a high risk of pneumothorax in one case, we decided to operate without first trying conservative treatment. Literature includes a case of pulmonary hernia who underwent emergency surgery due to incarceration (8).

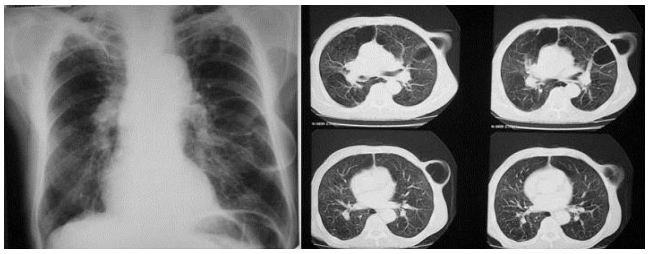

Figure 3: *CT section of Case 3 showing PA Chest X-ray and bulla hernia*

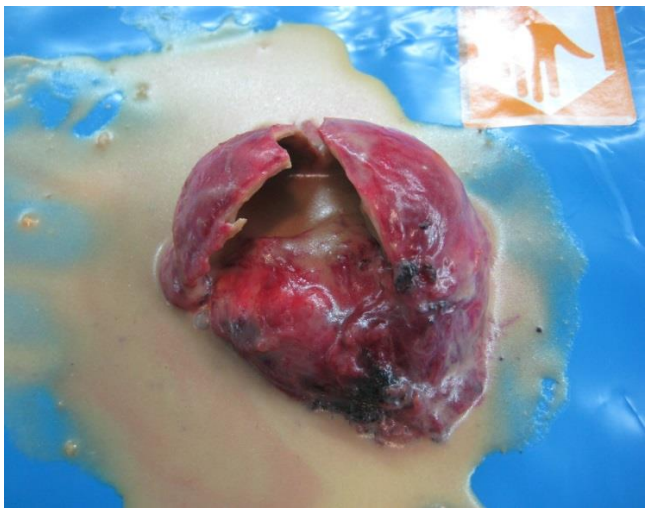

Figure 4: *The excised surgical material in Case 4*

The criteria for surgical repair are persistent symptoms or the development of complications. Surgery should be considered in patients with severe pain and cosmetic concerns, despite the application of a pressure dressing to the herniated area. The main principles in revision are the reduction of the herniated lung tissue, removal of intrathoracic adhesions and firm approximation of the ribs. In case of complications, a wedge resection of the lung parenchyma may rarely be required. Prolene mesh and PTFE mesh are the most preferred options for defect repair (9).

Although there is a dearth of information in literature on the methods and materials to be used for chest wall repair in lung hernia, publications on chest wall reconstructions have guided the selection of methods and materials to be used. Appropriate and patient-customizable materials should be preferred to ensure chest wall stability, to protect organs and muscle function, and to minimize the risk of infection. Polyglactin (Vicryl, Ethicon Inc., Somerville), polypropylene (Davol, Warwick; Prolene, Ethicon Inc., Somerville) and polytetrafluoroethylene (DUALMESH, W.L. Gore & Associates, Flagstaff) are materials that preserve muscle function, are customizable to the patient, and have a low risk of infection, making them superior to methylmethacrylate, nylon, silastic and silicone (10). Our facility uses PTFE mesh, based on clinical experience and literature. In Case 2, who underwent decortication for empyema, complications developed although PTFE mesh had been preferred due to the lower foreign body reaction and lower risk of infection, and it was necessary to perform myoplasty involving the removal of the PTFE mesh. In this case, we believe it due to the methotrexate use for the treatment of advanced stage rheumatoid arthritis, the infection could be brought under control in a very long time.

We have treated pulmonary hernias in four patients in our five-year clinical experience. While being very rare, lung hernia can have serious consequences, such as incarceration, pneumothorax and infection, and as in one of the cases presented here, can be seen even after tube thoracostomy. Furthermore, some risk factors of lung herniation following VATS procedures have been identified in literature, such as opening of an intercostal space larger than the skin incision, emphysema, chronic cough, weakness of the chest wall muscles and improper closure of the incision (7). Although taking precautions against these risk factors should be treated as a priority, when a lung hernia develops, when there is no response to conservative treatment or in emergency cases, repairs can be made very easily with prolene or PTFE mesh, as a practical and effective approach that responds positively to the expectations of the patient.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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A Rare Tumor of the Posterior Mediastinum: Well-Differentiated Liposarcoma

Posterior Mediastenin Nadir Bir Tümörü: İyi Diferansiye Liposarkom

Gözde Kalbaran Kısmet[1], Oguzhan Okutan[1], Seda Mazmanoğlu Atılman[2], Ismail Yilmaz[3]

Abstract

Liposarcoma is one of the most common forms of soft tissue sarcoma in adults, and usually occurs in the lower extremities and retroperitoneum. It has several histological subtypes, including myxoid, well-differentiated, dedifferentiated and pleomorphic. Liposarcomas originating from the mediastinum are extremely rare, and usually grow slowly and remain asymptomatic, but may become symptomatic when they become large enough to press on the adjacent structures. Computed tomography and magnetic resonance imaging provide useful data for diagnosis, while tissue biopsy based on typical pathological features is required for a definitive diagnosis. Complete surgical resection is the first-line treatment option as it is resistant to chemoradiotherapy. Due to the high risk of recurrence, long-term follow-up should be continued. We present here the rare case of a 56-year-old female patient with primary mediastinal liposarcoma who presented with a complaint of cough.

Key words: *Atypical Lipomatous Tumor, CDK4, Well-Differentiated Liposarcoma, MDM2.*

Öz

Liposarkom erişkinlerde en sık görülen yumuşak doku sarkomlarından biridir; genellikle alt ekstremitelerde ve retroperitonda ortaya çıkar. Miksoid, iyi diferansiye, farklılaşmamış (dediferansiye) ve pleomorfik olmak üzere çeşitli histolojik alt tipleri vardır. Mediastenden kaynaklanan liposarkomlar son derece nadirdir. Bu tümörler genellikle yavaş büyürler ve asemptomatik kalırlar ancak büyük boyuta ulaşıp komşu yapılara bası yaptığında semptomatik olabilirler. Bilgisayarlı tomografi ve manyetik rezonans görüntüleme tanı için faydalı veriler sağlar. Kesin tanı için doku biyopsisi gereklidir ve tanısı tipik patolojik özelliklere dayanır. Kemoradyoterapiye duyarlı olmadığından tam cerrahi rezeksiyon birinci basamak tedavi seçeneğidir. Nüks oranı yüksek olduğundan uzun süreli takip yapılmalıdır. Bu yazıda öksürük şikayeti ile başvuran primer mediastinal liposarkomlu 56 yaşında kadın olgu nadir görülmesi sebebiyle sunuldu.

Anahtar Sözcükler: *Atipik Lipomatöz Tümör, CDK4, İyi Diferansiye Liposarkom, MDM2.*

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Liposarcoma, a common soft tissue tumor, accounts for approximately 20% of all mesenchymal malignancies (1), while mediastinal liposarcoma is a very rare primary malignant tumor that accounts for only 0.1–0.75% of all mediastinal tumors (2).

Well-differentiated liposarcoma (WDL), also known as atypical lipomatous tumor (ALT) – a locally aggressive form of adipocytic tumor – is the most common histological liposarcoma subtype, accounting for 40–45% of the total (3, 4). ALT/WDL occurs especially in the deep soft tissues of the proximal extremities (thigh and hip, shoulder and back), and in the retroperitoneum and paratesticular area (5). Although ALT and WDL are morphologically and genetically identical, the term WDL is used for tumors of the retroperitoneum, mediastinum and deep pelvis (in which the chance of reaching negative margins is reduced and local recurrence is increased), while the term ALT includes tumors of the extremities and superficial regions (in which complete excision is possible and curative) (1).

ALT/WDL occurs most frequently in the 5th and 7th decades, and predominantly in adult males (6, 7). Although surgical excision is the optimal treatment option for mediastinal liposarcomas, postoperative recurrence rates range from 50–90% (8).

In this case report, we present to literature a patient with ALT/WDL located in the posterior mediastinum who underwent excision by thoracotomy.

CASE

A 56-year-old female patient with known type-2 diabetes mellitus, coroner artery disease (2 years ago, coronary stent) and hyperlipidemia was admitted with complaints of cough and difficulty in sputum production for a week. She was an active smoker with a 20 pack/year smoking history. A physical examination of all systems was normal, and hemogram and biochemical values were within normal limits. A pulmonary function test revealed FEV1/FVC: 88.7% and FEV1: 87% (2.11 L).

A posteroanterior chest radiograph showed increased opacity in the paratracheal area and mediastinal enlargement in the right upper zone (Figure 1A).

Thorax computed tomography (CT) revealed a sharply defined, lobulated, hypodense mass lesion with a mean density of -99 Hounsfield units (HU), reaching 13x8x7cm in diameter, reaching the largest transaxial diameter, extending from the carina level to below to the neck level, and deviating the trachea and esophagus anteriorly in the retroesophageal area of the posterior mediastinum (Figure 2). A neck ultrasonography revealed a well-circumscribed solid lesion at the mid-lower zone level of the right and left lobes of the thyroid gland starting in the posterior neighborhood of the thyroid gland and continuing to the mediastinum, containing linear echoes and slightly hypoechoic when compared to the thyroid and with very sharp borders. No pathological F-18 fluoro-2-deoxy-glucose (FDG) uptake was observed in the lesion on positron emission tomography (PET-CT), and no significant hypermetabolic findings were identified that could be evaluated in favor of malignancy with FDG affinity in other parts of the body included in the PET-CT examination.

The patient was consulted to thoracic surgery, and a mass excision was performed by thoracotomy (Figure 1B and Figure 3).

Macroscopically, a 12x9x3.5 cm fatty tissue mass was observed, surrounded by a capsule with a smooth surface in most areas and irregularities in focal areas, as well as a collective 6x5x3 cm fat tissue mass, which was sent in parts. The section was in the appearance of homogeneous dirty yellow mature oil. Microscopically, few atypical stromal cells with hyperchromatic large nuclei were observed in the tumor that included fibrous septations in places (Figure 4 and 5). In an immunohistochemical examination, cyclin-dependent kinase 4 (CDK4) was identified in histiocytic and atypical stromal cells (Figure 6). ALT/WDL was first considered due to the presence of atypical stromal cells, the size difference between the lipocytes, the >10 cm lesion diameter and the deep localization of the mass. A molecular analysis was performed for murine double-minute type 2 (MDM2) and CDK4 amplification for definitive diagnosis and typing. Amplification was detected in the CDK4 and MDM2 gene regions by fluorescence using the in situ hybridization (FISH) technique (Figure 7).

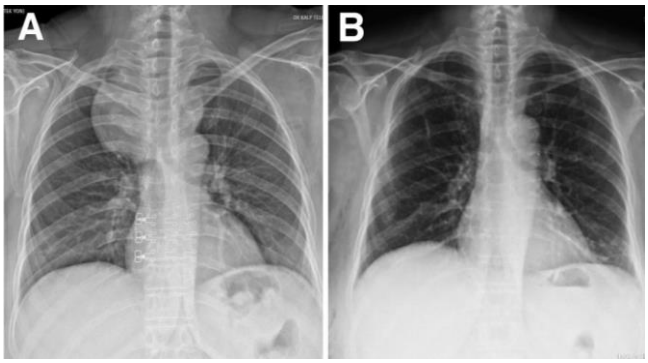

Figure 1: Posteroanterior chest radiograph showing increased opacity in the paratracheal area and mediastinal enlargement in the right upper zone (A); Post-thoracotomy chest X-ray of the patient (B)

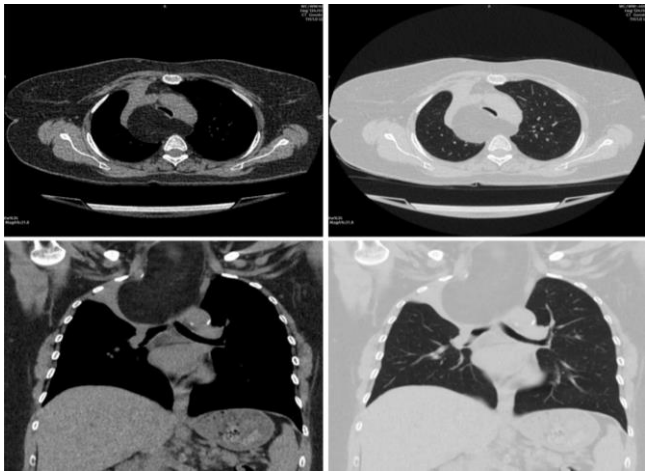

Figure 2: Thorax CT image of the patient at the time of diagnosis in which a sharply demarcated, lobulated contour, hypodense mass lesion compatible with lipoma can be seen in the retroesophageal area in the posterior mediastinum, starting from the carina level below and extending to the neck level above, deviating the trachea and esophagus anteriorly

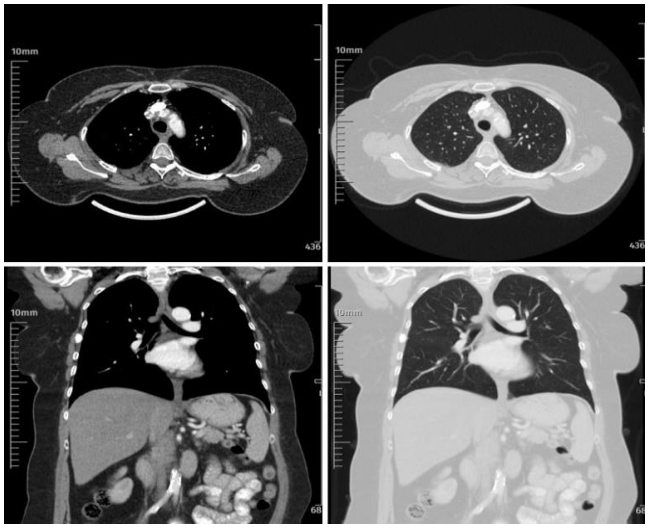

Figure 3: Post-thoracotomy chest thorax CT of the patient

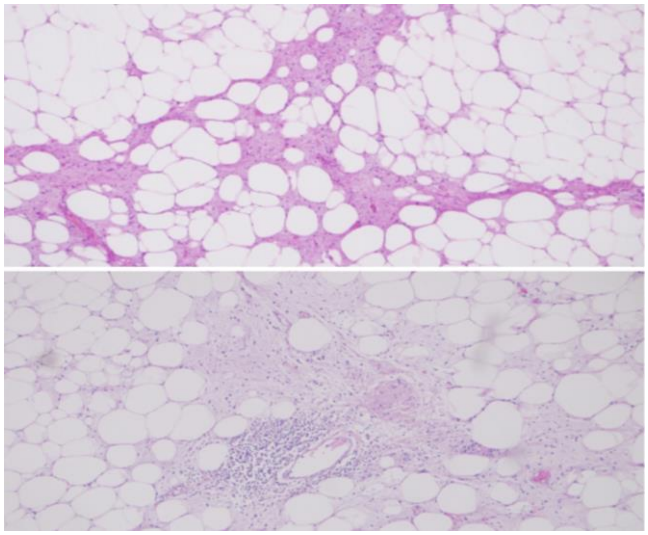

Figure 4: Adipose tumor containing fibrous septations and chronic inflammatory cells between fat lobules (H&E X10)

Since the tumor size was very large (>10 cm), 25 postoperative adjuvant radiotherapy (RT) sessions were given to the chest and neck region in order to prevent local recurrence. The patient was asymptomatic at 5 months postoperatively, and no recurrence or metastasis was detected. She continues to be followed closely by oncology, both clinically and radiologically.

DISCUSSION

Primary mediastinal liposarcomas are very rare (9). Liposarcomas have several histological subtypes, such as myxoid, well-differentiated, dedifferentiated and pleomorphic, and all of these liposarcoma subtypes have been reported to occur in the mediastinum. ALT/WDL is the most common type of liposarcoma in the mediastinum (10, 11).

ALT/WDL can be categorized histologically as adipocytic (or lipoma-like), sclerosing, spindle cell and inflammatory types, with the most common forms being adipocytic (or lipoma-like) and sclerosing (12). Adipocytic (or lipoma-like) liposarcomas can reach large sizes with well-circumscribed, lobulated masses, as in the present case, and may not be differentiated from benign lipomas macroscopically, making microscopic examination necessary. ALT/WDLs are adipocytic neoplasms characterized by a proliferation of pleomorphic mature adipocytes in different patterns containing atypical hyperchromatic stromal cells. They intersect with fibrous septa, and may have myxoid or fibrous components and areas of fat necrosis (5). Our case was diagnosed based on a histological examination and molecular pathological test. The molecular pathological examination of CDK4 and MDM2 genes is considered the optimum approach to the distinguishing of well-differentiated liposarcoma from lipoma. The immunostaining technique for MDM2 and CDK4 is low cost and is regularly adopted due to its high compatibility with the FISH method, although the FISH approach to the detection of MDM2 and CDK4 gene amplification, however, is more sensitive and specific than immunohistochemistry. A histological material FISH technique should be used to differentiate between the tumor and other adipocytic neoplasms when the tumor is larger than 10 cm, and in suspicious atypical lesions, recurrent lesions, in those with retroperitoneal and abdominal localizations, and in cases with alarming clinical and radiological features (13, 14). In our case, the FISH method was used due to the presence of atypical stromal cells, the size difference between the lipocytes, the lesion diameter greater than 10 cm and the deep localization of the mass,

and the amplification was positive in the MDM2 and CDK4 genes, leading to the diagnosis being clarified as ALT/WDL.

Based on the limited number of cases reported in literature, ALT/WDL mostly occurs in the anterior mediastinum (12, 15-17), and is more common in adult males between the ages of 40 and 60 (7). Our 56-year-old female case had a tumor originating from the posterior mediastinum.

The behaviors of tumors in the mediastinum are similar to those in the lower extremities and retroperitoneum, which are the most common sites, respectively. Mediastinal ALT/WDL usually grows slowly and up to 15% of patients may be asymptomatic. The laxity and mobility of tissues and the mediastinal state of these structures allow them to gradually adapt and accommodate slow-growing tumors. Tumors can thus reach large sizes, and subsequently, to press on neighboring structures causing such symptoms as superior vena cava syndrome, Horner's syndrome, dysphagia, dyspnea, cough, spinal nerve palsy and tachycardia (3, 7). In our case, the patient presented to us with acute cough.

The predominant finding of mediastinal liposarcoma on conventional chest radiography is an enlarged mediastinum, although trachea and vessel deviation may also be prominent. The mediastinal enlargement was detected in the posteroanterior chest X-ray of our case.

Mediastinal liposarcomas can appear as a fat-containing masses to solid masses with low attenuation values ranging from -50 to -150 HU on thorax CT (18), while larger values may be related to necrosis, heterogeneity or the soft tissue component of liposarcomas. When well-differentiated, they are more radiolucent, homogeneous and well-circumscribed like lipomas, while other liposarcomas may be irregularly-circumscribed, of greater density and radiopaque. The CT findings of ALT/WLD are similar to those of lipomas, and usually involve a large amount of fat covering more than 75% of the tumor volume (9). In our case, a hypodense mass lesion compatible with a lipoma of -99 HU density (low density) was observed. Thorax CT is also useful for determining the size of the lesion before surgery, as well as the size and location of the residual tumor after surgical resection (17). Magnetic resonance imaging provides more valuable information in terms of revealing any mediastinal vessel invasions (2).

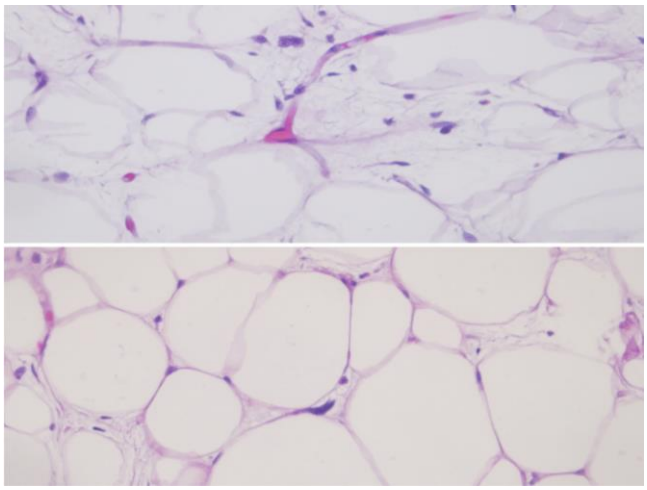

Figure 5: Atypical stromal cells, with significant shape and size differences discernible between adipocytes (H&E X40)

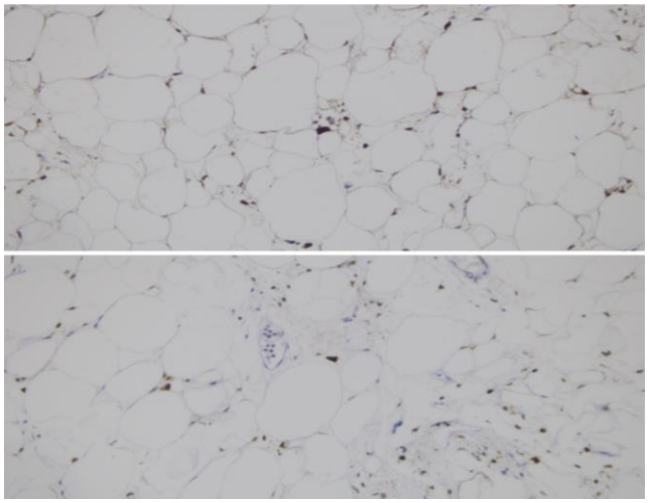

Figure 6: CDK4 positivity in histiocytic and atypical stromal cells in immunohistochemical examination

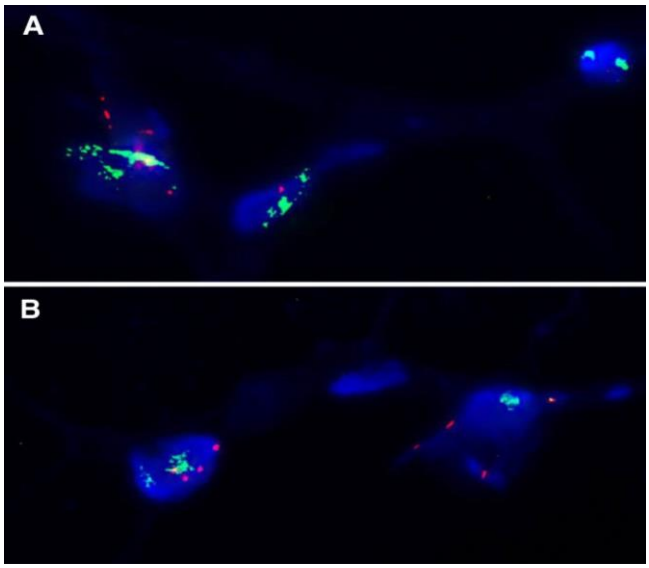

Figure 7: Amplification positivity in the MDM2 gene regions using the FISH technique (A); Amplification positivity in CDK4 gene regions using the FISH technique (B)

There have been several earlier studies identifying the FDG PET properties of lipomatous tumors, including PET

studies showing a correlation between SUVmax (degree of metabolic activity) and liposarcoma tumor grade, and higher grade tumors tending to have greater FDG uptake (19). If a fat-containing lesion has significant (>25%) internal soft tissue content on CT, it should be considered suspicious for liposarcoma, regardless of FDG activity, as both ALT/WDL and myxoid liposarcoma can occur with low metabolic activity. In other words, low FDG activity should not be assumed to be a sign of benignity (19). In our case, no pathological FDG uptake was observed on PET-CT. Since ALT/WDL is a low-grade malignant atypical lipomatous, well differentiated tumor, FDG uptake may not be observed.

In patients with mediastinal liposarcoma, a complete surgical resection with largely negative margins is usually curative and is considered the optimum treatment approach. ALT/WDL is considered a low-grade malignancy that rarely metastasizes, but should be followed carefully as recurrence or differentiation may occur (6), and it should be kept in mind that ALT/WDLs have no potential for metastasis unless dedifferentiated (20). It has been reported that patients can benefit from repeated surgical resections in cases of recurrence (6).

Since these tumors are resistant to chemotherapy and RT, such treatments have limited effect on survival (8). Radiotherapy may be valuable for the palliation of unresectable cases, but is very likely to result in mediastinal fibrosis in this region, and the effect of chemotherapy has not yet been determined (12). The application of radiotherapy before and after the operation has also been suggested. In our case, a wide surgical resection was performed and a negative surgical margin was achieved, and adjuvant RT was given after the operation to prevent local recurrence given the large size of the tumor.

Histological typing is very important in determining the type and extent of treatment. Due to differences in the treatment approaches, prognosis and long-term follow-up, it is important to preoperatively differentiate between simple lipoma and well-differentiated liposarcoma (4) as the survival of patients with differentiated or pleomorphic liposarcoma is significantly shorter than those with myxoid or well-differentiated liposarcoma (7).

The most important factor in prognosis is anatomical location. If the tumor is deeply located (mediastinum, retroperitoneum, spermatic cord), the chance of achieving negative surgical margins decreases, the risk of local recurrence increases, and the risk of death increases as a result of uncontrolled local effects (5,9). In such cases, local recurrence is more common than metastasis. with a prevalence of around 40%, often occurring within the first 6 months (20). Tumors located in central body cavities, however, tend to envelop vital structures or may simulate normal adipose tissue, making negative margins very difficult to obtain.

CONCLUSION

Although primary mediastinal liposarcomas are very rare, they should be considered in the differential diagnosis of mediastinal tumors (16). Their anatomical location may complicate complete surgical resection, and recurrences may develop in the event of positive margins. Furthermore, despite their slow growth, these tumors are associated with a poor prognosis, and so it is important to ensure the continued postoperative clinical follow-up of patients, given the likelihood of recurrence.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

YAZAR KATKILARI

Fikir - G.K.K., O.O., I.Y., S.M.A.; Tasarım ve Dizayn - G.K.K., O.O., I.Y., S.M.A.; Denetleme - G.K.K., O.O., I.Y., S.M.A.; Kaynaklar - G.K.K., S.M.A.; Malzemeler - G.K.K., I.Y.; Veri Toplama ve/veya İşleme - G.K.K., O.O.; Analiz ve/veya Yorum - G.K.K., O.O.; Literatür Taraması - G.K.K., S.M.A.; Yazıyı Yazan - G.K.K.; Eleştirel İnceleme - O.O., I.Y.

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RESPIRATORY CASE REPORTS

A Case of Osseous Sarcoidosis Mimicking Metastatic Cancer

Metastatik Kanseri Taklit Eden Osseöz Sarkoidoz Olgusu

Tuğba Akkale, Gülden Sarı, Adem Koyuncu, Ceprail Şimşek

Abstract

Sarcoidosis is a chronic granulomatous multisystem disease that often progresses with lung, lymph nodes, skin and eye involvement, while bone involvement may occur more rarely. All bones can be affected, however, although the short bones, such as fingers and toes, are the most commonly affected, while vertebral involvement is rare. Bone involvement is usually determined incidentally due to the asymptomatic course of the disease. We present here the case of a 62-year-old female osseous sarcoidosis case who was diagnosed with pulmonary sarcoidosis seven years earlier and re-evaluated in our clinic due to recently developed low back pain.

Key words: *Sarcoidosis, Bone, Malignancy, Osseous sarcoidosis.*

Öz

Kronik granülomatoz multisistem bir hastalık olan sarkoidoz sıklıkla akciğer, lenf nodları, cilt ve göz tutulumları ile seyreder. Nadir olarak kemik tutulumları da görülür. Tüm kemikler etkilenebilir ancak en sık el ve ayak parmakları gibi kısa kemikleri tutar. Vertebra tutulumu ise daha nadirdir. Asemptomatik seyirli olması nedeni ile kemik tutulumları genellikle tesadüfen tespit edilir. Yedi yıl önce pulmoner sarkoidoz tanısı alan ve yeni gelişen bel ağrısı şikayeti nedeniyle kliniğimizde tekrar değerlendirilen 62 yaşında bir osseöz sarkoidoz olgusu sunduk.

Anahtar Sözcükler: *Sarkoidoz, Kemik, Malignite, Osseöz sarkoidoz.*

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*****This case report was presented as an e-poster at the Turkish Respiratory Society 43rd Annual Congress with International Participation, which was held between October 29- November 3, 2021.

Sarcoidosis is an inflammatory disease of unknown cause that is characterized by the presence of pathologically non-caseating granulomas, and that can frequently involve multiple organs such as the lungs, lymph nodes, skin and eyes (1). In sarcoidosis, the pulmonary system is affected in 90% of cases, while bone involvement is rarer, developing in 3–13% of sarcoidosis cases (1-3). Due to the asymptomatic course of bone sarcoidosis, however, this rate is estimated to be lower than it should be (4). Symptomatic patients describe nonspecific complaints such as pain, swelling and tenderness that increase with movement in the involved bone. Bone lesions are usually detected when assessing sarcoidosis with other system involvement (5). Lytic, sclerotic or both lesions can be observed in the bone upon radiological evaluation, although these findings are not specific to sarcoidosis. A biopsy is required for definitive diagnosis in cases where the clinical and radiological findings are compatible with sarcoidosis (2,3,6). The presence of multiple bone lesions in a patient with a diagnosis of sarcoidosis should also suggest bone involvement of sarcoidosis in the differential diagnosis (7).

CASE

A 62-year-old female patient diagnosed with pulmonary sarcoidosis was admitted with a complaint of low back pain lasting three months. The patient, a housewife, had no smoking, environmental or occupational dust exposure history. A granulomatous inflammation had been detected during a mediastinal lymph node biopsy 7 years earlier, and the patient had been diagnosed with stage 2 sarcoidosis. Deflazocort 90 mg/day was initiated but was discontinued within 1 year through dose reductions in intermittent outpatient clinic follow-ups. No symptoms or radiological progression were observed in the follow-up evaluations. In the current evaluation of the patient, no pathological system finding was determined from a physical examination, while the laboratory test results revealed platelet level 420x103/microL, creatinine 1.12mg/dL, alkaline phosphatase 164 IU/L (30-120 IU/L), C-reactive protein (CRP) 7 mg/mL (N= 0-5 mg/mL) and sedimentation 44 mm/h (N= 0-20 mm/h), while calcium was 322 mg (N= 100-300 mg/24h) and ACE 64 U/L (N= 13-64 U/L) in 24-hour urine. There were no pathological findings in the eye or in the dermatological examination, and pulmonary function test results were within normal limits, although there was a slight decrease in diffusion capacity for carbon monoxide (5.03 mmol/min/kPa; 65% predicted). High-resolution computed tomography (HRCT) revealed multiple mediastinal lymphadenopathies, multiple nodules measuring 11 mm scattered across both lungs, and interstitial density increases in reticulonodular weight in the parenchyma (Figure 1). Although these findings suggested metastatic nodules, no significant progression was detected when compared to the patient's HRCT findings from 7 years earlier. She had been examined with lumbar and thoracic magnetic resonance imaging (MRI) in the center to which she had applied with low back pain. On MRI, T1 hypointense and T2 hyperintense focal lesion areas were observed in the T3, T8, T10, T11 and T12 vertebral corpus, and multiple bone lesions measuring 26x20 mm in the L4 vertebra (Figure 2). With a preliminary diagnosis of malignancy, bone scintigraphy and abdominal computed tomography (CT) examinations were carried out. The bone scintigraphy revealed increased activity in the lateral part of the right humerus neck, the lateral part of the right fifth rib, and in the T12, L1 and L3-4 vertebrae, while hypodense nodular areas were noted in the vertebral column that could not be differentiated from lytic lesions in abdominopelvic CT.

A biopsy was performed at the level of the L3 vertebra with a preliminary diagnosis of osseous sarcoidosis and malignancy. Granulomatous inflammation was reported in the histopathological evaluation, while no staining was observed in mycobacterium bacillus in the granuloma structures with Zielh-Neelsen and histiocytes with CD68. Furthermore, no significant staining was observed with CD30 performed for the differential diagnosis of infiltrative tumoral pathology and lymphoma with immune histochemical pan-cytokeratin (Pan-CK) and epithelial membrane antigen (EMA). Based on the present findings, the patient was diagnosed with osseous sarcoidosis and treatment was initiated, and she was taken to follow-up.

DISCUSSION

Osseous sarcoidosis is known to affect primarily the bones in the hands and feet, and less frequently, the skull, vertebrae and pelvis (7-9). Vertebral sarcoidosis is generally asymptomatic, while the majority of symptomatic patients describe low back pain, and some may develop neurological symptoms (10). Vertebral involvement of sarcoidosis presents on radiography and CT as lytic or sclerotic lesions, or a combination of both (11), and pulmonary involvement in the form of mediastinal lymphadenopathy and/or parenchymal abnormalities accompanies in 80–90% of osseous sarcoidosis patients (12). Our patient had been diagnosed with sarcoidosis 7 years earlier, and presented with new-onset low back pain but

no neurological deficit. HRCT revealed multiple mediastinal lymphadenopathies, multiple scattered nodules in both lungs and reticulonodular lesions in the parenchyma, and abdominopelvic CT revealed hypodense nodular areas in the vertebral column that could not be distinguished from lytic lesions.

Axial skeletal involvement in sarcoidosis has been reported only rarely, although new imaging methods such as MRI and Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET-CT) may increase the identification of axial involvement (11). PET-CT is a highly sensitive test that shows bone lesions that cannot be visualized by radiography or CT, although granulomas also show increased involvement in PET-CT, leading to false positive results and making it difficult to differentiate from malignancy (12). In such cases, MRI may provide a more accurate evaluation of the bone structure (13), although neither PET-CT nor MRI alone is sufficient to differentiate malignancy (14).

MRI is diagnostically significant as it offers a good guide to the differential diagnosis of osseous sarcoidosis lesions and bone biopsy (12). Sarcoidosis lesions appear hypointense in T1 and hyperintense in T2 on MRI (7,14). These findings are not specific for sarcoidosis, and so a differential diagnosis should rule out metastatic cancers, Paget's disease, osteomyelitis, multiple myeloma and lymphoma should be made (15). Multiple lesions were detected in our patient on a thoracic and lumbar spine MRI. A biopsy was performed at the L3 vertebral level with increased uptake on MRI for the differential diagnosis. A histopathological diagnosis of granulomatous inflammation was made, and based on her clinical, radiological and histopathological findings, the patient was determined to have osseous sarcoidosis.

Studies investigating the radionuclide imaging of sarcoidosis are scarce. In a study carried out by Cinti et al. (11), numerous involvements were detected in the ribs and calvarium that regressed following steroid treatment. In the present study, bone scintigraphy revealed increased activity in the lateral part of the right humerus neck, the lateral part of the right fifth rib, and in the T12, L1 and L3-4 vertebrae.

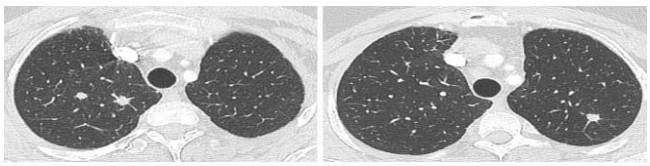

Figure 1: Bilateral scattered multiple nodular densities and interstitial density increases in reticulonodular weight in the parenchyma on HRCT imaging

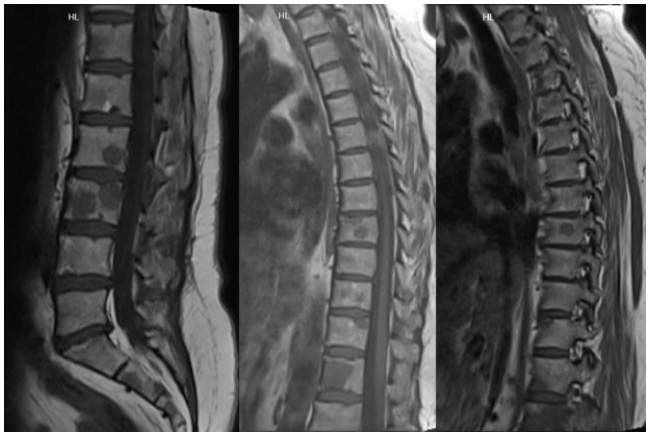

Figure 2: Low-density multiple involvement areas on T1-weighted sagittal MR imaging of the thoracolumbar spine

There is a lack of consensus on the treatment of osseous sarcoidosis. Spontaneous remission is observed in some patients, and no treatment is needed (16), while hypercalcemia, bone destruction and the presence of symptoms have been identified as indications for treatment (17). The main aim of treatment is to reduce the granuloma burden (5). Corticosteroids are used as first-line therapy, and the treatment response is generally good due to their efficiency in relieving inflammation and relieving symptoms. Bone lesions persist, however, even when symptoms are controlled in some cases. If adverse effects to corticosteroid develop or in resistant cases, methotrexate, hydroxychloroquine, adalimumab and infliximab treatments can be substituted or used in combination (18,19). Since our patient was symptomatic, we initiated corticosteroid treatment with planned dose reduction based on the adverse effects and symptoms in the controls.

In conclusion, sarcoidosis may affect many organs and systems, although bone involvement is rare, and is thought to be underdiagnosed because due to usually asymptomatic course. Bone scintigraphy, PET-CT and MRI are beneficial in diagnosis radiologically, while a final diagnosis should be based on biopsy, clinical and radiological evaluations together. Immunosuppressive agents such as corticosteroids, methotrexate and tumor necrosis factor-α blockers can be used to treat symptomatic cases.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - T.A., G.S., A.K., C.Ş.; Planning and Design - T.A., G.S., A.K., C.Ş.; Supervision - T.A., G.S., A.K., C.Ş.;

Funding - T.A., G.S., A.K.; Materials - T.A., G.S., A.K.; Data Collection and/or Processing - T.A., G.S.; Analysis and/or Interpretation - T.A., G.S.; Literature Review - T.A., G.S.; Writing - T.A., G.S.; Critical Review - T.A., G.S., A.K., C.Ş.

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A Case of Endobronchial Sarcoidosis with Recurrent Pneumonia

Tekrarlayan Pnömoni ile Seyreden Endobronşiyal Sarkoidoz Olgusu

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Abstract

Sarcoidosis is a chronic, multisystem and non-caseating granulomatous disease of unknown etiology. Its diagnosis is based on a combination of clinical and radiographic findings and the demonstration of typical granulomas, and can often be made based on the exclusion of other granulomatous diseases. There is lung involvement in 90% of cases, often in the form of parenchymal disease, while involvement in the form of an endobronchial mass is a rarer condition. Our patient underwent bronchoscopy after being diagnosed with sarcoidosis around 3 years earlier, and was followed up without treatment due to a history of pneumonia that had recurred three times in the same localization in the previous year. An endobronchial lesion was identified on bronchoscopy, while a biopsy revealed granulomatous inflammation. Progressive sarcoidosis was considered based on the clinical and radiological findings and the patient was started on steroid treatment. We present this study of a case of sarcoidosis with recurrent pneumonia in the same localization and endobronchial involvement to emphasize the need to consider sarcoidosis in the differential diagnosis of endobronchial mass lesions.

Key words: *Sarcoidosis, endobronchial, treatment.*

Öz

Sarkoidoz etiyolojisi bilinmeyen, kronik, multisistemik nonkazeifiye granülomatöz bir hastalıktır. Tanısı, klinik ve radyografik bulguların birlikteliğine, tipik granülomların gösterilmesine dayanır ve çoğu zaman diğer granülomatöz hastalıkların dışlanmasıyla konulabilir. Akciğer tutulumu %90 oranındadır. Sarkoidozda akciğer tutulumu sıklıkla parankimal hastalık şeklindeyken, nadiren endobronşiyal kitle şeklinde tutulum görülebilir. Yaklaşık 3 yıl önce sarkoidoz tanısı konan ve tedavisiz izlemde olan olgumuza son bir yıl içinde aynı lokalizasyonda üç kez tekrarlayan pnömoni öyküsü olması nedeniyle bronkoskopi yapıldı. Bronkoskopide endobronşiyal lezyon görülüp alınan biyopsisinde granülomatöz inflamasyon saptanan hastada klinik, radyolojik bulgularla progresif sarkoidoz düşünüldü ve steroid tedavisi başlandı. Aynı lokalizasyonda tekrarlayan pnömoni ile gelen ve endobronşiyal tutulum gözlenen sarkoidoz olgusunu, endobronşiyal kitle lezyonların ayırıcı tanısında sarkoidozu vurgulamak için sunduk.

Anahtar Sözcükler: *Sarkoidoz, endobronşiyal, tedavi.*

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Sarcoidosis is a multisystem disease of unknown cause that is characterized by non-caseating granulomas. Although lung involvement is observed in 90% of cases, there may also be eye, skin, liver, bone, joint, heart and brain involvement (1). Lung involvement is often in the form of parenchymal disease and nodular involvement may be seen in the bronchial mucosa, while involvement in the form of endobronchial masses is very rare (2). Our patient underwent bronchoscopy, having been diagnosed with sarcoidosis around 3 years earlier, and had been followed up without treatment due to a history of pneumonia recurring three times in the same localization in the previous year. An endobronchial lesion was noted on bronchoscopy, while a biopsy revealed aggranulomatous inflammation. Progressive sarcoidosis was considered based on the clinical and radiological findings, and steroid treatment was started. We present here a case of sarcoidosis with recurrent pneumonia in the same localization and endobronchial involvement.

CASE

A 31-year-old male patient presented with complaints of fever, cough, joint pain and shortness of breath for the last 10 days. The patient had been using quinolone antibiotics for about 1 week following a diagnosis of pneumonia, and had no additional disease or smoking history. His medical history revealed that he applied to a health institution twice with the same complaints around 6 months earlier and had been treated with antibiotics twice with a diagnosis of pneumonia. It was further learned that the diagnosis of sarcoidosis had been made based on endobronchial ultrasonography and a biopsy of the mediastinal lymph nodes in 2018, and he was under follow-up without treatment. A thorax computed tomography (CT) taken in 2018 revealed bilateral hilar and paratracheal lymphadenopathy, as well as micronodular infiltrations of the parenchyma. Upon admission to our hospital, bilateral diffuse rhonchi were detected during a physical examination of the patient. Laboratory results revealed leukocytosis and C-reactive protein to be high in a complete blood count, while the patient's biochemical parameters were normal. Angiotensin converting enzyme: 32 U/L, Calcium: 9.9 mg/dl and 24-hour urine calcium normal. Bilateral hilar fullness was observed on a chest X-ray, along with a homogeneous increase in density extending from the hilus to the periphery in the upper zone of the right lung (Figure 1). On Thorax CT, on the other hand, revealed peribronchial density increments in the right hilar area adjacent to the right lung upper lobe minor fissure, and a ground glass area in the right upper lobe anterior with an appearance of peripheral consolidation (Figure 2). The patient, who had fever and was thought to have postobstructive pneumonia was started on piperacillin + tazobactam treatment, having used quinolone group antibiotics before. A fiberoptic bronchoscopy performed due to recurrent pneumonia revealed a smooth-surfaced mass that almost completely occluded the anterior segment of the right lung upper lobe and a biopsy was taken (Figure 3). The histopathological examination of the endobronchial lesion revealed a granuloma structure in the bronchial mucosa but no necrosis (Figure 4). In a microbiological examination of the bronchoalveolar lavage, no acid resistance bacillus was observed and no growth was detected in the culture. Pulmonary function tests revealed FVC: 68%, FEV1: 57% FEV1/FVC: 87% Diffusion: 66% and moderate restriction. A diagnosis of progressive sarcoidosis with clinical, radiological and physiological findings was made, and the patient was started on a 32-mg steroids treatment. The patient's complaints have since decreased, and his treatment and follow-up is continuing. Regression was observed on a chest X-ray in the 3rd week of treatment (Figure 5).

DISCUSSION

A diagnosis of sarcoidosis is based on clinical and radiographic findings, histopathological evidence, non-caseating granulomas on biopsy and the absence of alternative etiologies (3). Common complaints at admission include nonproductive cough, dyspnea on exertion, chest pain and hemoptysis (rare) (50% of cases). Systemic complaints such as fatigue, fever and anorexia may be present in up to 45% of cases, while approximately 35% of patients may present with acute fever, polyarthralgia, erythema nodosum and bilateral lymphadenopathy (Lofgren's Syndrome) (3). Cough, fever and chest pain were present in our case, and the symptoms regressed several times after antibiotics, although the patient applied again with the same complaints.

Invasive methods such as mediastinoscopy, open lung biopsy, scalene lymph node biopsy and skin biopsy are used for pathological sampling in the diagnosis of sarcoidosis, although fiberoptic bronchoscopy – a less invasive method – can also be employed (4,5). Transbronchial biopsy, transbronchial fine needle aspiration, endobronchial biopsy and Bronchoalveolar Lavage (BAL) are performed as interventional procedures in fiberoptic bronchoscopy (5).

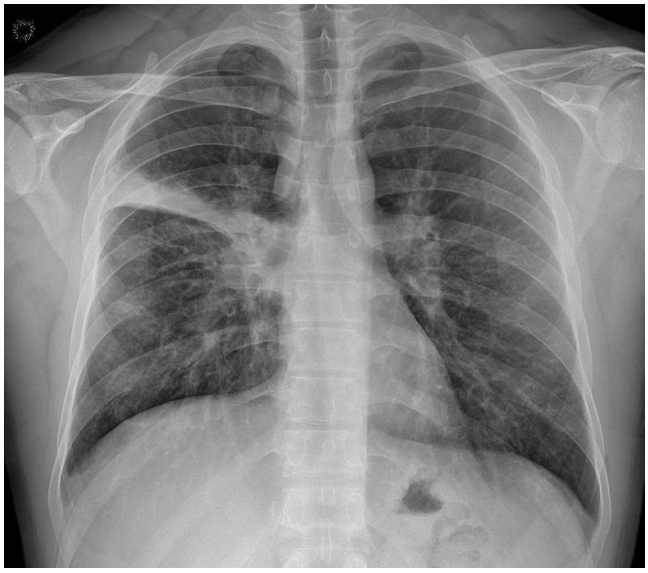

Figure 1: Bilateral hilar fullness and homogeneous increase in density extending from the hilus to the periphery in the upper zone of the right lung on Chest X-ray

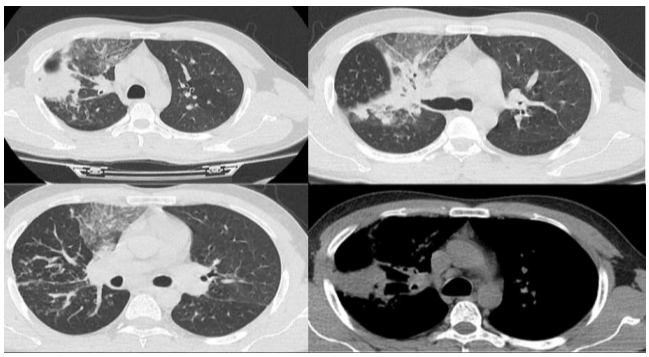

Figure 2: Peribronchial density increments notable in the right hilar area, adjacent to the right lung upper lobe minor fissure, while the ground glass area in the right upper lobe anterior has an appearance that creates peripheral consolidation on Chest CT

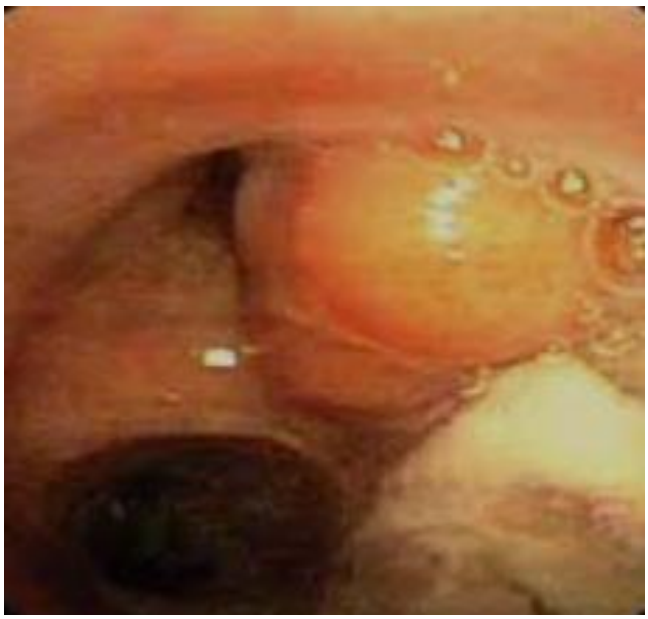

Figure 3: Flexible bronchoscopy revealed an endobronchial mass lesion at the anterior segmental bronchus of the right lung upper lobe

Endobronchial mucosal involvement is a common finding in fiberoptic bronchoscopy, and is characteristically described as a curbstone or pebble appearance. These may have areas with a nodular appearance that when biopsied take the form of granulomas (5). In cases of sarcoidosis, other abnormalities that may be detected from fiberoptic bronchoscopy include mucosal hyperemia, mucosal infiltration, bronchostenosis, or rarely, endobronchial mass lesions, as in our case (4). In a case series study by Kiter et al. (6), 0.4% endobronchial mass lesions were reported, while no endobronchial involvement was detected in other sarcoidosis series (7-9). Kumbasar et al. (10), Akpinar et al. (11) and Güngör et al. (12) all detected endobronchial mass lesions, as in our case, with granulomas observed in their biopsies of the lesions. Our case was followed-up with previous diagnosis of sarcoidosis and the absence of symptoms at the time of diagnosis, and was considered to have progressive sarcoidosis due to the presence of an endobronchial lesion, the recurrent postobstructive pneumonia and indicative symptoms.

The narrowing of the bronchial lumen in sarcoidosis can be a result of three mechanisms: the mechanical narrowing of the lumen due to compression of the enlarged lymph nodes; the submucosal invasion of sarcoid granulomas; and the presence of an endobronchial mass. Endobronchial masses have been reported only rarely, while the first two mechanisms are more common (13). Whether the endobronchial mass lesion is a form of sarcoidosis or an indicator of the extent of lung involvement of the disease has yet to be fully elucidated. Bjermer et al. (14) reported inflammatory activity in BAL to be greater in cases with granuloma detected during endobronchial biopsy than in cases without granuloma identified from an endobronchial biopsy.

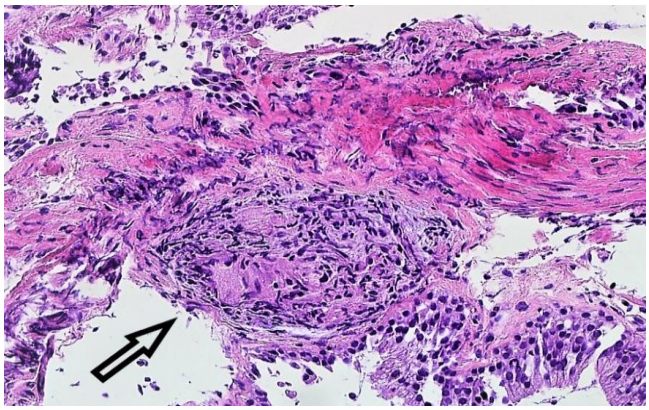

Figure 4: Granulomatous inflammation of the bronchial mucosa (H&E X200)

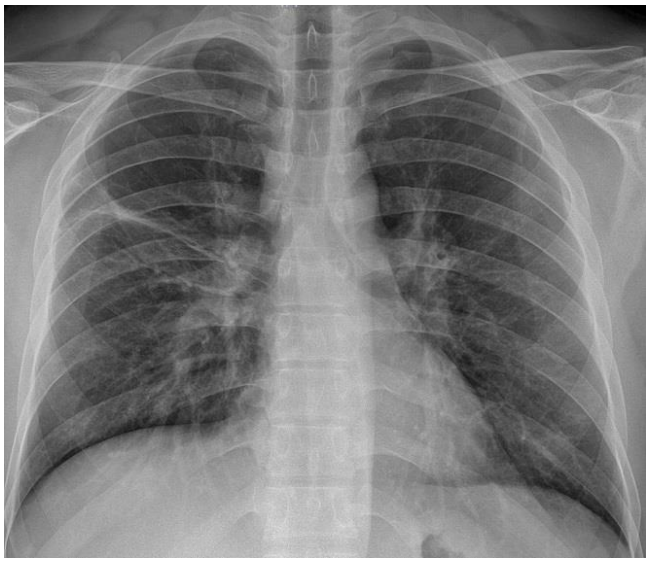

Figure 5: Regression was observed in chest X-ray in week 3 of treatment

Although the exact pathogenesis is not known yet, it is commonly assumed that sarcoidosis is an exaggerated immune response to an unidentified pathogen. Recent studies have suggested that T-cells play a central role in the development of the disease, possibly due to their excessive cellular immune response (15). A CD4:CD8 ratio of >3.5 in bronchoalveolar lavage can be detected in 50% of cases, which is most likely an outcome of the accumulation of CD4 cells and the release of interleukin-2 at disease activity sites. This leads to the development of non-caseating granulomas that are rich in epithelioid cells, which is a hallmark of sarcoidosis, on microscopic examination (although not specific) (3). In a BAL analysis, Kumbasar et al. (10) reported a CD4/CD8 ratio of 5, while Akpınar et al. (11) found it to be 3.5. No BAL analysis was performed in the present study.

It has been reported that endobronchial lesions can disappear upon corticosteroid treatment in sarcoidosis cases with endobronchial involvement (16). Akpinar et al. (11) reported the disappearance of an endobronchial mass lesion after corticosteroid treatment, and the CD4/CD8 ratio in BAL decreased to 1.18 in their case. Güngör et al. (12) reported that complete remission was achieved in both of their cases with drug-free follow-up, and emphasized that a drug-free cure could be achieved with close follow-up in cases of endobronchial sarcoidosis. Cases that have improved without treatment have been reported in the literature (17), but in our case, a radiological and clinical response was obtained with steroid treatment.

In conclusion, we describe here a case of sarcoidosis that presented as an endobronchial mass, which highlights the notion the need to include sarcoidosis in a differential diagnosis in patients presenting with an endobronchial mass, as early treatment may improve the outcome. It is recommended that a flexible bronchoscopy be performed to search for endobronchial masses in patients with suspected sarcoidosis based on CT findings and who show recurrent pneumonia at the same localization, even when CT scans reveal no such endobronchial mass lesion, as in our patient. In cases of endobronchial sarcoidosis, treatment can be provided with steroids.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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