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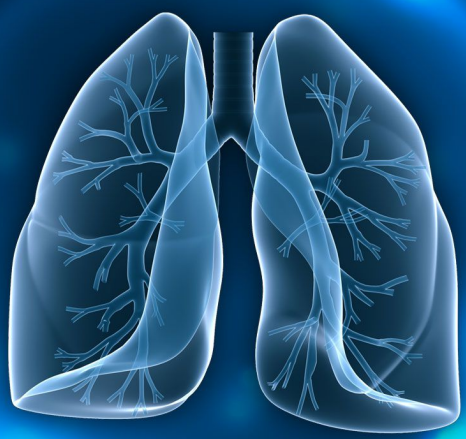

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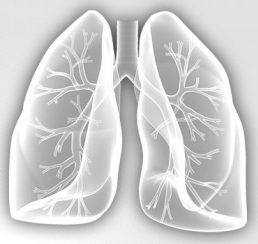

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Effectiveness of Favipiravir prior to Admission to the Intensive Care Unit in COVID-19 Pneumonia

COVID-19 Pnömonisinde Yoğun Bakım Ünitesi Öncesinde Favipiravir'in Etkinliği

Önder Öztürk[1], Volkan Bağlan[1], Onur Kaya[2], Esra Nurlu Temel[2], Onur Ünal[2], Veysel Atilla Ayyıldız[3], Mümtaz Cem Şirin[4], Fevziye Burcu Şirin[5], Gül Ruhsar Yılmaz[2], Füsun Zeynep Akcam[2], Münire Çakır[1], Ahmet Akkaya[1]

Abstract

After emerging in Wuhan city in December 2019, the coronavirus disease 2019 (COVID-19) rapidly spread throughout China. Although high rates of hospitalization are seen with COVID-19, no specific treatment has been reported, and the choice of antiviral therapies is limited. Favipiravir, approved in Japan for influenza, is one of the drugs that targets RNA-dependent RNA polymerase (RdRP). It significantly decreases the duration of fever, cough dyspnea, and the need of oxygen therapy or noninvasive mechanical ventilation, especially in moderate COVID-19 cases. In the current paper we presented four cases with worsening clinical conditions and the development of hypoxia who were treated with Favipiravir before being admitted to the intensive care unit, and who recovered from the disease.

Key words: *SARS-CoV-2 (COVID-19), antiviral treatment, favipiravir.*

Özet

Aralık 2019'da Wuhan şehrinde ortaya çıkmasından bu yana, koronavirüs hastalığı (COVID-19) Çin'e hızla yayıldı. COVID-19 enfeksiyonuna bağlı yüksek oranda hastaneye yatış görülmesine rağmen, spesifik bir tedavi bildirilmemiştir. Bu bağlamda antiviral tedavi seçimi sınırlıdır. Japonya'da influenza için onaylanan Favipiravir, RNA'ya bağımlı RNA polimerazı (RdRP) hedefleyen ilaçlardan biridir. Özellikle orta şiddetteki COVID-19 olgularında ateş, öksürük dispnesi ve oksijen tedavisi veya noninvazif mekanik ventilasyon ihtiyacını önemli ölçüde azalttığı bilinmektedir. Bu yazıda, hastaları yoğun bakım ünitesine kabul etmeden önce klinik durumları kötüleşen ve favipiravir ile takip edilerek iyileşen dört olguyu sunduk.

Anahtar Sözcükler: *SARS-CoV-2 (COVID-19), antiviral tedavi, favipiravir.*

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Coronavirus disease 2019 (COVID-19) is a viral respiratory disease caused by the 2019 novel coronavirus (SARS-CoV-2) that has spread rapidly throughout China, and from there to the rest of the World. The SARS-CoV-2 outbreak has resulted in high rates of hospitalization and intensive care unit (ICU) admissions all over the world (1). Although high rates of hospitalization are seen, only a limited number of treatments are available, such as oseltamivir, chloroquine, azithromycin, Favipiravir, lopinavir/ritonavir and tocilizumab, although no specific antiviral drugs have been shown to have clinical efficacy in COVID-19 (2).

Favipiravir, known originally as T-705 (3), is one of these antiviral drugs that strongly inhibit the RNA-dependent RNA polymerase (RdRP) of influenza and many other RNA viruses. It inhibits all the serotypes and strains of the influenza A, B and C viruses against which it has been tested, including those resistant to the currently approved neuraminidase inhibitors. The mechanism of Favipiravir, involving the direct inhibition of viral replication and transcription, makes it unique among other anti-influenza drugs. Since RdRP domains are not present in human cells and are conserved among RNA viruses, this distinct specific mechanism targeting viral RNA-dependent polymerases makes Favipiravir an attractive drug candidate (4). SARS-CoV-2 and influenza viruses are both RNA viruses that depend on viral RNA-dependent RNA polymerase (RdRp) replication (5). It was approved for the treatment of a novel virus on February 15, 2020 in China and is currently undergoing clinical trials for the treatment of COVID-19, especially in the intensive care unit (ICU).

Favipiravir has proven to be more effective than other drugs in improving clinical outcomes and recovery rates, and alleviating fever, cough and breathing difficulties, being particularly superior to drugs for ICU use. Unlike the in standard approach, the patients were treated with Favipiravir prior to admittance to the ICU when the patients' clinical conditions were worsening and hypoxia was developing.

CASE

COVID-19-positive cases, diagnosed based on RT-PCR testing for SARS-CoV-2, are hospitalized and treated in line with the guidelines established by the Ministry of Health of the Republic of Turkey. Written informed consent was obtained from the patients presented here.

Case 1: A 65-year-old man with a history of hypertension and prostate hypertrophy was admitted with fever, cough and radiological findings compatible with COVID-19 (Figure 1). The initial treatment was oseltamivir, hydroxychloroquine, azithromycin and ceftriaxone (2x1gr). Although his good general condition, the treatment regimen was changed to meropenem, linezolid, moxifloxacin, methylprednisolone (1mg/kg) and favipiravir (initial: 2x1600mg, maintenance: 2x600mg for five days) due to hypoxemia and worsening laboratory findings on third day of the hospitalization (Table 1). On the seventh day of hospitalization, the patient's clinical and laboratory findings were within the normal range, with pulse oxygen saturation of 90% without symptoms of COVID-19.

Case 2: A 62-year-old man with a history of diabetes mellitus was admitted with cough, shortness of breath, fever and the radiological findings compatible with COVID-19 (Figure 2). The initial treatment included oseltamivir and hydroxychloroquine. On the third day of the hospitalization, the treatment regimen was changed to ceftriaxone (2x1gr), methylprednisolone (1mg/kg) and Favipiravir (initial: 2x1600mg, maintenance: 2x600mg for five days) after a worsening of clinical and laboratory findings (Table 1). Under oxygen therapy of 6 l/min, saturation increased from 80% to 89% (PaO_2/FiO_2: 228). On the seventh day of the hospitalization, the patient's clinical and laboratory findings were within the normal range, with pulse oxygen saturation of 94% and no symptoms of COVID-19.

Case 3: A 58-year-old man with a history of diabetes mellitus and coronary artery disease was admitted with cough, fever and radiological changes compatible with COVID-19 (Figure 3). The initial treatment included oseltamivir, hydroxychloroquine, azithromycin and 4000 anti-Xa IU enoxaparin sodium. On the fifth day of hospitalization, the patient's pulse and oxygen saturation decreased to 86% with dyspnea, and CRP increased to 152.77 mg/l, and so treatment was changed to ceftriaxone (2x1gr), theophylline, 4000 anti-Xa IU enoxaparin sodium, methylprednisolone (1mg/kg) and Favipiravir (initial: 2x1600mg, maintenance: 2x600mg for five days). In addition to medical treatment, oxygen saturation was kept between 85–89% using a reservoir mask (10–12 l/min.), and prone ventilation was provided before admission to the ICU. Oxygen saturation was >90% without oxygen supply after Favipiravir treatment. The patient was discharged once an RT-PCR test for COVID-19 was negative and no symptoms were present.

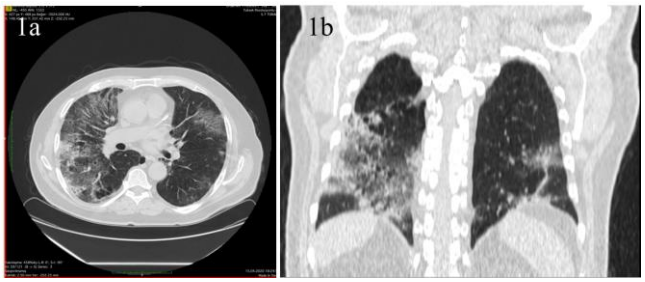

Figure 1a and b: *Axial and coronal plane chest CT. In the form of bilateral peripheral consolidated areas, areas with the ground-glass density that affect the large part of both lungs are observed*

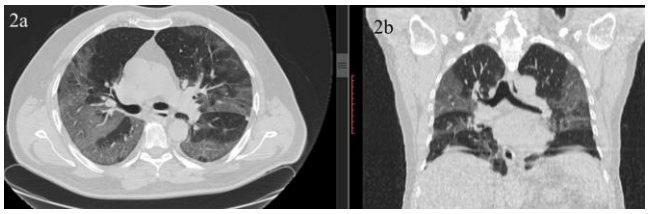

Figure 2a and b: *Axial and coronal plane images of Chest CT. In the form of bilateral peripheral consolidated areas, areas with the ground-glass density that affect the large part of both lungs are observed*

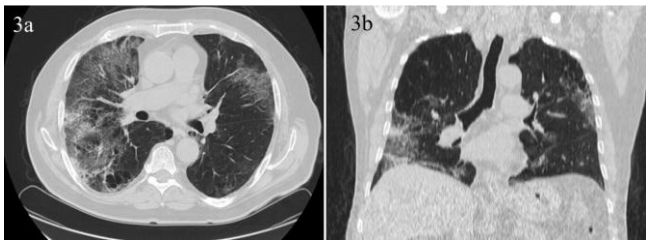

Figure 3a and b: *Axial and coronal plane images of Chest CT. Parenchymal ground glass infiltrations, more pronounced on the right*

Case 4: A 62-year-old man with a history of hypertension was admitted with cough and the radiological findings compatible with COVID-19 (Figure 4). The initial treatment was oseltamivir, hydroxychloroquine and azithromycin, however, the disease subsequently progressed to hypoxemic respiratory failure with increased body temperature, warranting the initiation of invasive mechanical ventilation (Table 1). Oxygen saturation was 90% with an 8 l/min oxygen supply (PaO_2/FiO_2: 200). The treatment regimen was changed to ceftriaxone IV (2x1gr), oral methylprednisolone (1mg/kg) and Favipiravir (initial: 2x1600mg, maintenance: 2x600mg) on the fifth day of hospitalization, after which improvement was noted in clinical and laboratory findings. Oxygen saturation was 95% with a 3 l/min oxygen supply on the fourth day of treatment. On the 10th day of the medical treatment, pulse oxygen saturation was 90% without oxygen therapy, and the patient was discharged with no symptoms of COVID-19.

During follow-up, the radiological recovery of the lungs could not be ascertained through thorax CT or posterior-anterior (PA) chest film in our cases, although in one case (Case 4), recovery was noted in a radiological follow-up with chest films.

DISCUSSION

COVID-19 continues to spread at a rapid speed in the absence of any effective treatment or prophylactic agent. In this case series, Favipiravir was used as antiviral therapy in patients with severe COVID-19 (+) to prevent the need for intensive care, and was found to be successful as a treatment in this regard.

Favipiravir, approved in Japan for influenza, is an antiviral drug targeting RNA-dependent RNA polymerase (RdRP), and is considered to be a potential candidate for the treatment of COVID-19 (5-7). Chang C et al. (5) compared the clinical efficacy and safety of Favipiravir with that of umifenovir as a treatment for COVID-19 in a randomized clinical trial, and reported that Favipiravir did not improve the clinical recovery rate (61.21%) when compared to the umifenovir group (51.67%). It did, however, significantly improve the latency to relief for cough and decreased the duration of fever. The post-doc analysis also found Favipiravir treatment to significantly decrease de novo incidences of dyspnea, and the need for oxygen therapy or noninvasive mechanical ventilation, especially in moderate COVID-19 cases. These results suggest that Favipiravir may be effective in halting disease progression into ARDS, shock and multiple organ failure in moderate COVID-19 patients (5). In a non-randomized control trial, Favipiravir recorded significantly better treatment effects against disease progression and the viral clearance of COVID-19. Although the treatment duration with Favipiravir was twice as long as that used for the treatment of influenza, the adverse effects were rare and tolerable. The authors of the study stated that the treatment duration with Favipiravir may be prolonged if necessary, and that it may be considered an effective treatment for COVID-19 (3). The present study included patients who were clinically deteriorating, confirmed by

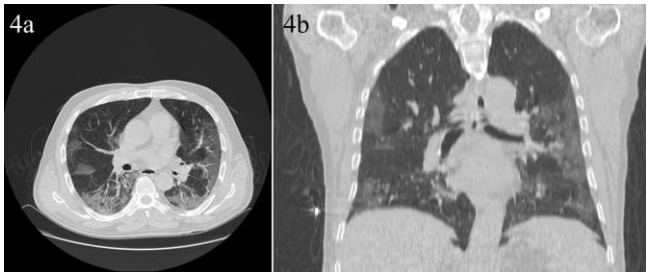

Figure 4a and b: *Axial and coronal plane images of Chest CT. Bilateral, ground glass densities in the form of consolidated areas, more prominent in the middle-lower zones were seen*

Tablo 1: Clinical Characteristics and Laboratory Results

Characteristics	Case 1	Case 2	Case 3	Case 4
Days from the disease onset to favipiravir therapy	3	3	5	5
"Laboratory findings" before favipiravir therapy				
WBC (per mm^3) (5.2-12.4)	4300	7300	4000	5900
Differential count (per mm^3)				
Total neutrophils (2.1-6.1)	3.6	5.5	3.5	5.1
Total lymphocytes (1.3-3.5)	0.5	0.8	0.4	0.5
Total monocytes (0.3-0.9)	0.2	0.5	0.1	0.2
PLT (per mm3) (156-373)	141	369	171	206
HGB (g/dL) (13.6-17.2)	14.2	13.9	14	13.3
Glucose (mg/dL) (74-106)	102.06	197.74	212.84	101.46
Albumin(g/liter) (3.5-5.2)	-	-	3.62	2.91
ALT (U/liter) (0-34)	57.03	48.81	26.25	29.77
AST (U/liter) (0-31)	87.38	41.67	35.33	41.46
LDH (U/liter) (0-247)	753.78	363.71	407.82	318.9
Cr (mg/dL) (0.67-1.17)	1.2	0.72	0.76	0.71
CPK (U/liter) (26-308)	656.43	-	226.36	53.14
EGFR (ml/min/1.73 m2)	63.52	100.68	100.57	100.00
Troponin T (ng/ml)(0-0.014)	0.008	0.006	0.004	0.003
PT (sec) (9.4-112.5)	13.4	14.9	14.7	12.6
aPTT (sec) (25.4-38.4)	30.6	20.5	32.3	34.3
Fibrinogen (mg/dL) (200-393)	563	609	500	683
D-dimer (ng/ml) (69-243)	328	920	816	874
Serum ferritin (ng/ml) (28-365)	>1920	1682	610.4	862.3
Procalcitonin (ng/ml) (<0.5 negative)	0.073	0.086	0.081	0.072
CRP (mg/liter) (0-5)	92.80	144.48	152.77	126.38
Blood Gases				
Laktat	2.73	1.29	2.52	1.74
Ph	7.40	7.53	7.39	7.44
PCO_2(mmHg)	35.2	26.4	37.6	41.6
PO_2(mmHg)	44.7	64.3	45.4	31.2
$SatO_2$%	-	92.4	-	54
HCO3act(mmol/mL)	21.5	21.9	22.7	27.4

EGFR: estimated glomerular filtration rate, High-sensitivity C-reactive protein: CRP, Activated partial thromboplastin time: aPTT, Prothrombin time: PT, Creatine kinase: CPK, Lactate dehydrogenase: LDH, Aspartate aminotransferase: AST, Alanine aminotransferase: ALT, White-cell count: WBC, Platelet count. PLT, Hemoglobin: HBG, Creatinine: Cr

laboratory and radiology findings, while being treated following a diagnosis of COVID-19. We found Favipiravir treatment to be effective in decreasing the need for oxygen therapy, and in decreasing the symptoms of fever and dyspnea in our patients, as described previously in medical literature. However, unlike the previous findings in the literature, it was found also to improve clinical outcomes and recovery rate, and the disease did not progress to septic shock, multiple organ failure or ICU admission.

In conclusion, we found Favipiravir to be effective in the treatment of COVID-19 patients and in reducing admissions to the ICU. This might be attributed to the prevention of virus replication and to the reduction of the anti-

genic load of the COVID-19 virus and cytokine production. We suggest, therefore, using Favipiravir as the first choice antiviral therapy in COVID-19 patients at the beginning, although randomized wide-ranging studies are needed to show its full effects.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - Ö.Ö., V.B., O.K., E.N.T., O.Ü., V.A.A., M.C.Ş., F.B.Ş., G.R.Y., F.Z.A., M.Ç., A.A.; Planning and Design - Ö.Ö., V.B., O.K., E.N.T., O.Ü., V.A.A., M.C.Ş., F.B.Ş., G.R.Y., F.Z.A., M.Ç., A.A.; Supervision - Ö.Ö., V.B., O.K., E.N.T., O.Ü., V.A.A., M.C.Ş., F.B.Ş., G.R.Y., F.Z.A., M.Ç., A.A.; Funding - Ö.Ö., V.B.; Materials - M.C.Ş., F.B.Ş.; Data Collection and/or Processing - O.Ü., V.A.A.; Analysis and/or Interpretation - A.A., G.R.Y., F.Z.A.; Literature Review - E.N.T., V.B.; Writing - Ö.Ö.; Critical Review - A.A., M.Ç.

YAZAR KATKILARI

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Kimura Disease: Cervical, Supraclavicular and Mediastinal Lymphadenopathy Mimicking Lymphoma

Kimura Hastalığı: Lenfomayı Taklit Eden Servikal, Supraklavikular ve Mediastinal Lenfadenopati

Cenk Balta[1], Mustafa Kuzucuoğlu[2], Eren Altun[3]

Abstract

Kimura disease is rarely seen benign chronic inflammatory disease, the etiology of which is unknown. The diagnosis of the disease is challenging, and so histopathological sampling is necessary. Eosinophilia, increased serum immunoglobulin E levels and subcutaneous nodules in the head and neck are the classical triad indicators of the disease. Herein, we present the case of a 33-year-old man with multiple lymphadenopathies in the area of neck, supraclavicular and mediastinum. The patient was pre-diagnosed with lymphoma. After a supraclavicular lymph node excision, the diagnosis was re-evaluated as Kimura Disease.

Key words: *Kimura Disease, lymphoma, immunoglobulin E, Eosinophilia.*

Özet

Kimura hastalığı nadir izlenen benign kronik inflamatuar bir hastalıktır ve etyolojisi belirsizdir. Tanı koymak oldukça zor ve tanıda doku örneklemesi gereklidir. Eozinofili, artmış serum immunoglobulin E değerleri ve baş ve boyunda subkutan nodüller klasik triadını oluşturmaktadır. Burada, servikal, supraklavikular ve mediastende multiple lenfadenopati ile başvuran 33 yaşında bir hastayı sunduk. Olgumuz lenfoma ön tanısıyla danışıldı. Supraklavikular lenf nodu eksizyonu sonrasında Kimura Hastalığı olarak tanı konuldu.

Anahtar Sözcükler: *Kimura Hastalığı, lenfoma, İmmunoglobulin E, Eosinofili.*

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Kimura disease (KD) is a rare, benign disorder that usually manifests with painless subcutaneous soft tissue swellings and/or lymphadenopathy in Asian males aged between 20 and 30 years (1). Common localizations are the head and neck, including the salivary glands and lymph nodes. Eosinophilia and increased levels of serum immunoglobulin (Ig) E are other components of this disorder (2).

The etiology is still unknown, although there are hypotheses of trauma, allergic reaction, autoimmune response and viral or parasitic paths (3). To clarify the diagnosis, a histopathological examination and lymph node biopsy must be performed. The treatment modality is still unclear. The preferred method is surgical excision, but in large and/or multiple masses, or to avoid recurrence, radiotherapy and immunosuppressive therapy are referred to as additional methods (2).

We present here the case of a 33-year-old male with a complaint of swelling mimicking lymphoma in the right supraclavicular area who was diagnosed with KD following an excisional biopsy.

CASE

A 33-year-old man was admitted to our clinic with a prediagnosis of an anterior mediastinum mass. A physical examination revealed a pruritic multiple cervical and supraclavicular lymphadenopathy (Figure 1). No fever, night sweats or weight losses were detected in a clinical examination.

Laboratory values were as follows: White Blood Cell (WBC) count: 26.1x103/μL (range 4.5–11x103/μL); hemoglobin (HGB): 12.7 g/dL (range 13.1–17.2 g/dL); neutrophil count: 23x103/μL (range 1.9–8x103/μL) with 88.4% (range 40–74); eosinophil count: 0.7x103/μL (range 0–0.2x103/μL) with 3.5% (range 0–7); serum C-reactive protein (CRP): 172 mg/L (range 0–5 mg/L); erythrocyte sedimentation rate (ESR): 86 mm/h (range 0–15mm/h); total IgE: 527.8 IU/mL (range 0–100 IU/mL); and serum IgG: 21.3 g/dL (range 7–16 g/dL). Liver and renal function tests were normal. Serology tests were performed to rule out viral hepatitis, HIV, CMV and EBV.

An enlargement in the upper mediastinum and a right deviation of the trachea was detected in a chest radiograph (Figure 2a). Multiple lymphadenopathy involving cervical, supraclavicular and prevasculary mediastinal areas were detected upon a computed tomography (CT) (Figure 2b and c). An ultrasonography showed a heterogeneous lobulated solid conglomerate lymphadenopathy measuring 43x23 mm in diameter in the right supraclavicular area.

A fine needle aspiration biopsy was performed, and a cytological examination showed fibrous connective tissue with rare lymphoid infiltrates and increased eosinophil. Kimura disease and angiolymphoid hyperplasia with eosinophilia were also investigated in a differential diagnosis. We decided to perform cervical lymph node excision to clarify the diagnosis, and the enlarged lymph node was reported by the histopathology department to be fibrous tissue involving eosinophilic inflammation on a fibrohistocytic ground, centered on necrotizing areas. The tissue was compatible with KD (Figure 3), and the diagnosis was confirmed by the increased serum levels of IgE and eosinophilia.

The patient underwent corticosteroid therapy (prednisone: 0.5 mg/kg/day), and the lymphadenopathy and eosinophilia decreased gradually in the first month of follow up.

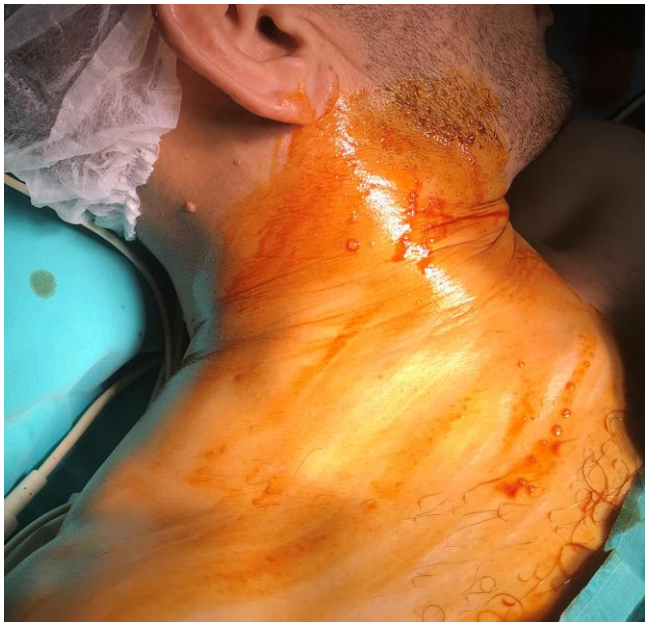

Figure 1: *View of lymphadenopathy in the right supraclavicular area*

DISCUSSION

KD was first described by Kim in 1937, but was more widely recognized after the publication of Kimura's study in 1948 (4,5). It is a rare and benign disease involving subcutaneous tissue and lymph nodes. The lesion may be pruritic and painless. KD is endemic to the Asia region, although non-Asian cases have also been published (1,6). It is usually seen in men, with a male to female ratio of 19:1 (7). Our patient was 33-year-old Caucasian male with a pruritic right cervical lymphadenopathy.

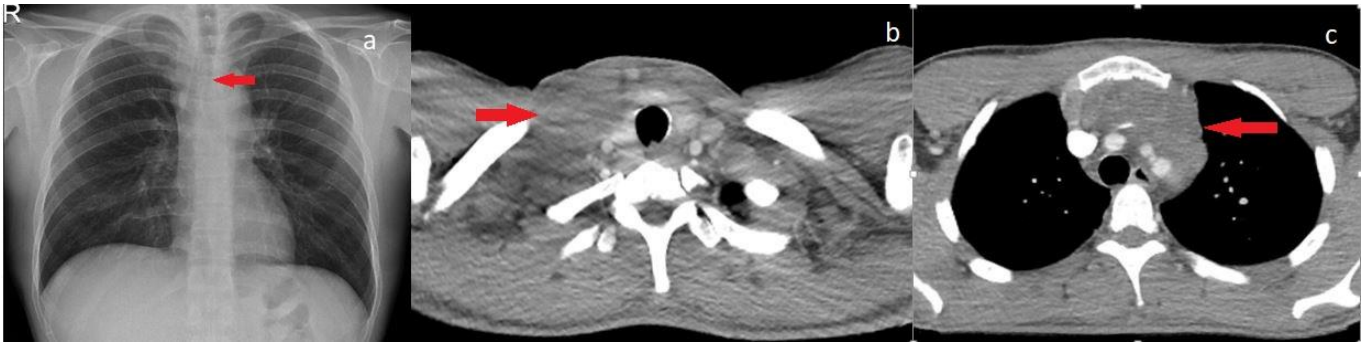

Figure 2a, b and c: *Tracheal deviation in a chest X-ray (a), enlarged lymphadenopathy in the right supraclavicular (b), prevascular mediastinal region (c)*

Although the etiology is unclear, trauma, allergic reaction, autoimmune process or T-helper 2 immunoregulation, and the release of eosinophilic cytokines (IL 4, IL 5, IL 13, TNFα) in response to a viral or parasitic trigger, may be suspected (2,3,6,7).

The initial presentation of the disease is a slow and progressive unilateral subcutaneous mass or enlarged lymph node of the head and neck area in up to 76% of patients (2,3,8). Other localizations of KD are cervical, retro auricular, inguinal, in the epicranial area, eyelids, axillary area, and in the oral cavity and nasal sinuses (6). The mediastinum is rarely involved (1,9).

Differential diagnoses include angiolymphoid hyperplasia with eosinophilia (ALHE), Hodgkin's disease, T-cell lymphoma, Langerhans cell histiocytosis, Castleman disease and parasitic lymphadenitis (2). Since the CT findings of lymphoma and KD are similar, a pathological examination of lymph node is essential. Eosinophilia and increased serum levels of Ig E are mandatory for a positive diagnosis. ALHE and KD can be histopathologically similar, although fibrohistiocytic involvement and lymphoid follicles can help to differentiate between the two (6).

Although KD is a local disorder, activated T cells may increase the permeability of the renal glomerular membrane and cause proteinuria and nephrotic syndrome in 12–16% of patients (1,3,6-8). It may present with asthma, allergic rhinitis, atopic dermatitis and peripheral eosinophilia due to the increased serum Ig E levels (9). In our case, renal functions were normal, but the patient had asthma in their childhood history.

Radiological findings is nonspecific as homogeneous lymphadenopathy and/or enlarged salivary glands (6,8,9). A histopathological diagnosis is mandatory to rule out lymphoma if the mediastinal, extra pleural, epigastric, mesenteric and retroperitoneal areas are involved (8). In our case, KD presented with cervical, supraclavicular, axillary and mediastinal lymphadenopathy. The lymphoma was suspicious in a differential diagnosis.

A fine needle aspiration cytology (FNAC) is suggested as an initial diagnostic method to differentiate between malign disease and reactive hyperplasia, being more cost-effective than an excision biopsy. Kapoor et al. (10), however, report FNAC to be of limited use in the diagnosis of KD. In our case, FNCA was performed on the cervical lymph node and the cytological diagnosis was inadequate.

The histopathological features of KD include follicular hyperplasia with a reactive germinal center; eosinophilic micro abscesses; germinal center necrosis; and eosinophilic infiltrates in the germinal center and sclerotic areas (2,10).

Although KD is benign, the recurrence rate is high (6). The optimum treatment is unclear. Surgical excision is recommended for solitary lesions, where possible (1,2). In generalized lymphadenopathy systemic corticosteroids, cytotoxic agents and irradiation may be effective (8,9,10). Corticosteroids are essential if the kidneys are affected (2,6). Local radiotherapy (25–30 cGy) is proposed when systemic steroids are unsuccessful. Cyclosporine, imatinib, azathioprine, leflunomide, cetirizine, pranlukast, all-trans-retinoic acid and cyclophosphamide are other treatment options (2,3,6). Chen et al. (11) reported young age and high blood eosinophil counts to be associated with recurrence, and eosinophil count to be correlated with the size of the lymphadenopathy and the response to therapy.

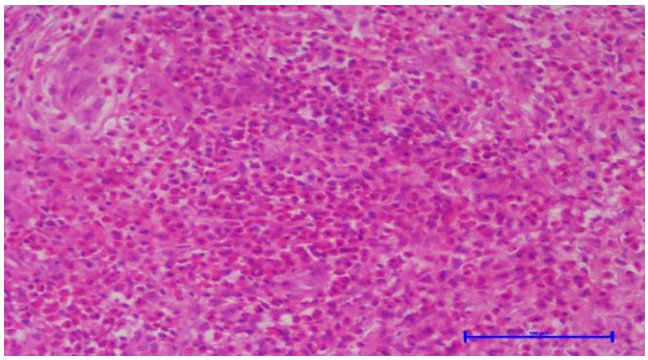

Figure 3: *Eosinophilia infiltration with fibrohistocytic grounds (H&E X200)*

In conclusion, KD is a benign lymphoproliferative disease of unknown etiology. Differentiating between KD and lymphoma can be difficult, and the treatment modality is still controversial, although surgical excision, corticosteroids, radiation therapy and cytotoxic agents are suggested.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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A Case of Pulmonary Capillary Hemangiomatosis in a Worker with Exposure to Foundry Dust and VOCs

Döküm Dumanına ve Uçucu Organik Bileşiklere Maruz Kalım ile ilişkili Olabilecek Pulmoner Kapiller Hemanjiomatozis Olgusu

Ayse Coskun Beyan[1], Arif Cimrin[1], Duygu Gürel[2]

Abstract

Pulmonary capillary hemangiomatosis (PCH) is a rare and progressive vascular disease of the lung that causes pulmonary hypertension, as they frequently overlap. The occupational risk factor associated with PCH is rarely discussed. In the present report, three of the eight patients admitted from the same company had similar radiological findings, and one agreed to undergo a biopsy. A 40-year-old male who was working as a foundry worker with no symptoms underwent CT, which showed moderate peribronchial thickening in both lungs and a mosaic perfusion pattern in the lower zones. There was no evidence of right heart failure. A microscopic examination of the lung by thoracoscopic resection showed capillary-like vascular proliferation in the alveolar septa. As there were workers with similar radiological findings from the same company he was diagnosed with occupational PCH. The etiology of PCH remains unknown. Occupational exposure should be kept in mind if a disease does not meet the classic epidemiological characteristics.

Key words: *Foundry, Occupational disease, foundry dust, VOC.*

Özet

Pulmoner kapiller hemanjiomatozis (PKH) nadir görülen, ilerleyici ve çoğunlukla pulmoner hipertansiyon ile birlikte bulunan akciğerlerin vasküler bir hastalığıdır. Hastalıkla ilişkili mesleksel risk faktörleri ile ilgili araştırma azdır. Aynı işletmeden başvuran 8 olgunun 3 'ünde benzer radyolojik bulgulara rastlandı, olguların yalnızca bir tanesi akciğer biopsisini kabul etti. Kırk yaşında erkek olgunun herhangi bir yakınması yoktu. Bilgisayarlı tomografide her iki akciğerde orta derecede peribronşiyal kalınlaşma ve alt bölgelerde mozaik perfüzyon paterni izlendi. Kardiyak değerlendirmede sağ kalp yetmezliği saptanmadı. Akciğer biopsisinde alveolar septada kapiller benzeri vasküler proliferasyon görünümü izlendi. Aynı işletmeden benzer 3 radyolojik bulgu olması ve literatür bulguları eşliğinde mesleksel maruz kalım ile ilişkili PKH olgusu olabileceği düşünüldü. PKH etiyolojisi halen bilinmeyen bir hastalıktır. Mesleki maruziyetler PKH için potansiyel bir risk faktörü olarak bildirilmektedir. Herhangi bir hastalık için bilinen klasik epidemiyolojik özelliklerin karşılanmadığı durumlarda mesleki etiyolojinin değerlendirilmesi unutulmamalıdır.

Anahtar Sözcükler: *Döküm, meslek hastalığı, döküm dumanı, uçucu organik bileşikler.*

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Pulmonary capillary hemangiomatosis (PCH) is a rare disease with unknown etiologies. It mostly manifests progressive dyspnea, hypoxemia and pulmonary hypertension due to refractory capillary proliferation within the alveolar septae. PCH has been identified in patients aged from newborn to 71 years in literature (1,2).

In radiological assessments, basilar reticulonodular opacities and large-sized ground-grass opacities are common, while air-trapping, cystic lesions and focal bronchiectasis may also be observed in the whole lung fields, mimicking an airway-disease pattern. PCH remains challenging to treat. New agents are currently under examination with positive results (3).

Only around 100 cases of PCH have been reported to date. The cause or risk factors of PCH are yet to be clearly identified, although some cases have suggested an association with connective tissue diseases or hereditary origins (4,5). There have been two different hypotheses put forward with regard to the etiology of PCH. The first suggests a neoplastic process, while the other, a secondary change due to other diseases. Occupational risk factors have rarely been discussed (6,7).

In 2018, eight workers from the same factory were referred to the outpatient clinic with suspicion of pneumoconiosis. A work history and job analysis, a qualitative exposure assessment (QEA), PPE use, and any specific self-reported exposure to high-risk substances were obtained by occupational medicine specialists (Table 1). Of the eight workers, three had similar radiological findings, although only one patient agreed to a lung biopsy. In this case report we present a case of PCH diagnosed by biopsy to draw attention to the occupational risk factors in the etiology of PCH.

CASE

A 40-year-old married male, living in Manisa and with four healthy children, had been working at a foundry factory since 2016. A normal physical examination revealed no symptoms. He reported a 15 pack years smoking history, and but had quit 2 years ago. PA Chest X-ray: digital graphy, quality 1, p/s 1/0 (Figure 1c). Thorax HRCT: Moderate peribronchial thickening in both lungs and a mosaic perfusion pattern in the lower zones (Figure 1a and b).

Respiratory functional test (RFT) (% predicted): FEV1: 3.39 L (97%), FVC: 4.17 L (99%), FEV1/FVC: 85%, PEF: 6.17 L (101%), DLCO test normal

The patient's work history and job analysis is presented in Table 1. He had been working as a foundry operator since 2016, before which, he was employed in the leather sector. He was exposed to high risk of VOC in both work histories. No health records were available from the leatherworking period. Health records were obtained from the last workplace. According to the documents submitted by the occupational physician (initial and periodical examination forms): normal, RFT, and blood tests were normal, ILO assessment quality 2, p / p 1/1 (January 2019).

A biopsy was planned due to the patient's work history and atypical radiological findings.

A video thoracoscopic wedge resection of the right bottom lobe was performed for histopathologic diagnosis. A microscopic examination of the lung wedge resection showed patchy involvement of pulmonary capillary hemangiomatosis (H&E, X1.25) (Figure 2a); a capillary-like vascular proliferation in the alveolar septa with hematoxylin & eosin sections and CD34 in pulmonary capillary hemangiomatosis (Figure 2b and c); and a thickening of vessel walls in pulmonary capillary hemangiomatosis (H&E, X10) (Figure 2d). The findings were consistent with PCH.

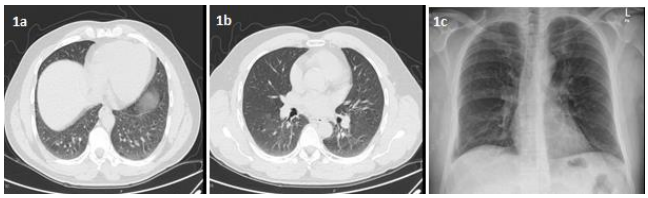

Figure 1a, b and c: *Radiological imaging of the case; Thorax HRCT images show that moderate peribronchial thickening in both lungs and mosaic perfusion pattern in the lower zones (a and b), PA chest X-ray, ILO classification: p/p 1/1*

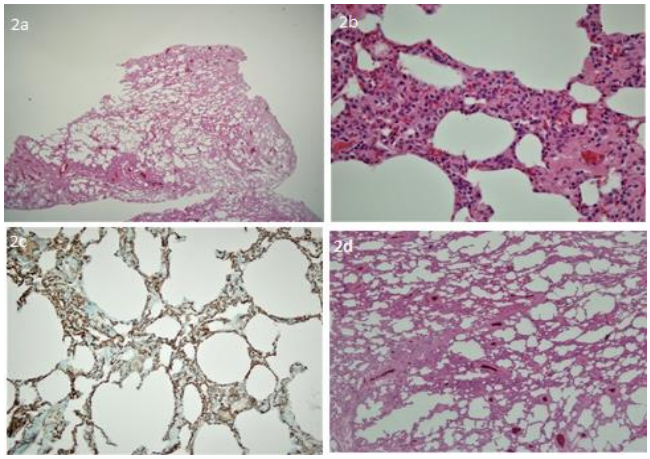

Figure 2a, b, c and d: *Histologic findings of the case; patchy involvement of pulmonary capillary hemangiomatosis (H&E, X1.25) (a), capillary-like vascular proliferation in alveolar septa with hematoxylin & eosin sections and CD34 in pulmonary capillary hemangimatosis (b and c), thickening of vessel walls in pulmonary capillary hemangiomatosis (H&E, X10) (d)*

Tablo 1: Work history and job analysis

Job	Task	Time	Suspected Risks	Occupational Hygiene Measurements	QEA*
2016-ongoing Foundry operator	Cleaning	1 h/per shift	Dust (silica, mix metal dust, graffits)	Poor	Medium
	Melting and pouring metal into molds	4 h/per shift	Heavy metal dust (aluminum, iron, lead)	Poor	High
	Removing castings from molds and dressing castings (para-occupational exposure)	8h/per shift	Silica and organic solvents	Poor	Low
Between times (1995-2016) Leather sector	Leather Tanning and Processing	8h/per shift	Chemical risks (Chromium, sulfuric acid, leather dust, H2S, DDT, formaldehyde, phenols)	Very poor	High

**: Qualitative Exposure Assessment by occupational medicine specialist*

Cardiology assessment: Normal cardiac function, EF%60; right and left ventricles normal; and normal pulmonary wedge pressure. The patient had no symptoms or laboratory findings associated with connective tissue disorder.

He was diagnosed with occupational PCH due to the fact that the initial and periodic examinations were normal (based on the principle of temporal relationship in the diagnosis of OD), and workers with similar radiological findings were employed in the same enterprise (based on the principle of having cluster case groups in the diagnosis of OD). The case was reported to the Social Security Institution.

DISCUSSION

PCH is a rare disease that is classified as a subgroup of pulmonary arterial hypertension. We identified pathologically diagnosed PCH in a young male who was exposed to occupational risk factors (mixed foundry dust and volatile organic solvents) without elevated right ventricular systolic pressure.

The etiology of PCH remains unknown, and the occupational risk factors associated with PCH are rarely discussed. Montani et al. (6) conducted a case-control study using the job-exposure matrix (JEM), and stated that occupational exposure to organic solvents (trichloroethylene) may be a risk factor for PCH. Yeo et al. (7) reported the case of a female worker who had worked in a bathtub factory without proper respiratory protection. The authors stated that based on her occupational history, the worker could have been exposed to silica or organic solvents. A lung biopsy and revealed a microscopic atypical proliferation of capillary channels within the alveolar walls.

Bone morphogenetic protein receptor type 2 (BMPR2) gene and bi-allelic EIF2AK4 mutations have been identified as the main predisposing factor behind heritable PCH (8). We did not perform this test; however there was no family history of any suspected respiratory or cardiac diseases.

Most cases of PCH present with pulmonary hypertension and progressive clinical symptoms, aside from in a few reports (1,9). The typical clinical course of PCH includes rapid deterioration due to the progressive increase in pulmonary artery pressure, which leads to right ventricular failure and death. The uncontrolled proliferation of pulmonary capillaries infiltrating the vascular, bronchial and interstitial pulmonary structures could be a reason for this (10). Our case has no PHT findings, even on echocardiography. In the present case, the histology revealed capillaries infiltrating the alveolar and bronchial walls and a moderate thickening of the vessel wall, which may have contributed to the maintenance of pulmonary blood flow in the early stage of the natural disease course.

Radiographic findings are typically nonspecific and include changes consistent with pulmonary hypertension. Chest HRCT scans usually show lobular ground-glass opacification in the area of increased pulmonary perfusion, a mosaic pattern of attenuation of pulmonary parenchyma and a thickening of the interlobular septa (11). In our cases, a mosaic perfusion pattern was dominant, but the other suspected cases also had centrilobular

ground-glass opacities. The definitive diagnosis of PCH is based on histopathological findings (12).

Finally, it is necessary to state how OD is diagnosed. We evaluate according to causality criteria in occupational disease evaluation. The various definitions, however, have two main mandatory elements in common: the fact that the disease occurs in groups of exposed workers with a higher frequency rate than in the rest of the population; and the temporality criteria that define the exposure of interest preceded the disease by a period of time (13). Our case met these two main criteria, being diagnosed with occupational PCH based on clinical and radiological findings, besides his occupational history.

CONCLUSION

We explain here the pathological diagnosis of PCH. The worker had been exposed to occupational chemical risks. We were unable to assess other workers from the same company, although this group may lead to the identification of a new disease associated with occupational exposure. The occupational etiology should be kept in mind if a disease occurs at the same time in a group of workers that does meet the classic epidemiological characteristics.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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Septic Pulmonary Embolism Associated with Acinetobacter Pneumonia

Acinetobacter Pnömonisi İlişkili Septik Pulmoner Emboli

Emine Afşin

Abstract

Septic pulmonary embolism is an infective lung disease that leads to infarction in the pulmonary arteries and bilateral multiple nodules and/or cavitations in the lung parenchyma resulting from the circulation of thrombus in the bloodstream as infected with microorganisms in the primary infectious focus. A 58-year-old case we have presented was hospitalized with the diagnosis of COPD exacerbation and was taken to the intensive care unit to be monitored in the invasive mechanical ventilator because of fever, cough, increased dyspnea and development of bilateral diffuse infiltration encountered by chest x-ray. Thoracic computed tomography encountered peripherally localized and partly cavitary nodules, infiltration, mediastinal lymphadenomegaly with a maximum diameter of 1 cm, bilateral pleural effusion and feeding vessel sign. After exitus of the patient who was unresponsive to broad spectrum antibiotic and antifungal therapy; tracheal aspirate culture test indicated the growth of *Acinetobacter baumannii /calcoaceticus* (resistant to all the antibiotics in the antibiogram). The detection of Gram Negative Pneumonia has been rarely reported in the etiology of septic pulmonary embolism that presents a high mortality rate, therefore, we aimed to discuss that case in the light of literature data.

Key words: *Acinetobacter, pneumonia, septic pulmonary embolism.*

Özet

Septik pulmoner emboli, birincil enfeksiyon kaynağındaki mikroorganizma içeren trombüsün dolaşıma karışması sonucu, pulmoner arterlerde enfarkt ve akciğer parankiminde bilateral multipl nodül ve/veya kaviteye yol açan nadir bir enfektif akciğer hastalığıdır. Olgumuz, 58 yaşında KOAH alevlenme tanısıyla yatırılmış olup, yatışının 4. gününde ateş, öksürük, nefes darlığında artış, akciğer grafisinde bilateral yaygın infiltrasyon gelişmesi üzerine yoğun bakımda invazif mekanik ventilatörde takip edildi. Toraks bilgisayarlı tomografisinde; periferik yerleşimli ve bazıları kaviter olan nodüller, infiltrasyon, maximum 1 cm olan mediastinal lenfadenomegali, bilateral plevral effüzyon ve besleyici damar belirtisi izlendi. Geniş spektrumlu antibiyotik ve antifungal tedaviye yanıt alınamayan hastanın exitusundan sonra trakeal aspirat kültüründe *Acinetobacter baumannii / calcoaceticus* (antibiyogramındaki antibiyotiklerin tümüne dirençli) üremesi saptandı. Mortalitesi yüksek olan septik pulmoner emboli etyolojisinde gram negatif pnömoni saptanması nadir bildirilmiş olup, bu nedenden dolayı olguyu literatür eşliğinde tartışmayı amaçladık.

Anahtar Sözcükler: *Acinetobacter, pnömoni, septik pulmoner emboli.*

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Septic pulmonary embolism is an infective lung disease that leads to infarction in the pulmonary arteries and bilateral multiple nodules and/or cavitations in the lung parenchyma resulting from the circulation of thrombus infected with microorganisms in the primary infectious focus in the bloodstream (1). The clinical symptoms and radiological findings of the case we have presented were consistent with septic pulmonary embolism and its differential diagnoses were eliminated. *Acinetobacter baumannii/calcoaceticus* grew in the tracheal aspirate culture of the patient who became exitus due to unresponsiveness to broad spectrum antibiotic and antifungal therapy. We have reported this case for the presence of rarely reported septic pulmonary embolism associated with Acinetobacter pneumonia in the literature, its high mortality rate and necessity of early treatment with broad spectrum antibiotic therapy because of its high mortality rate.

CASE

The 58-year-old male patient was monitored as diagnosed with COPD and admitted with diagnosis of COPD exacerbation due to the increased complaints of cough, sputum and dyspnea. He had no feature except previous cholecystectomy operation in his medical history. His history of smoking cigarette was 35 pack/year and he had no smoking since 4 years. His measures were as following: Fever: 38.5°C, TA: 110/60mmHg, Pulse: 94/min, and respiratory rate: 20/min. The baseline values at admission to the ward were as following: C-Reactive Protein (CRP): 31 mg/dL (normal range:0-5 mg/dL), Leukocytes: 8600/mm^3 and sedimentation: 10 mm/h. Decompensated respiratory acidosis developed on the 4th day of admission and the patient was taken to the intensive care unit as intubated because of unresponsiveness to non-invasive mechanical ventilator treatment. The patient had no pathological lesion in the chest x-ray (Figure1) at admission while blood parameters at admission to the intensive care unit (Figure 2) were CRP: 137 mg/d, Leukocytes: 33400/mm^3 and neutrophil rate: 32%, consequently initial ceftriaxone treatment was stopped and meropenem treatment was initiated. Linezolid was added to the treatment regimen in the patient with persisting high fever and CRP levels accompanied with diffuse infiltrations as encountered in the chest x-ray. Anidulafungin treatment was initiated because of unresponsiveness to the treatment and detection of oral candida lesions. The creatinine level raised to 3.68 mg/dL whereas creatinine levels were normal during monitoring and the patient was taken to dialysis due to development of anuria. Peripherally located and partly cavitary nodules, infiltration, mediastinal lymphadenomegaly with a maximum diameter of 1 cm, bilateral pleural effusion and feeding vessel sign were encountered in the thoracic computed tomography (CT) performed in the next day (Figure 3). No thoracentesis was performed since pleural effusion was minimal. Septic embolism was considered in the patient, immune markers for Wegener Granulomatozis as well as ARB and mycobacteria culture from the tracheal aspirate for tuberculosis were tested for differential diagnosis. Sedimentation and rheumatoid factor levels were 140 mm/h and 8.4 IU/mL (Range: 0-30 IU/mL), respectively, ANA, c-ANCA, p-ANCA, PR3-ANCA assays were negative. No metastasis was considered since baseline chest x-ray at admission was normal. No finding of infective endocarditis was detected in the transthoracic echocardiography. No microbial growth was found in the blood, urine and catheter cultures. No hyphe was encountered in the tracheal aspirate culture while fungal culture indicated no growth. The patient became exitus on the 14th day of admission in the intensive care unit. *A. baumannii /calcoaceticus* grew in the tracheal aspirate culture 4 days after exitus. The culture test material was tested using VITEK 2 system in accordance with the recommendations of European Committee on Antimicrobial Susceptibility Testing (EUCAST) and tested respiratory tract samples were found resistant to all the antibiotics listed in the guideline.

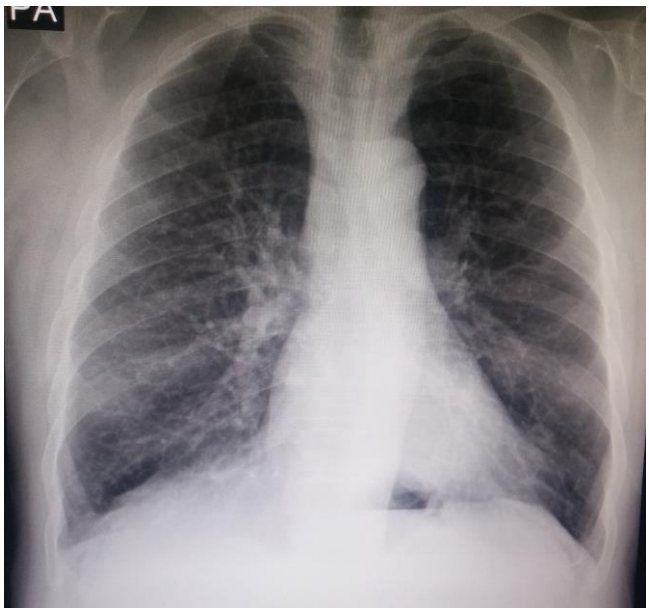

Figure 1: *Chest x-ray at admission to hospital*

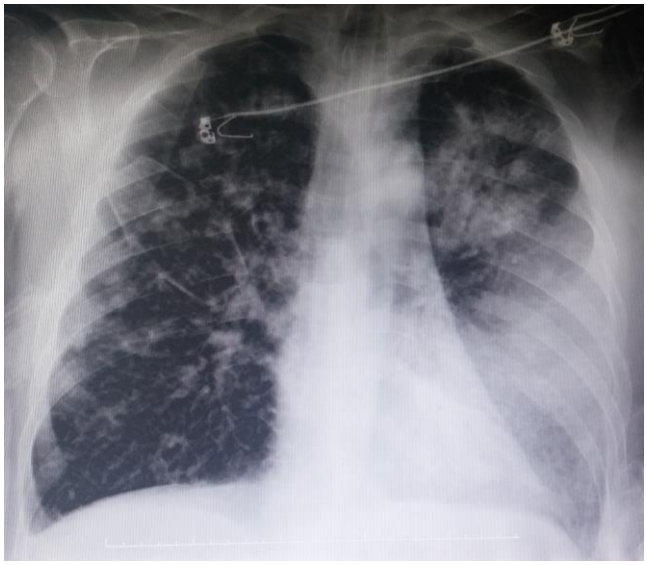

Figure 2: *Chest x-ray in the intensive care unit*

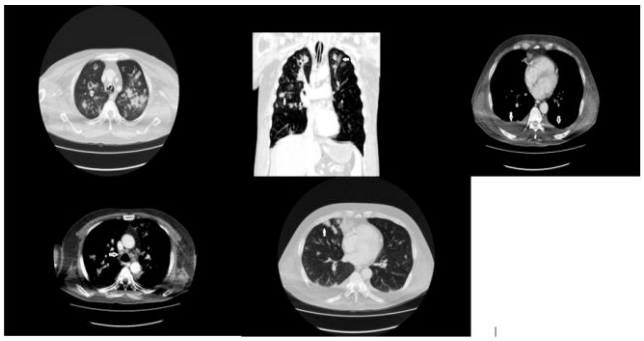

Figure 3: *Thoracic tomography reveals partly cavitary nodules, feeding vessel sign, bilateral pleural effusion, mediastinal lymphadenomegaly, wedge-shaped peripheral lesions and parenchymal infiltration*

DISCUSSION

Septic pulmonary embolism is an infective lung disease that leads to infarction in the pulmonary arteries and bilateral multiple nodules and/or cavitations in the lung parenchyma resulting from the circulation of thrombus infected with microorganisms in the primary infectious focus in the bloodstream (1). It frequently emerges secondary to oropharyngeal infections, right-sided infective endocarditis, central venous catheter infection, infected pacemaker, liver abscess, peritonsillar abscess (Lemierre's syndrome), osteomyelitis, mastoiditis, A-V shunts in hemodialysis patients, septic abortus, skin-soft tissue infections and administration of intravenous drugs (1,2). The essential characteristics of septic pulmonary embolism are fever, pulmonary infiltration and presence of an extrathoracic infection focus that may cause this infiltration. The progression to septic fever, dyspnea, cough, pleuritic chest pain progressing to respiratory distress and hemoptysis in the advanced period are monitored in the cases with septic pulmonary embolism (3,4). The symptoms cough, fever and increased dyspnea were present in also our case.

Chest x-ray may be normal; hence, thoracic tomography is superior for diagnosis (1). The most common thoracic CT findings of septic pulmonary embolism have been defined as peripheral nodules, wedge shaped peripheral lesions, cavitations and feeding vessel sign, respectively (5). The lesions are located in the neighborhood of pleura and at the end of the vessels. This appearance is termed as feeding vessel sign indicating hematogenous source of the lesion and it may be encountered also in the lung metastases. The lesions may lead to cavitation and suppuration by rapid progression (2). Cavitation may occur in also aseptic embolisms; however, it should be taken into account that a bacterial infarction may be added onto the thromboembolic infarction in the presence of cavitation. Hilar or mediastinal lymph node growth may accompany when acute septic pulmonary embolism is massive (6). Partly cavitary nodules, mediastinal lymphadenomegaly with diameter of maximum 1 cm, infiltration and bilateral pleural effusion were encountered in our case by Thoracic CT. The patients are mostly diagnosed based on primary infection focus and tomography findings (7). The blood and urine cultures revealed no growth while fungal direct exam and fungal culture indicated no feature in our case. The growth of *Acinetobacter* was detected in the tracheal aspirate culture after the patient became exitus.

Tuberculosis, fungal and Gram (–) infections, parasitic infections (cyst hydatid), metastasis, lymphoma, benign and malignant neoplasms of the lung, rheumatoid arthritis, Wegener granulomatosis, Churg-Strauss syndrome and sarcoidosis should be considered in differential diagnosis (8). Echocardiography should be performed in the patients with septic pulmonary embolism because tricuspid valvular vegetation, valvular regurgitation and paravalvular abscesses may be identified in these cases. Transesophageal echocardiography is a superior diagnostic technique to transthoracic echocardiography in imaging small vegetation (5). No pathological image compatible with endocarditis was encountered in the echocardiography of our case.

Sakuma et al. (9) have reported that infective endocarditis was present in 11% of the cases with septic pulmonary embolism and that a higher frequency of fungal embolism was found compared with bacterial embolism in these patients with mostly underlying hematogenous malignancies such as lymphoma and leukemia. *S. aureus, K. pneumoniae* and *Viridans Streptococci* are the most

commonly detected infectious agents in the blood cultures (7,9,10). Chou et al. (11) have reported that multiorgan dysfunction syndrome developed in 85% of the patients and acute respiratory distress syndrome ARDS was the most commonly seen organ failure (75%). Liver abscess (40%) was the most frequently seen primary infectious focus followed by pneumonia (25%). The most prevalent two casual pathogens were *K. pneumoniae* (50%) and *S.aureus* (35%). Serum creatinine, arterial partial carbon dioxide pressure, APACHE II and (SOFA) (The Acute Physiology and Chronic Health Evaluation and Sequential Organ Dysfunction Evaluation) scores were significantly higher in the exitus patients while also acute kidney injury, disseminated intravascular coagulation and lung abscess were determined with higher rates in those patients than the survivors. Intrahospital mortality rate was reported as 30%. The patients with septic pulmonary embolism that requires treatment in the intensive care unit, particularly those with pneumonia and liver abscess, were found to be associated with high mortality rates. The patients with pneumonia (60%) as the primary source of pulmonary embolism indicated manifested the highest mortality rate. Acute kidney failure developed during monitoring our case and he was taken to hemodialysis. No regression could be obtained in hypercapnia despite implementation of the appropriate ventilation strategies and APACHE II score was high.

It has been reported that nodules in the Gram-positive septic embolism were larger than those in the Gram-negative septic embolism. Cavitation and air bronchogram were more frequently seen in the Gram-positive embolism while halo and feeding vessel sign with ground-glass intensity around a nodule were more commonly monitored in the Gram-negative embolism (10). Both cavitary nodules and feeding vessel sign were present in our case.

Septic pulmonary embolism is not only associated with increased mortality and prolonged hospital stay duration, it is also related with complications such as abscess, empyema and also bronchopleural fistula that requires different therapeutic interventions (12). *Acinetobacter* as an aerobic gram negative cocobacillus is an important pathogen in nosocomial pneumonia. However, it may rarely cause community-acquired pneumonia. *A. baumannii* species of *Acinetobacter* genus is a common cause of community acquired pneumonia in the tropical/subtropical region and also other places with a warm and humid climates (13). It was identified as the hospital-acquired pneumonia agent in our case. Although, *Acinetobacter* strains that cause community-acquired infections are usually sensitive to aminoglycosides, broad-spectrum penicillin, ceftazidime, kinolon, imipenem ve ciprofloxacin (13), *Acinetobacter* strain was reported to be resistant in our case. Wade et al. (12) have reported *Acinetobacter* strain that grew in the blood culture as the responsible infectious agent for the septic pulmonary embolism that developed due to pneumonia in an 11-month-old infant (12). The presence of bacteremia explains the development of septic pulmonary embolism. In also our case; no other infectious agent that may explain the etiology of septic pulmonary embolism was identified and inability to detect the growth in the blood culture may be resulting from technical and laboratory circumstances.

As a conclusion; pneumonia also should be beard in mind in the etiology of septic pulmonary embolism and the administration of broad spectrum antibiotic therapy should be initiated early for this clinical manifestation with high mortality rate.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

YAZAR KATKILARI

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

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Diagnosis of Pulmonary Hydatid Cyst with Point of Care Ultrasound in an Emergency Department: A Case Report

Acil Serviste Point of Care Ultrasound ile Pulmoner Kist Kidatik Tanısı: Olgu Sunumu

Nalan Kozaci[1], Mustafa Avcı[2]

Abstract

Ultrasonography is widely used for diagnostic and invasive purposes in emergency departments. We present here a case with acquired immune deficiency syndrome who was diagnosed with a hydatid cyst and pneumonia in the lung parenchyma during a point-of-care-ultrasonography examination.

Key words: *AIDS, cyst hydatid disease, lung, point of care ultrasonography, POCUS.*

Özet

Ultrasonografi acil servislerde tanısal ve invazif amaçlar için yaygın olarak kullanılmaktadır. Bu yazıda, point-of-care-ultrasonography incelemesi ile akciğer parankiminde kist hidatik ve pnömoni tanısı konulan edinilmiş immün yetersizlik sendromlu bir olguyu sunuyoruz.

Anahtar Sözcükler: *AIDS, akciğer, kist hidatik hastalığı, point of care ultrasonografi, POCUS.*

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Cyst hydatid disease (CHD) is one of the parasitic diseases, resulting from an Echinococcus granulosus pathogen infection. It is mostly encountered in areas where sheep and cattle are raised, and particularly in Mediterranean countries, Central Asia, Northern and Eastern Africa, Australia and South America (1,2). The most common organ to be affected in adults is the liver, followed by the lungs. A CHD diagnosis is based on clinical findings, serologic tests and imaging features (3,4).

Conventional X-ray (XR), computed tomography (CT) and magnetic resonance imaging (MRI) of the lungs are the various modalities that can reveal the presence of a thoracic hydatid cyst, although both CT and XR imaging involve potential radiation exposure (2,4,5). MRI is not always accessible in emergency situations. Ultrasonography (US) is the primary imaging modality used to diagnose and evaluate CHD in the liver, although it may be used for diagnoses in any area accessible by the US probe and with a good acoustic window. These extrahepatic locations include the spleen, kidneys, pelvis and heart (4,5).

In the last decade, many clinicians have started to use US for specific purposes, known as "focused US" or "point of care US" (POCUS). Clinicians prefer POCUS for the visualization of many parts of the body in intensive care, the emergency department and pre-hospital settings (6-8). In this report, we present a case with acquired immune deficiency syndrome (AIDS) who was diagnosed with a hydatid cyst and pneumonia in the lung parenchyma upon a POCUS examination. The patient provided written informed consent for their anonymized information to be published in this article.

CASE

A 35-year-old female patient was admitted to the emergency department with complaints of dyspnea and hemoptysis. The patient reported also fever and cough, and HIV infection. The vital signs of the patient were as follows: fever 37.7°C; arterial blood pressure 125/82 mmHg; heart rate 119 beats/min; respiration rate 28/min; and pulse oximetry 95% in room air. Upon examination, the patient was found to be in respiratory distress. Lung examination revealed decreased breathing sounds in the left lung. Other physical examination findings were normal. In lab tests, an arterial blood gas analysis revealed no hypoxia, although she had mild compensated respiratory alkalosis. The other laboratory test findings were as follows: C-reactive protein level 256 mg/L (reference range (RR): 0-9); hemoglobin 11.3 g/dl (RR: 12-15); leukocyte count 28.0 (RR: 3.6–10.2x103); and platelet count 608,000/mm3 (RR: 159–388x103). Alanine aminotransferase was 137 U/L (RR<50); aspartate aminotransferase was 284 U/L (RR<50); gamma glutamyl transferase was 114 U/L (RR<38); alkaline and phosphatase was 283 U/L (RR: 30–120). Kidney function tests were normal; an HIV-specific enzyme-linked immunosorbent assay (ELISA) antibody test was positive; a hydatid cyst (indirect hemagglutination) test was 1/1280 g/L; and parenchymal opacity and siluet sign on the lower surface of the left lung were observed in the posterio-anterior lung XR (Figure 1). A lung examination with POCUS was performed by an emergency physician using 7.5 MHz linear and 3.5 MHz convex transducers with a standard US tool (Mindray DC-T6, Germany). After clinical and POCUS examinations, a CT scan was performed, revealing cyst, pleural effusion and infiltration areas in the left lung (Figure 1). The cyst was a well-circumscribed, fluid density lesion with homogenous content, 90 mm in diameter, and left lung volume was decreased due to the mass effect of the cyst. Another cyst was observed in the medial part of the spleen.

The patient was admitted to the intensive care unit with a diagnosis of pneumonia and CHD. An operation for the resection of the cyst was recommended by the thoracic surgeon, but the patient declined and discharged herself from hospital on the sixth day of hospitalization.

Ultrasound Technique: Each hemithorax was divided into six areas, with longitudinal lines passing through the midsternal, midclavicular and anterior axilla, and with transverse lines passing through the areola of the breast. Each area was evaluated with linear and convex transducers in the longitudinal and transverse planes. Ultrasound findings, such as artifacts (A line, B line), lung sliding, alveolar consolidation and pleural effusions, were recorded in all areas.

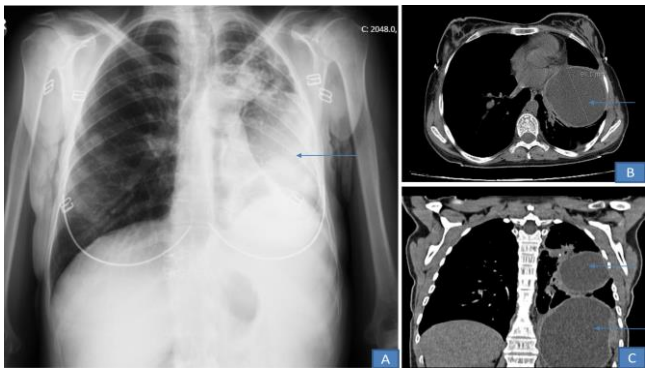

Figure 1: *Posterioanterior chest X-ray (A), Thorax Computed Tomography cross-section (B), Thorax computed tomography coronal section (C)*

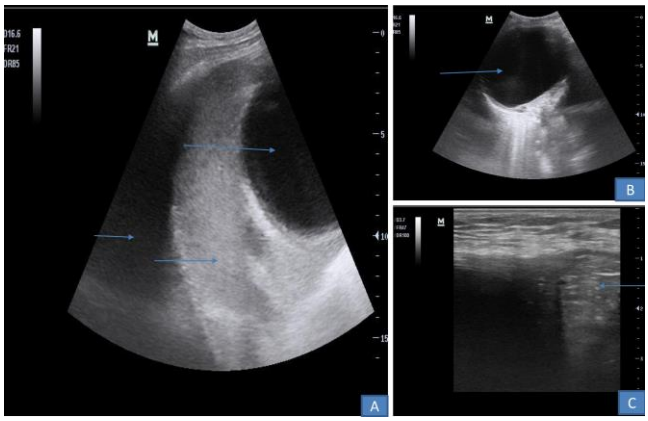

Figure 2: *POCUS, abdominal Hydatid Cyst, Spleen and pleural fluid, (A), POCUS, hydatid cyst in the lung parenchyma (B), POCUS, pneumonic infiltration (C)*

Ultrasound Findings: Pleural effusion, infiltration areas and cystic structure were revealed in the left upon the POCUS examination. The diameter of the cyst, which was well-circumscribed, unilocular and round, was 76x87 mm, with anechoic and homogeneous content (Figure 2).

The cyst was considered to be a hydatid cyst, and so the emergency physician performed an abdominal examination with US. The liver, gall-bladder, right kidney, pancreas, left kidney, spleen, bladder and uterus were examined sequentially with US and screened for cysts. A cyst was detected in the abdomen adjacent to the spleen measuring 11.12x8.73 cm in diameter, of a type similar to the lung cyst. The cyst was well-circumscribed, anechoic and had homogenous content (Figure 2).

DISCUSSION

The lungs are one of the main target organs for HIV-related diseases, and almost 70% of patients experience at least one respiratory complication during their illness. The common lung manifestations of HIV/AIDS are opportunistic infections, emphysema and bronchiolitis, lymphoproliferative diseases and AIDS-related malignancies. The broad spectrum of the disease makes differential diagnosis difficult, and so clinical and radiological findings should be evaluated together for accurate diagnosis (9).

Pulmonary CHD may cause chest pain, dry cough and hemoptysis, while large cysts can cause shortness of breath with the effect of the mass. Acute onset symptoms and anaphylactic reactions should suggest cyst rupture. In some cases, CHD may be asymptomatic and detected only incidentally. Pulmonary hydatid cysts may be single or multiple, and single cysts are more common. CHD should be suspected when well-defined homogeneous radiopacity is seen on the chest X-ray. The CT features of uncomplicated hydatid cysts appear as well-circumscribed fluid attenuation lesions with homogenous content and smooth, hyperdense walls (2,3). CHD treatment can be both medical and surgical, with indications for surgery including large cysts that are superficial and likely to rupture, infected cysts, cysts in vital anatomical locations, and cysts that cause mass effect (2).

Ultrasound (US) has long been used to aid diagnosis and to guide therapy in many tropical infectious diseases. Over past two decades, technological advances have improved image quality and significantly reduced the size and price of US equipment (5). As a result, US has emerged as a preferred point-of-care test in clinical decision-making and for procedural guidance in various medical specialties (3). Bedside POCUS by clinicians is common today (4,10). The fundamental difference between POCUS and a conventional US examination is that POCUS is performed by the treating physician. POCUS aims to answer simple, usually binary questions related to immediate patient management (e.g., "Is there a pleural or pericardial effusion? Yes or no") (5,10), rather than being a comprehensive US assessment (11).

Nowadays, clinicians use US for the diagnosis of such lung diseases as pneumothorax, lung contusion, pulmonary edema and pneumonia. US is also used for the diagnosis of pulmonary abscess, pleural fluid with mass and consolidation (6,11-13). The BLUE protocol is an approach used for the diagnosis of lung diseases in which the physician is directed step-by-step from differential diagnosis to diagnosis in patients with acute dyspnea (11). In a study of HIV-infected patients, the pulmonary US characteristics of five different common lung diseases (bacterial pneumonia, Pneumocystis jirovecii pneumonia, tuberculosis, cytomegalovirus pneumonia and non-Hodgkin's lymphoma) were investigated. Characteristic US patterns have been observed in Pneumocystis jirovecii pneumonia and pulmonary lymphoma (14).

US is widely used as an imaging modality in the diagnosis of CHD, and a sonographic classification has been developed to standardize the diagnostic and therapeutic steps of CHD (cystic echinococcosis (CE)), in which CE1 stage refers to a simple round or oval unilocular cyst with anechoic content and a visible double cystic wall; CE2 stage refers to a cyst that is completely filled with daughter vesicles; CE3 is divided into two stages: CE3a and CE3b, the first of which is characterized by a "water lily" sign, represented by floating membranes, while the latter is predominantly a solid lesion with daughter vesicles. Finally, CE4 and CE5 stages refer to involution and solid-

ification of cyst content with increasing degrees of calcification (2,3,15).

US is not used in routine practice for the diagnosis of pulmonary hydatid cyst. In one study, US findings related to the cystic wall were investigated in the diagnosis of a pulmonary hydatid cyst. In this study, a double-layered wall in univesicular cysts and a double-layered septum in multivesicular cysts were described as the "wall sign" related to pulmonary hydatid cysts (16).

In the present case, symptoms and clinical findings that were suggestive of lung pathology were predominant. Parenchymal opacity and silhouette sign in the left lung were revealed in XR, after which a POCUS examination was performed. The bedside POCUS examination revealed pneumonic infiltration, cyst and pleural effusion in the left lung. The cyst was large and had a mass effect. It was concluded that the pneumonic infiltration and mass effect of the cyst together had caused a decrease in AC capacity. The cyst was thought to be hydatid disease due to being very large simple, anechoic and well-limited, and due to the patients HIV status. Accordingly, the abdominal organs were screened for cysts with POCUS. A cyst of a similar structure to the lung parenchyma was imaged in the spleen, strengthening the preliminary diagnosis of CHD. The cyst in the spleen was classified as CE1. Furthermore, the size and localization of the cysts were determined by POCUS, and the laboratory tests results confirmed the diagnosis of CHD. The treatment decision was made based on the POCUS findings and laboratory tests results. This issue is important for the diagnosis and treatment decision of CHD.

CONCLUSION

In conclusion, POCUS can be used for differential diagnosis in cases where lung pathology is suspected in the emergency department. US may be used as an alternative to other imaging modalities for the imaging of cystic structures in lung CHD, and for the identification of cyst size and other features.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

YAZAR KATKILARI

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Thoracoabdominal Rebar Injury: A Case Report

İnşaat Demiri ile Torakoabdominal Yaralanma: Olgu Sunumu

Tolga Semerkant

Abstract

The removal of the foreign body form the body after a penetrant injury is critical. A 32-year-old male patient presented to our facility after falling on an iron reinforcement bar (rebar) while working on a construction site. The iron bar had entered the lateral side of the patient's left umbilicus and exited from the posterior scapula. After a physical examination and the necessary radiological investigations, the patient was operated on. Due to the position of the iron bar, the physical examination, radiological examinations, intubation and surgery were conducted with the patient slightly left of the lateral decubitus position, and the iron bar was removed. Although such cases are encountered only rarely, we consider it to be crucial for the emergency and surgical teams to work in coordination.

Key words: *Torakoabdominal yaralanma, acil torakotomi, acil laparotomi.*

Özet

Penentran yaralanma sonrası yabancı cismin çıkarılması önemli bir problemdir. Otuz iki yaşında erkek hastanın inşaat demiri üzerine düşme sonrası demir parçası sol umlikusun lateralinden girip skapula arkasından çıkmıştı. Fizik muayene ve gerekli radyolojik tetikler yapıldıktan sonra hasta ameliyata alındı. Demir çubuğun konumundan dolayı fizik muayene, radyolojik tetkikler, entübasyon ve ameliyat, hafif sol lateral dekübit pozisyonda yapılarak demir parçası çıkarıldı. Sonuç olarak, bu tür olgular az görülmekle birlikte; acil ve cerrahi ekibin koordineli olarak çalışması çok önemlidir.

Anahtar Sözcükler: *Thoracoabdominal injury, emergency thoracotomy, emergency laparotomy.*

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Penetrating injuries in which the item remains in the body are rare. Many patients die at the scene. In cases where vital signs are stable, it is important to remove such objects (1). Here, we present the case of a thoraco-abdominal injury involving rebar.

CASE

A 32-year-old male patient was evaluated in the emergency room after falling from a height of around 7 meters onto a reinforcement bar. Upon physical examination, the patient's blood pressure was 110/50mmhg, pulse was 98/min and saturation was 98%. The iron bar was noted to have entered the left lateral of the umbilicus and exited below the scapula on the right (Figure 1). Respiratory sounds were minimally reduced in the right hemithorax. For transportation and the radiological examinations, the patient was placed in a slightly left lateral decubitus position due to the position of the foreign body. A thorax-abdominal computed tomography showed minimal pneumothorax in the right hemithorax, minimal fluid around the liver, intra-abdominal free air, and a foreign body in the thorax and abdomen (Figure 2). The patient was taken for an emergency operation with general surgery. Due to the position of the iron bar, the patient was placed on the operating table in a slightly left lateral decubitus position. To remove the iron bar in a controlled manner, the patient underwent simultaneous thoracotomy and laparotomy after normal intubation. In an exploration after the thoracotomy, it was observed that the iron bar had caused an approximately 2.5 cm laceration to the diaphragm, a 1.5 cm laceration of the lung and a rib fracture. Simultaneous laparotomy revealed minimal laceration in the colon, small intestine and liver. The iron bar was removed from the abdomen in a controlled manner. No hemorrhages were observed, aside from minimal liver bleeding. The diaphragm and lung lacerations were repaired with primary suture. The liver, colon and small bowel lacerations were primarily sutured in general surgery. After the operation, the patient was extubated and taken to the intensive care unit. The thoracic and abdominal drains were removed on 5th and 6th postoperative days, respectively. The patient developed no postoperative complications, and was discharged with healing.

DISCUSSION

Penetrating traumas can occur in a wide spectrum, with injuries ranging from mild to life-threatening (2). Impalement injuries are a potentially dramatic rare form of penetrating trauma. Most patients die at the site of occurrence. The removal of a foreign body from patients who present to hospital can be complicated. There are two types of impalement injuries. In type 1, the impalement is a result of the movement of the body onto a fixed object (e.g. falls from height onto a piece of rebar); while in type 2, a moving object enters the body (for example, when an object enters a vehicle) (3). The case presented here was type 1.

The majority of deaths arising from penetrating traumas result from severe vascular injuries, and so vital signs should be evaluated quickly and carefully. The location of the piercing item should not be changed during the physical examination, radiological examinations or transport to the operating room (2). No time should be lost in imaging hemodynamically unstable cases, although in some cases, some imaging methods may be hindered by the positioning of the foreign body. In such cases, imaging should not be insisted upon, as it may lead to the foreign body being disturbed, leading to serious problems (4). Our case was hemodynamically stable, and so a careful physical examination was performed prior to emergency surgery. Afterwards, the necessary radiological examinations were requested, after which, the location of the iron rebar in relation to visceral structures was determined. The patient was then quickly transferred to the operating room. Attention was paid not to disturbing the position of the iron rebar.

Figure 1: *The entry point (A) of the iron rebar into the abdomen and the exit point (B) from the thorax*

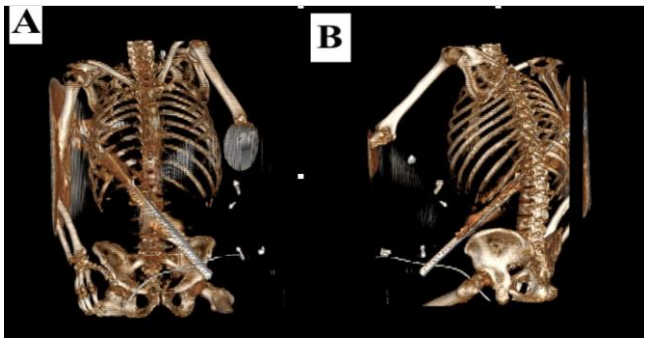

Figure 2: *Three-dimensional CT image (A and B)*

In such cases, the location of the foreign body may prevent the patient from being placed in a supine position, creating considerable problems for the surgeon and anesthesiologist. The patient should be transferred to the operating table using maneuvers that take into account the position of the foreign body, which also determines the surgery to be performed. The aim is to provide better airway control and to permit a more comfortable surgery (5). A simultaneous thoracotomy and laparotomy were to be performed, a mild left lateral decubitus position was decided upon after considering the current position of the iron rebar. The operation was started only after airway control was assured through anesthesia.

The uncontrolled removal of the penetrating item can cause massive bleeding, and so it should be removed in a controlled manner by taking foreign bodies into the operation. Potential bleeding sites should be identified prior to surgery, and the kind of surgery required for the removal of the object should be decided upon (6). We carried out a physical examination to determine possible bleeding areas, and opted for a simultaneous operation to allow interventions in these areas.

Conclusion

Penetrating injuries can be difficult to manage, and require the emergency and surgical team to work in a coordinated manner. Careful physical examinations and radiological examinations should be performed in hemodynamically stable cases as a priority, through which the relationship with important visceral organs can be determined. The removal of the foreign body should be carried out in a controlled manner, and so simultaneous surgeries should not be avoided.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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

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A Rare Case of Pulmonary Fibrosarcoma Treated by Sleeve Lobectomy

Sleeve Lobektomi ile Tedavi Edilen Nadir Bir Pulmoner Fibrosarkom Olgusu

Demet Turan[1], Mehmet Akif Ozgul[1], Levent Cansever[2], Mehmet Ali Bedirhan[2]

Abstract

A 28-year-old male presented to the emergency department with hemoptysis. A pulmonary examination revealed diminished lung sound on left side, and a CT scan of the chest showed an endobronchial polipoid lesion in the left main bronchus. A rigid bronchoscopy showed a polipoid lesion in left the main left bronchus, while the orifice of the lower lobe was not visible. The lesion was cut into two pieces with a snare and removed with cryotherapy, and hemostasis was achieved. A pathological examination of the lung bronchial biopsy specimen revealed fibrosarcoma. A left lower sleeve lobectomy was performed, and as surgical margins were tumor free, no chemo/radiotherapy was considered necessary. Primary endobronchial pulmonary fibrosarcomas exhibiting polypoid growths are rare. Surgical excision is the preferred treatment option in such patients.

Key words: *Endobronchial fibrosarcoma, endobronchial therapy, Hemoptysis, lung surgery, snare electrocautery.*

Özet

Yirmi sekiz yaşında erkek hasta, acil servise hemoptizi şikayetiyle müracaat etti. Solunum sistemi muayensinde solda solunum sesleri azalmıştı ve tomografide alt lobda tıkayıcı polipoid bir lezyon ve distalinde atelektazi vardı. Bronkoskopide sol ana bronşa taşan polipoid lezyon görüldü. Lezyonun görünen kısmından snare ile biyopsi alındı ve cryo ile hemostaz sağlandı. Patolojisi fibrosarkom gelen hastaya sleeve sol alt lobektomi uygulandı. Lenf nodları ve cerrahi sınırlar negatif bulundu. Hastaya kemo/radyoterpi tedavi uygulanmadı. Primer pulmoner fibrosarkomların polipoid olarak büyümesi nadir görülmektedir. Bu hastalarda tercih edilen tedavi şekli cerrahi eksizyondur.

Anahtar Sözcükler: *Endobronşial fibrosarkom, endobronşial terapi, hemoptizi, akciğer cerrahisi, elektrokoter.*

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Primary sarcomas of the thorax are rare, but can occur in the lung, mediastinum, pleura and chest wall, while fibrosarcomas usually develop in the chest wall. Although primary thoracic sarcomas commonly manifest as large, heterogeneous masses, they may also develop as solitary pulmonary nodules, central endobronchial tumors and intraluminal masses within the pulmonary arteries (1). Early diagnosis is vital, although it is important to exclude other spindle cell proliferations and sarcomatous neoplasms with a similar morphological appearance. This report describes the case of a primary pulmonary fibrosarcoma presenting as a polypoid endobronchial growth mass, which can be treated surgically.

CASE

A 28-year-old man presented to the emergency department with hemoptysis. He had been in a usual state of health until 2 months prior to presentation, when he experienced hemoptysis. In a physical examination he was found to be in mild respiratory distress. A pulmonary examination revealed diminished lung sounds on the left side. A chest radiography revealed volume reduction in the left lung and a mediastinal shift toward to the left side (Figure 1). A CT scan of the chest showed an endobronchial polypoid lesion in the left main bronchus and atelectasis on the left upper lobe in the apicoposterior segment, the lingular segment and the lower lobe subsegments (Figure 2). A rigid bronchoscopy was carried out. A polypoid lesion was observed in the main left bronchus, and mucosal hypervascularity was present (Figure 3). The lesion was cut into two pieces with a snare and removed with cryotherapy. A pathological examination of lung bronchial biopsy specimens revealed a spindle cell mesenchymal tumor with low malignancy potential. The results of immunohistochemistry staining were: Pancitokeratin (-), Vimentin Clone V9 (+), Desmin (+), CD34 (-), S100 (-), ALK (-), CD 56 (-), Synaptophisin (-) and Kİ 67 (+). A consultation with another pathology service confirmed the diagnosis of spindle cell mesenchymal tumor; there was no necrosis and mitosis was 3/10. Differentiations were excluded based on immunohistochemistry staining: Miyogenin (-) and SOX (-). The final diagnosis was fibrosarcoma (Figure 4). A left lower sleeve lobectomy was performed to achieve tumor negative margins after the diagnosis was confirmed. A pathological examination of the lobectomy material revealed no residual tumor. The chest X-ray following surgery is shown in Figure 5. After 4 months of surgery, a PET/CT scan showed no FDG uptake in any part of the body. A fiberoptic bronchoscopy was applied 1 month after the PET/CT scan, and no endobronchial lesion was observed in the left upper lobe or lingula. The patient's status was stable at postoperative 24 months. No chemo/radiotherapy was considered necessary after surgery.

DISCUSSION

Fibrosarcoma is a malignant neoplasm of mesenchymal origin, and is a very rare malignancy that can occur anywhere in the body and in any age group. Primary pulmonary sarcoma occurs in 0.1% of all primary pulmonary malignant neoplasms (2). Intrathoracic fibrosarcomas tend to present as endobronchial masses in the main or lobar bronchi in children and young adults, while in adult lungs they tend to occur as solitary or multiple nodules or masses (3). Although intrapulmonary fibrosarcomas often produce no symptoms, especially when small, endobronchial lesions typically manifest with cough, hemoptysis or chest pain. Our patient presented only with hemoptysis.

In radiological analyses, fibrosarcomas in the chest wall and heart usually manifest as masses that are often heterogeneous in attenuation and signal intensity on CT and MR images (4). In the lung, fibrosarcomas manifest as well-marginated smooth or lobular nodules, or as masses on CT (3). Endobronchial tumors can manifest as atelectasis or post-obstructive pneumonitis. Our patient's chest radiographic finding was similar to those of previously reported cases, involving atelectasis and no pulmonary/pleural mass.

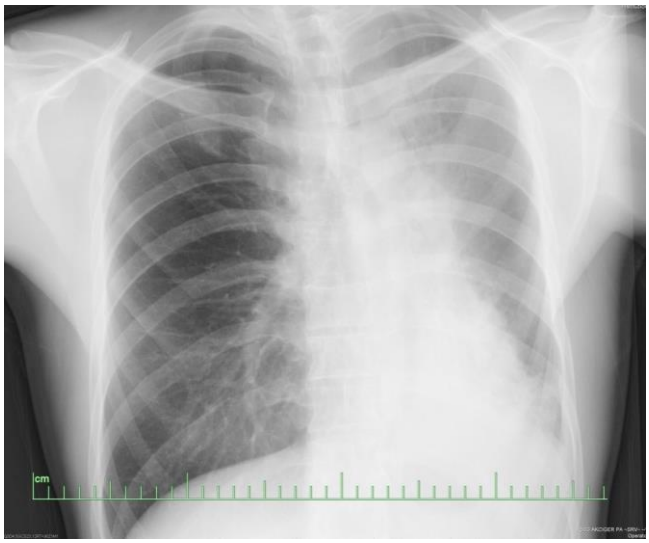

Figure 1: *Chest radiography revealed volume reduction in the left lung, and a mediastinal shift toward to the left side*

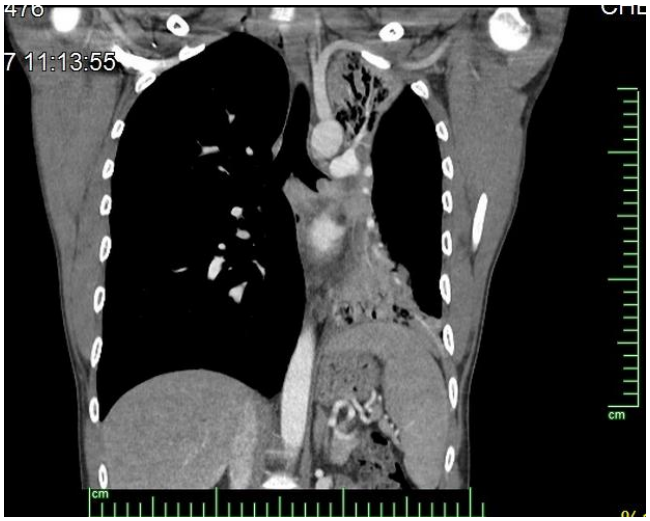

Figure 2: *A CT scan of the chest showed an endobronchial polipoid lesion in the left main bronchus, and atelectasis on the left upper lobe apicoposterior segment, lingular segment and lower lobe subsegments*

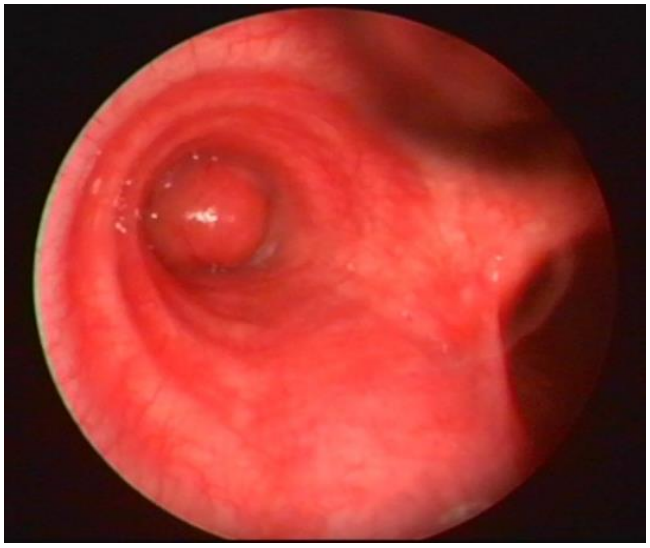

Figure 3: *A polipoid lesion was observed in the main left bronchus, and mucosal hypervascularity was also present*

The histological immunohistochemical evaluation and electron microscopy of tumor cells is critical for tumor diagnosis. Immunohistochemistry is helpful when differentiating fibrosarcoma from other similar tumors in the chest (fibrous mesotheliomas, malignant fibrous tumors of the pleura, and other sarcomas, such as myxofibrosarcoma, synovial sarcoma or nerve sheath sarcoma). Tumors are usually highly cellular, consisting of spindle cells with a fusiform nucleus, arranged in a herringbone or broad fascicular pattern (5). The diagnosis of our patient was confirmed through an immunohistochemical evaluation of the resected endobronchial mass.

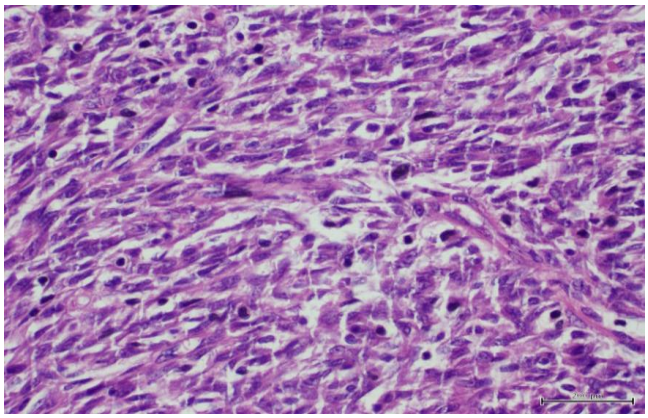

Figure 4: *Microscopy of fibrosarcomatoeus cells (H&E – 20x10)*

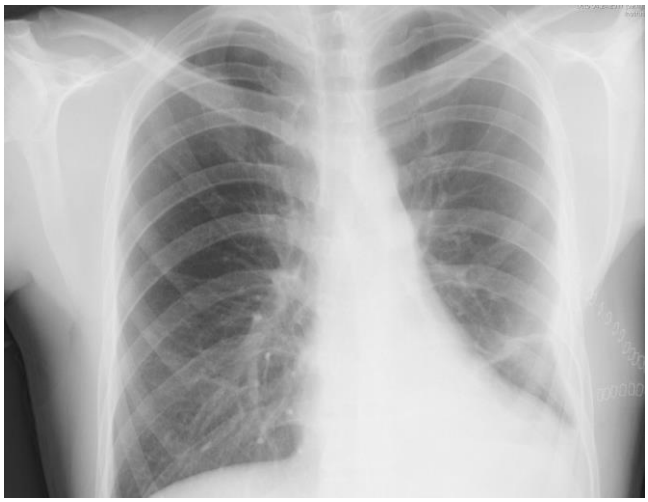

Figure 5: *A chest X-ray after surgery revealed no atelectasis*

Endobronchial lesions are usually treated with local excision, and long-term survival is common. The treatment of chest wall and mediastinal lesions is resection, with preoperative chemotherapy used to improve resectability. Postoperative radiation therapy is applied if the surgical margins are positive or if a complete resection is not possible (6). There are several reports in literature highlighting the effective role of adjuvant chemotherapy after tumor resection for the treatment of infantile fibrosarcoma. The Mayo Clinic reported 40 patients with infantile fibrosarcoma who were treated with only surgery and radiotherapy (7). Our patient's endobronchial lesion was treated with local excision, cryotherapy and APC. Following diagnosis, the patient underwent a left lower sleeve lobectomy, and no adjuvant treatment options were recommended.

The response to therapy is often poor, with larger masses tending to recur locally, whereas smaller lesions have a high likelihood of metastasis (3). Our case had no hematogenous or lymphatic metastasis. Prognosis is correlated with tumor size, histologic grade, mitotic count and the location of the tumor (endobronchial vs. intra-

parenchymal) (3,8). In one case series, all patients with a primary fibrosarcoma of the lungs larger than 5 cm in diameter eventually died of the tumor (9). Primary pulmonary sarcomas are generally associated with worse overall survival than with soft tissue sarcomas of the extremities (10). An aggressive approach to treatment is advocated, with radiotherapy and chemotherapy preferred for unresectable cases. Endobronchial tumors are usually detected earlier and have a better prognosis. Intraparenchymal tumors often behave in a highly malignant fashion, with death occurring within 2.5 years. Tumors with eight mitotic figures per 10 high-power fields behave in an aggressive fashion, while others remain stationary or tend to grow slowly (11). Our patient is still alive, although the ultimate prognosis remains unknown.

In conclusion, primary pulmonary fibrosarcomas with polypoid endobronchial growth are rare. Although interventional bronchoscopy can rapidly and efficiently remove endobronchial tumors, surgical excision is the preferred treatment option in such patients.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

YAZAR KATKILARI

Fikir - D.T., M.A.O., L.C., M.A.B.; Tasarım ve Dizayn - D.T., M.A.O., L.C., M.A.B.; Denetleme - D.T., M.A.O., L.C., M.A.B.; Kaynaklar -; Malzemeler - D.T.; Veri Toplama ve/veya İşleme - D.T.; Analiz ve/veya Yorum - L.C.; Literatür Taraması - L.C.; Yazıyı Yazan - M.A.O.; Eleştirel İnceleme - M.A.B.

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Solitary Langerhans Cell Histiocytosis of the Rib

Kostada Soliter Langerhans Hücreli Histiositozis

Demet Yaldız[1], Mehmet Sadık Yaldız[1], Peyker Temiz[2], Cihan Göktan[3]

Abstract

Isolated rib involvement is one of the rarest sites for the clinical presentation of Langerhans cell histiocytosis (LCH). We report here on the case of 29-year-old female whose only symptom was pain, radiating to the solitary osteolytic lesion at the posterolateral aspect of her seventh rib. The 7th rib was resected for diagnostic confirmation and treatment, and histopathological findings were found to be compatible with the LCH.

Key words: *Langerhans Cell Histiocytosis, rib, surgery.*

Özet

İzole kosta tutulumu, Langerhans hücreli histiyositozisin (LCH) en nadir tutulum bölgelerinden biridir. Biz burada, tek yakınması sol 7. kostanın posterolateral bölgesinde soliter osteolitik lezyona bağlı ağrı olan, 29 yaşında bir kadın olguyu sunuyoruz. Hastada 7. kosta, tanı ve tedavi amaçlı rezeke edildi. Histopatolojik bulgular LCH ile uyumlu bulundu.

Anahtar Sözcükler: *Langerhans hücreli histiositozis, kosta, cerrahi.*

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Langerhans cell histiocytosis is a reactive proliferative disease of unknown etiology characterized by a proliferation of Langerhans cells. It involves mostly bone, lung, liver, skin, central nervous system, lymph node and thymus (1). Bone involvement mostly occurs in the skull, followed in prevalence by the femur, jaw, pelvis, spine, scapula, humerus and sternum (2). Though rare, cases of LCH of the rib have been reported (3,4).

CASE

A 29-year old female presented to the clinic with a left-sided pain for almost 6 months in the posterolateral aspect of the seventh rib. There was no history of trauma or disease. Upon physical examination, no swelling or fluctuation was demonstrated over the7th rib area. Laboratory tests were normal. A chest X-ray revealed an expansile shadow on the lateral aspect of the seventh rib (Figure 1). A computed tomography (CT) scan revealed a destructive osteolytic lesion on the left 7th rib (Figure 2). Both benign and malign lesions of the rib were considered in the differential diagnosis. For diagnostic confirmation and treatment, a wide resection of the seventh rib with a tumor-free margin was performed. Upon histopathologic examination, no malignant cell was detected. Clusters of histiocytes with a reniform vesiculated nucleus and abundant foamy cytoplasm with numerous eosinophils confirmed the diagnosis of LCH (Figure 3). The patient had experienced no local recurrence or metastasis one year after the operation.

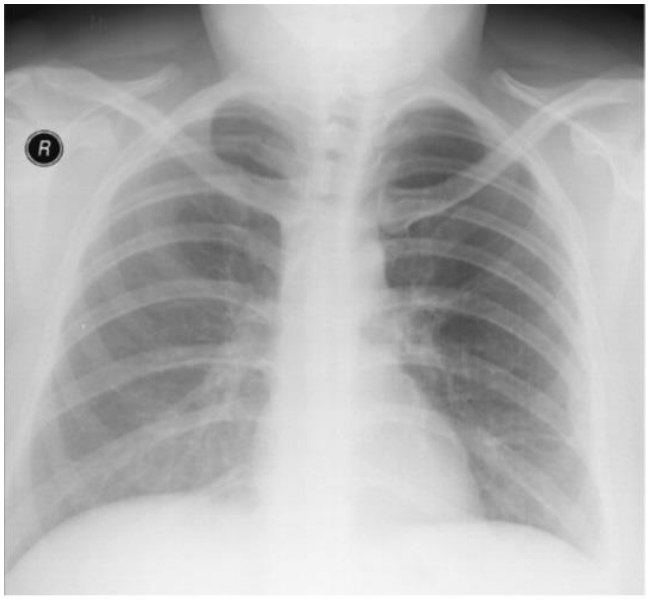

Figure 1: *An expansile shadow was noted on the lateral aspect of the seventh rib (arrow)*

DISCUSSION

LCH is characterized by an abnormal proliferation of tissue macrophage referred to as Langerhans cells. Since the etiology is still unknown, the most important question was whether the lesion is benign or malignant, or a reactive disease of activated Langerhans cells in an immune response. Since there have been very few studies of this subject to date, and none can be considered definitive, it is very difficult to resolve this issue (5). LCH is most commonly seen in children, with 80% of cases occurring in those under the age of 15 (6).

The clinical patterns of LCH are varied, and may affect single regions or different organs, being known to affect bone, lung, liver, central nervous system, thymus, lymph node and skin (1). Single solitary lesions on the rib, however, are extremely rare, with few studies reporting cases of this nature (3,4). Although it's clinical pattern may be varied, there is a strong tendency for the formation of an osteolytic lesion on the bone. Differential diagnoses of osteolytic lesions must consider multiple myeloma, primary bone malignancy, lymphoma, metastasis and osteomyelitis, and LCH also should be considered in the differential diagnosis of osteolytic lesions occurring in the rib.

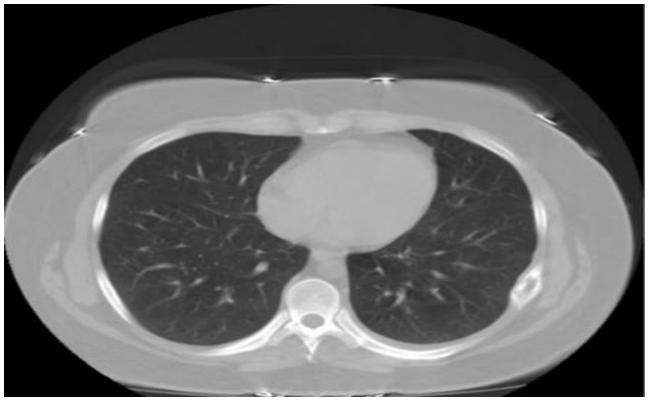

Figure 2: *A destructive osteolytic lesion on the left 7th rib was noted*

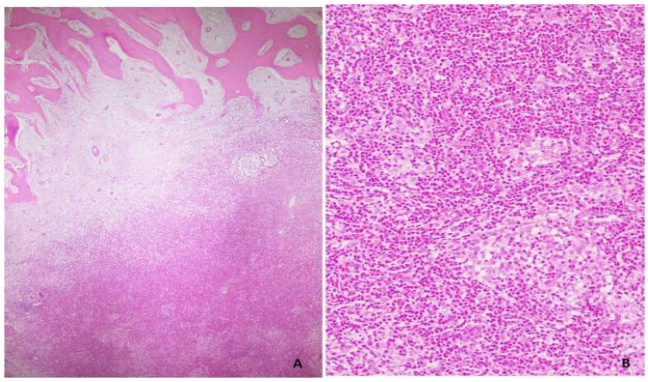

Figure 3: *The cellular infiltrate near the bone trabeculae (H&E, x20) (A), Clusters of histiocytes with a reniform vesiculated nucleus and abundant foamy cytoplasm, and with numerous eosinophil (H&E, x40) (B)*

Surgery, radiation therapy and chemotherapy are the treatment options, although surgery is usually sufficient for solitary lesions. A wide resection with tumor-free margins is required to provide the best chance of cure.

CONCLUSION

We report here a rare case in which a solitary LCH that developed in the rib was successfully treated through a surgical resection. Although uncommon, LCH should be considered in a differential diagnosis of osteolytic lesions in the rib.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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Surgical Treatment of a Case of Tracheobronchopathia Osteochondroplastica with a Thymic Cyst

Timik Kistin Eşlik Ettiği Trakeobronkopati Osteokondroplastika Olgusunda Cerrahi Tedavi

Kenan Can Ceylan, Hüseyin Mestan, Şeyda Örs Kaya

Abstract

Tracheobronchopathia osteochondroplastica is a rare benign disease that is characterized by multiple submucosal osseous and cartilaginous nodules in the tracheal bronchus. The etiology is not clear. A thoracic computed tomography of a 75 year-old female patient with complaints of dyspnea and cough for a year revealed two different lesions on the trachea and the anterior mediastinum. A bronchoscopy revealed a solid mass in the distal part of the trachea, affecting 4–5 cartilaginous rings and restricting the tracheal lumen by approximately 70%. The mass was located approximately two cartilaginous rings distant to the carina. A tracheal sleeve resection and thymectomy were performed through a right thoracotomy. The histopathological results indicated tracheobronchopathia osteochondroplastica and a thymic cyst. The postoperative follow up was uneventful. We report this rare case since the co-existence of tracheobronchopathia osteochondroplastica and the thymic cyst is a condition rarely seen in literature.

Key words: *Surgery, thymic cyst, Tracheobronchopathia Osteochondroplastica.*

Özet

Trakeabronkopatia osteokondroplastika nadir görülen, trakea ve bronş lümenine doğru çıkıntı yapan çok sayıda osseöz ve kartilajönez nodüller ile karakterize benign bir hastalıktır. Etyolojisi belli değildir. Yetmiş beş yaşında kadın hastaya bir yıldır devam eden dispne ve öksürük şikâyeti nedeni ile çekilen toraks bilgisayarlı tomografide trakea ve anterior mediastende kitle saptandı. Bronkoskopide trakeada yaklaşık 4-5 kıkırdak halka kadar ilerleyen, lümeni %70' ye yakın daraltan kitle lezyonu görüldü. Distalinde karinaya yaklaşık 2 kıkırdak halka mesafe yerleşimliydi. Hastaya sağ torakotomi ile trakeal sleeve rezeksiyon ile uç uca anastomoz ve timektomi operasyonu uygulandı. Histopatolojik incelemelerin sonucu trakeabronkopatia osteokondroplastika ve timik kist ile uyumlu olarak değerlendirildi. Postoperatif dönemde kompikasyon gelişmedi. Olgu trakeabronkopatia osteokondroplastika ve timik kist birlikteliği çok nadir görüldüğü için sunulmuştur.

Anahtar Sözcükler: *Cerrahi, timik kist, Trakeabronkopatia Osteokondroplastika.*

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Tracheobronchopathia Osteochondroplastica (TO) is a rare benign disease characterized by multiple osseous and cartilaginous nodules that protrude into the tracheal and bronchial lumen. The etiology of the disease is not clear. The disease usually presents as multiple lesions in the trachea, but can rarely manifest as a single lesion in the peripheral bronchi. Patients are usually asymptomatic. Chronic cough, wheezing, dyspnea and hemoptysis may be seen in symptomatic patients. Atelectasis and obstructive pneumonitis may develop recurrent respiratory infections, requiring surgical treatment or bronchoscopic management when a conservative treatment such as bronchodilators and antibiotics fails. A case of tracheobronchopathia osteochondroplastica accompanied by a thymic cyst is presented in the light of literature due to its rarity.

CASE

A 75 year-old female patient was examined with complaints of dyspnea and cough for one year. Thoracic computed tomography (CT) revealed nodules in the trachea and a mass lesion on the anterior mediastinum, 6 cm in diameter (Figure 1A and B). A Positron Emission Tomography CT evaluation showed no 18 F- fluorodeoxyglucose (FDG) uptake in the tracheal lesions, while a low 18F-FDG (standard uptake value: 1.3) uptake was observed in the anterior mediastinal mass. The patient had a history of type 2 diabetes mellitus, hypertension and coronary stenting due to coronary artery disease. There was no smoking history, and her forced expiratory volume (FEV1) was 1.49 L (73%), forced vital capacity (FVC) 1.70 L (69%) and FEV1/FVC ratio 87%. A rigid bronchoscopy revealed intraluminal nodules that progressed to approximately four to five cartilage rings and obstructed the lumen to 70%. Nodules were located on approximately two cartilaginous rings distant to the carina. No Myasthenia Gravis was detected in a preoperative neurology consultation. A tracheal segmental resection and anastomosis with maximal thymectomy operation via the right thoracotomy were performed. The performance of a right thoracotomy on the fourth intercostal space was helpful in controlling both the distal part of the trachea and the anterior mediastinum. The exact localization of tracheal lesion was ascertained from a preoperative bronchoscopy. The length of the intratracheal lesion was approximately 2.5 cm. A continuous 3/0 prolene suture technique was used for tracheal anastomosis. A microscopic examination of the tracheal nodules revealed subepithelial macrophage deposition, nodular development involving calcification, and ossification in the submucosa, whereupon the patient was diagnosed with tracheobronchopathia osteochondroplastica (Figure 2). A pathological examination of the mediastinal mass revealed it to be a simple thymic cyst. Bronchoscopy was performed for postoperative control, and the anastomosis line of the tracheal segmental resection and lumen diameters were evaluated as standard. The patient was discharged without event. Follow-up included an annual thorax CT, and the patient is now in the 33rd month of clinical follow-up without disease, and with no recurrence noted to date.

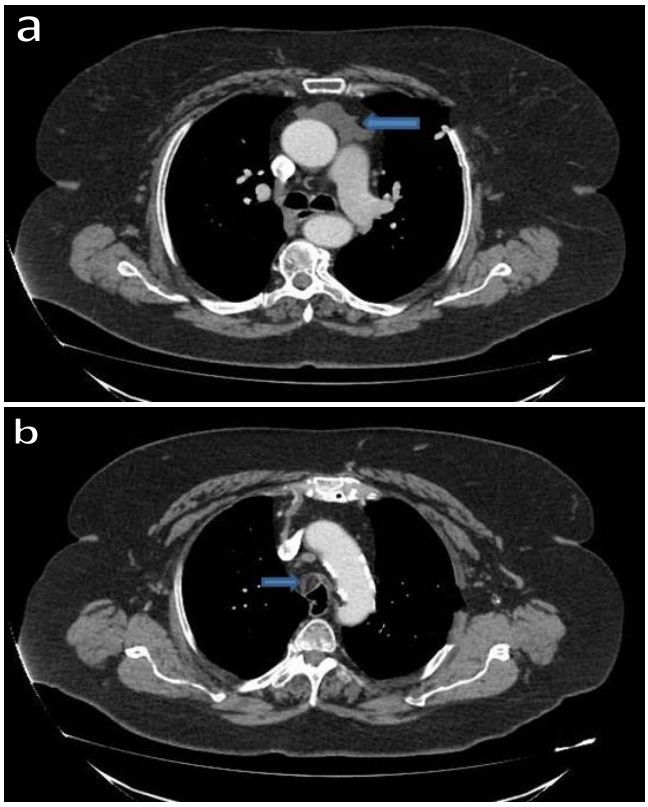

Figure 1a and b: *CT view of the mediastinal mass (A), CT view of the tracheal lesion (B)*

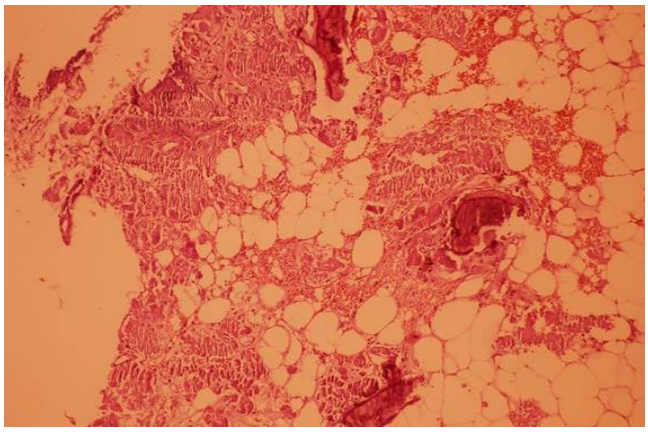

Figure 2: *Microscopic view of the TO (H&E x100)*

DISCUSSION

TO is a benign, rare disease that is characterized by multiple submucosal osseous and cartilaginous nodules involving the anterior and lateral walls of the trachea and the bronchial tree. The posterior membrane part of the trachea is typically unaffected by the disease, which was first described by Rokitansky in 1855, then by Luschka in 1856 and Wilks in 1857 (1). The actual incidence is higher than the reported cases, as the disease is generally asymptomatic. Symptomatic cases present with such nonspecific symptoms as cough, wheezing and hemoptysis (2). In symptomatic patients, the symptoms are related to complicated pulmonary infections, leading to tracheal/bronchial obstructions and dyspnea. There is an average of 4 years between the onset of symptoms and the diagnosis of disease.

In asymptomatic patients, the disease is diagnosed incidentally during bronchoscopy or radiological examinations for other pulmonary pathologies. Thorax CT may show diffuse submucosal calcific nodules protruding from the anterolateral wall of the trachea into the lumen. Chest radiographs usually reveal no pathology. The optimum approach to the diagnosis of TO is bronchoscopy, in which it is typical to observe white-colored irregular multiple nodules on the 2/3 lower part of the trachea involving the anterior and lateral walls. Women and men are equally affected by TO, which is usually observed in the fourth and seventh decades (3), although several cases have been reported in children and young adults (4-6). Our case was an elderly woman with dyspnea, in which a thoracic CT performed due to the symptoms of the patient showed intratracheal lesions and a mass measuring 6 cm in diameter in the anterior mediastinum. A rigid bronchoscopy revealed tracheal nodules that constricted the lumen of the trachea by 70%, and the patient was diagnosed with tracheobronchopathia osteochondroplastica following biopsy.

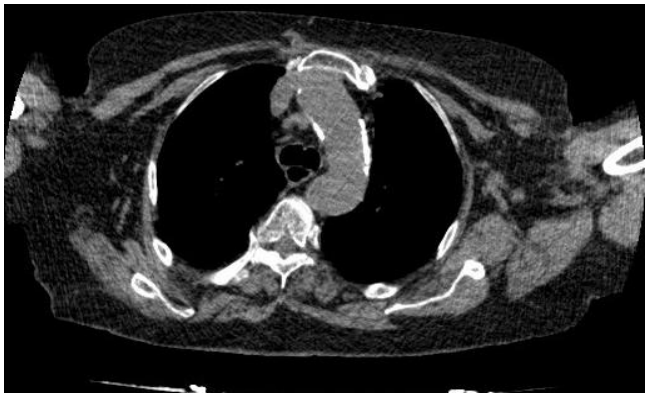

Figure 3: *Postoperative CT image*

TO may also present in the larynx and may be one of the causes of difficult intubation (7), and may be accompanied by diseases such as thyroid tumor, thymoma, atrophic rhinitis, lymphoma and epidermal cyst (8, 9). In our case, TO was accompanied by a thymic cyst, which are rare benign lesions of the mediastinum that are usually located in the anterior compartment. These lesions account for approximately 3% of all anterior mediastinal masses (10), and may be congenital or acquired. Factors such as trauma, inflammatory disease, previous surgical operations and radiation have been reported among the acquired causes (11). Thymic cysts are most commonly seen between the ages of 20 and 50 years, and are usually asymptomatic. Complaints may be related to the location and size of the lesion, leading to cough, shortness of breath and chest pain in symptomatic patients.

Despite intraluminal nodules, pulmonary lung function is generally preserved. In the present case, the pulmonary function test results were FEV1 1.49 L (73%), FVC 1.70 L (69%) and FEV1/FVC ratio 87%. Arterial blood gas indicated partial oxygen pressure of 90 mmHg, partial carbon dioxide 42 mmHg, pH 7.43 and saturation 95%.

No specific treatment has been defined for TO. Conservative treatment approaches may be applied in asymptomatic patients with no severe obstructions. In patients with airway obstructions, bronchoscopic treatment procedures and surgery are the options, selected according to the patients (12). Laser approaches provide the opportunity to obtain either fragmentations or indentations of nodules, which makes it easier to debulk from the submucosa mechanically by rigid bronchoscopy. A combination of laser treatment with stents can improve treatment success. Radiation therapy is the other option for the relief of symptoms. A surgical resection of the TO may be chosen in cases of localized disease and severe airway obstruction. The success of bronchoscopic treatments depends on the method used, such as neodymium-doped yttrium aluminum garnet laser ablation, cryotherapy or cauterization, although the results of laser ablation are superior. On the other hand, hard, debulking bony lesions may prove to be challenging with rigid bronchoscopy. The patient in the present had been suffering from deep dyspnea with effort and cough for one year, despite a year of medical treatment. Mediastinal mass compression may also explain dyspnea. Considering these factors, we prefer surgical treatment.

Surgical treatments of thymic cysts should be performed due to the likelihood of the disease leading to such complications as pneumothorax, dysphagia, vocal cord paral-

ysis, Horner syndrome and the potential to develop into thymic carcinoma over time (13).

TO progresses slowly, and prognosis is favorable. The patient in the present study developed no symptoms during the postoperative follow-up period of 33 months, similar to the findings reported in literature.

In conclusion, the co-existence of TO and thymic cyst is a very rare and benign condition, and is usually asymptomatic. Surgical treatment should be kept in mind in appropriate symptomatic cases. Patients with extensive lesions should be treated via bronchoscopic procedures, while conservative treatment can help relieve symptoms.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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Fikir - K.C.C., H.M., Ş.Ö.K.; Tasarım ve Dizayn - K.C.C., H.M., Ş.Ö.K.; Denetleme - K.C.C., H.M., Ş.Ö.K.; Kaynaklar -; Malzemeler - H.M.; Veri Toplama ve/veya İşleme - H.M.; Analiz ve/veya Yorum - K.C.C., H.M., Ş.Ö.K.; Literatür Taraması - K.C.C., H.M.; Yazıyı Yazan - K.C.C., H.M.; Eleştirel İnceleme - H.M., K.C.C., Ş.Ö.K.

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Marfan Syndrome: A Case Report

Marfan Sendromu: Olgu Sunumu

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Abstract

Marfan syndrome (MFS) is a connective tissue disorder inherited by autosomal dominant pattern that affects primarily cardiovascular, ocular, musculoskeletal and nervous systems. Even though, mutation in the fibrillin-1 gene (FBN1) located on Chromosome 15 was detected in 66-91% in the case with MFS, 27% of the cases were caused by novel mutations. The clinical diagnosis in adults is established according to Ghent Criteria. Early diagnosis, aortic valve-sparing medical and surgical treatments, and regular patient follow-up are helpful in preventing and delaying serious complications. In this case report, we have presented a 30-year-old case who admitted to the hospital due to the complaints of purulent bloody sputum, fever and sweating, and was diagnosed with Marfan syndrome.

Key words: *Marfan's Syndrome, lung, diagnosis.*

Özet

Marfan sendromu (MFS), otozomal dominant geçişli başlıca kardiyovasküler, oküler, kas-iskelet ve sinir sistemlerini etkileyen bir bağ dokusu bozukluğudur. MFS'lu olguların %66-91'inde 15. kromozomdaki fibrillin -1 (FBN1) gen mutasyonu saptanmış olmakla beraber, olguların %27'si yeni mutasyonlardan kaynaklanır. Yetişkinlerde klinik tanı Ghent kriterlerine göre yapılmalıdır. Erken tanı, aortu koruyucu medikal ve cerrahi tedaviler ve düzenli takip ciddi komplikasyonların önlenmesine veya geciktirilmesine yardım eder. Otuz yaşında pürülan kanlı balgam, ateş ve terleme şikayetleri olan Marfan sendromu tanısı koyduğumuz olgumuzu sunduk.

Anahtar Sözcükler: *Marfan Sendromu, akciğer, tanı.*

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Marfan Syndrome (MFS) is a rarely seen connective tissue disorder inherited by autosomal dominant pattern. It primarily affects skeletal, pulmonary, central nervous, oro-oculo-facial and cardiovascular systems. MFS has an incidence of 1:10,000 (probably 1/3000-1/5000) in the population. These rates make MFS one of the most commonly seen single-gene malformation syndromes (1,2). Although, the mutation of the fibrillin-1 (FBN1) gene located on Chromosome 15 was detected in 66-91% of the cases with MFS, it has been shown that 27% of the cases were caused by novel mutations. The mutations of the transforming growth factor b-receptor 2 (TGFBR2) and TGFBR1 genes were identified in 5-10% cases (3,4).

MFS is characterized by many clinical manifestations. These entities include annuloaortic ectasia, aortic aneurysm, aortic dissection, pulmonary artery dilatation and mitral valvular prolapse as well as cardiovascular involvement and aortic valvular regurgitation. Scoliosis, pectus excavatum and carinatum, arachnodactyly and acetabular protrusion are the examples of musculoskeletal involvement. Myopia and lens dislocation may be detected in the eyes (5). Since its clinical appearance is quite changeable, thin and tall body structure, long extremities, arachnodactyly, pectus deformities and occasionally scoliosis primarily in a young person suggest the diagnosis of Marfan syndrome (6).

Berlin 1986 Diagnostic Criteria were revised to diagnose MFS accurately and elevate the prognostic value of these criteria, and defined as 'Ghent Criteria' in 1996 (7). We aimed to review the diagnostic criteria of MFS in our case and to present its complications experienced during monitoring and management of these patients in the light of current literature.

CASE

A 30-year-old male patient was hospitalized due to the complaints of expectorating abundantly purulent and occasionally bloody sputum, fever and sweating. His medical history included diagnosed bronchiectasis 11 years ago, previous operation for scoliosis 6 years ago and previous implementation of bronchial artery embolization for hemoptysis 3 years ago. The patient had no smoking or drug abuse.

The inspection during physical examination revealed asymmetrical chest and less movement in the left hemithorax, reduced anteroposterior chest diameter, left-sided scoliosis, pectus excavatum appearance in the sternum and scar along the vertebra. The fingers and toes of the patient were remarkably long and digital clubbing was prominent. Auscultation indicated diffuse rhonchi and rales, predominantly in the bilateral lung bases. The baseline values of the patient were as following: Fever: 38.5°C, respiratory rate 24/min, Pulse: 110/min, O_2 saturation: 74%, WBC: $10.18x10^3$/uL, Hb: 15.5 g/dl, Creatinine: 0.62mg/dl, ALT: 9 U/L, AST: 44 U/L, pH: 7.40, pCO_2: 57 mmHg, pO_2: 42 mmHg.

Chest x-ray showed blockage of left sinus, nearly homogeneous increase of density in the lateral part of left lower lung zone and infiltration in the infrahilar region of right lower lung zone. The platinization used in scoliosis operation was patent (Figure 1).

A homogeneous increase of density with an appearance of "finger in glove" (bronchocele) on the right, diffuse bronchiectasis areas in the right lung middle lobe and right lung lower lobe superior segment. The appearance of consolidation and ground-glass in the left lung was encountered on Thoracic CT (Figure 2). The growth of Pseudomonas aeruginosa was detected in the sputum culture of the patient and appropriate antibiotic treatment, bronchodilator treatment and oxygen therapy were initiated.

The presence of scoliosis, pectus excavatum and arachnodactyly (long-thin spider-like digits) suggested the probability of MFS. The sum of the lengths of the bilateral arms and chest higher than height of the patient supported the diagnosis (Figure 3 and 4). Steinberg "thumb" sign (At apposition, thumb extending beyond the ulnar edge of the fisted hand) and Walker "wrist sign" (overlapping distal phalanxes in the first and fourth fingers of the hand curled around the wrist of the other hand) were positive (Figure 5, 6 and 7). The presence of the uncles with similar body morpholgies were reported in the family history.

EF 60%, thickened mitral valve and prolapse were encountered by echocardiography in the cardiological examination. No pathology was encountered in the ophthalmological examination. The antibiotic therapy was completed and control sputum culture indicated no growth, the patient was discharged by planning long-term oxygen therapy, and pneumococcal and influenza immunization, he was followed-up by pulmonary rehabilitation polyclinic.

DISCUSSION

MFS is a connective tissue disorder inherited by an autosomal dominant pattern that has been first identified in a five-year-old female patient in 1896 by Antonie Marfan, a French pediatrician (7). It has been discovered that the

mutations of the fibrillin-1 (FBN1) gene located on Chromosome 15q21.1 causes MFS approximately 100 years after its first identification. As a consequence, absence or deficiency of fibrillin leads to impairment of structural integrity in all the tissues and organs, primarily three cardinal systems (skeletal, ocular and cardiovascular systems). Although, autosomal dominant inheritance is well-known, spontaneous mutations cause MFS rather than inheritance from the parents in 25% of the patients. For instance, the mutations on the TGFβR1–2 gene and beside fibrillin 2 gene located on Chromosome 5 may cause classical MFS (7). MFS may be diagnosed in any age such as prenatal, neonatal, childhood or late adulthood periods. Its neonatal form manifests a more severe clinical course in the follow-up period than all others (8).

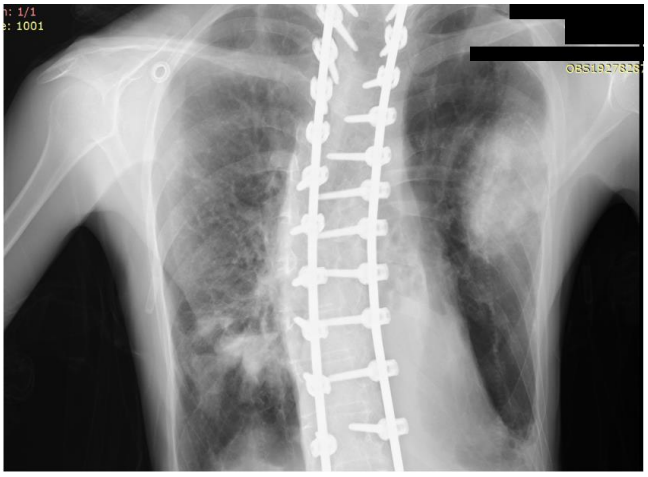

Figure 1: *PA chest x-ray revealed nearly homogeneous increase of density in the lateral part of left lower lung zone and infiltration in the infrahilar region of right lower lung zone. The platinization used in scoliosis operation was patent*

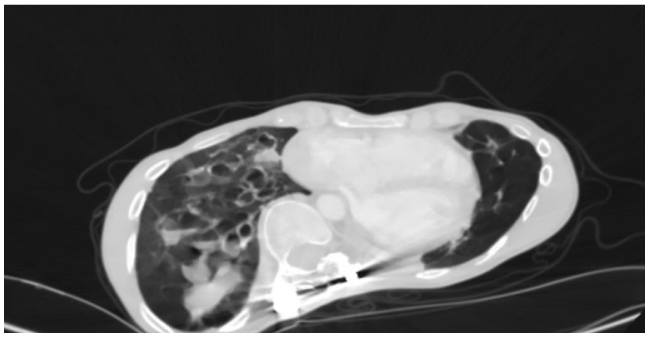

Figure 2: *A homogeneous increase of density with an appearance of "finger in glove" (bronchocele) on the right, diffuse bronchiectasis areas in the right lung middle lobe and right lung lower lobe superior segment. The appearance of consolidation and ground-glass in the left lung on Thoracic CT*

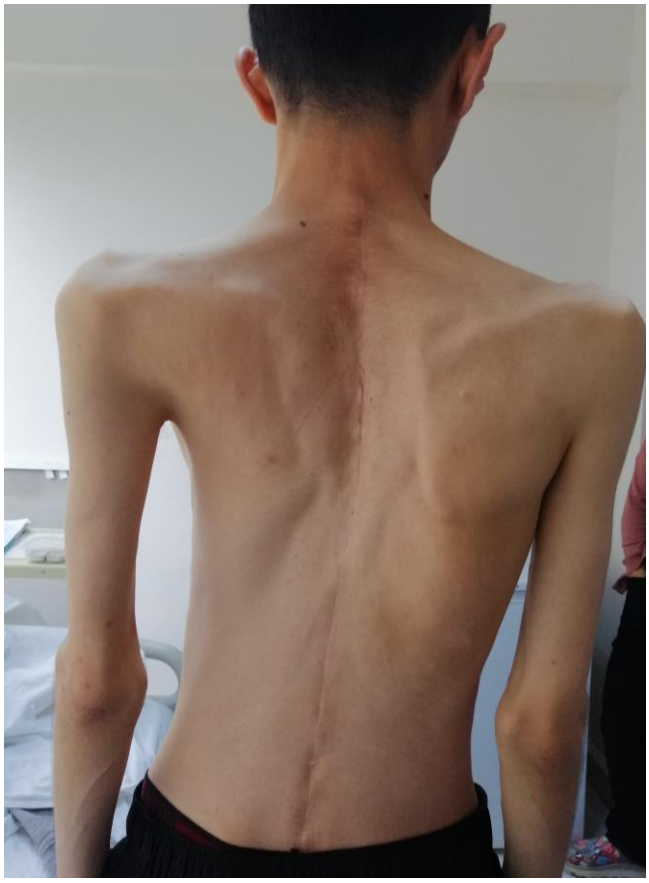

Figure 3: *Scoliosis and asymmetric thorax*

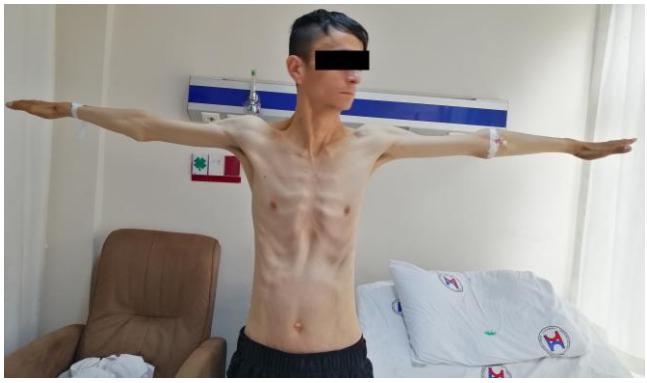

Figure 4: *Arm length disproportionately with chest length and pectus excavatum*

Berlin 1986 Diagnostic Criteria previously used in the diagnosis of MFS were revised and Ghent Criteria involving additionally family history and molecular data have been established. Ghent Criteria comprises three essential components as following:

1- The clinical symptoms from six distinct organ systems (Cardiovascular system, ocular, skeletal, pulmonary, skin and central nervous system),

2- Family history and

3- Molecular evidence.

Ghent Criteria revised for the diagnosis of MFS were summarized in Table 1 (2-9).

Tablo 1: Revised Ghent Criteria for diagnosis of Marfan syndrome (1996)

System	Major criteria	Minor criteria (Involvement)
Family history and genetic	• Parent, child or sibling meeting these diagnostic • FBN1 mutation known to be causing • The presence of a FBN1-linking haploid known to be associated with MFS in the family	N/A
Cardiovascular system	• Aortic root dilatation • The dissection of ascending aorta	• MVP, • (<40 years of age); mitral annular calcification or dilatation of pulmonary artery • Dilatation/dissection of the other aorta
Ocular	• Lens dislocation (ectopia lentis)	Two of following are required: • Flat cornea • Myopia • Increased axial length of eye globe, 'Elongated globe' • Hypoplastic iris or ciliary muscle (reduced miosis) • Glaucoma or cataract below 50 years of age (nuclear sclerotic)
Skeletal (*)	At least 4 of those: • Pectus excavatum • Pectus carinatum • Pes planus • Arachnodactyly • Scoliosis (>20 degree) or spondylolisthesis • Arm span-height ratio >1.05 or upper/lower segment ratio < 0.86, • Protrusio acetabuli • Reduced elbow extension (< 170 degrees)	Two of major criteria or 1 major criterium accompanied by two of the followings: • Moderate pectus excavatum • Dental crowding • Highly arched palate • Typical face features (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, downslanting palpebral fissures) • Joint hypermobility
Lung	N/A	• Spontaneous pneumothorax • Apical bullae
Skin	N/A	• Atrophic striae (striae distensae) • Recurrence of incisional hernia
Central nervous system	•Lumbosacral dural ectasia (**)	N/A

(*) The diagnosis of involvement in the skeletal system requires the presence of 2 major criteria or 1 major criterium accompanied by 2 minor findings.

(**) Lumbosacral dural ectasia and protrusio acetabuli can be diagnosed using magnetic resonance imaging or computed tomography scanning

According to Ghent Criteria; clinical diagnosis of MFS requires the presence of major criteria at least in two distinct organ systems and involvement in a third different system in the absence of family genetic history. If a genetic mutation known to cause MFS is detected; the presence of a major criteria in any organ and a minor involvement in a second system are adequate for diagnosis of MFS (7). The presence of scoliosis higher than 20 degrees from major criteria, arm span-height ratio >1.05, the presence of moderate degree pectus excavatum from minor criteria, the presence of mitral valve prolapse in the cardiovascular system from the minor criteria and family genetic history met the required diagnostic criteria for MFS in our case.

It has been reported that dentists face with these cases in the early ages because of orthodontic problems associated with highly-arched palate and mandibular retrognathia as well as dental crowding (10).

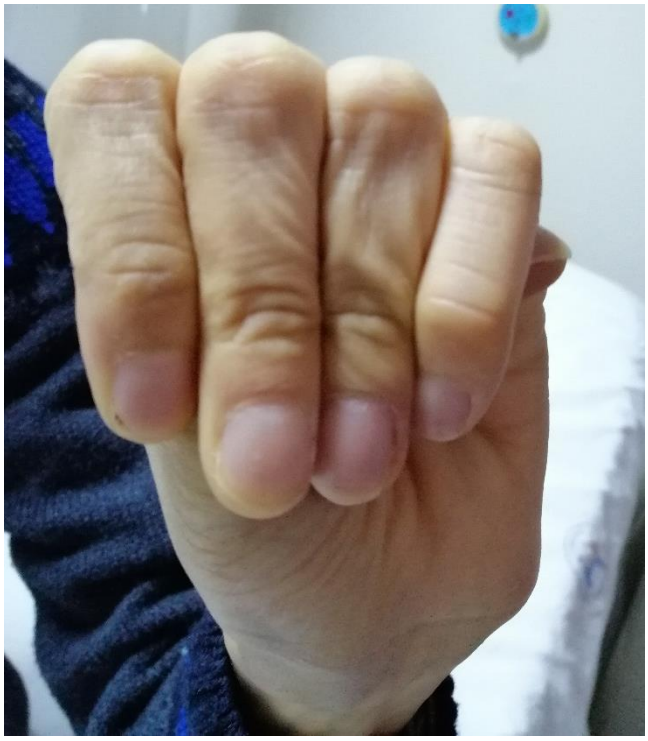

Figure 5: *Positive thumb (Steinberg) sign*

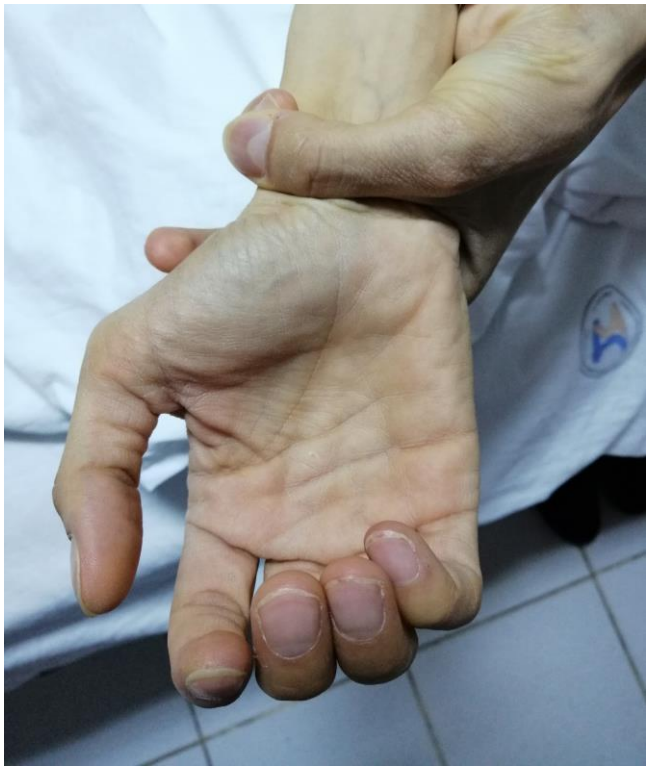

Figure 6: *Positive wrist (Walker) sign*

The differential diagnosis of MFS involves the genetic circumstances that caused by the mutations in FBN1, however, do not meet the diagnostic criteria of MFS such as MASS phenotype (myopia, mitral valve prolapse, mild aortic dilatation), familial mitral valve prolapse syndrome, familial ectopia lentis, familial Marfan-like appearance, and genetic entities such as Loeys-Dietz syndrome, congenital contractural arachnodactyly, familial thoracic aortic aneurysm and dissection, Homocystinuria, Stickler syndrome, Shprintzen-Goldberg syndrome (2).

No definite treatment has been identified for MFS; however, a well-regulated clinical follow-up process and also appropriate approaches for the emerging morbidities increase quality of life and lifetime duration in these patients (1).

The most common morbidity and mortality cause in MFS is cardiovascular involvement. That involvement comprises aortic-mitral valve prolapse and mitral regurgitation, left ventricular dilation, heart failure, pulmonary artery dilatation, aortic root dilatation and aortic dissection. Severe mitral regurgitation is the most common mortality factor in children while rupture of dissected aorta is the most common death cause in adults. Aortic root dissection may lead to myocardial infarction since it occludes coronary ostium. Compared with 70s; reduced mortality rates and prolonged lifetime durations have been reported thanks to successful treatment of aortic complications by performing medical and surgical interventions in the MFS patients (5). The patient can be followed-up under beta-blocker medication if aorta is dilated, however, lower than 4 cm in diameter. Aortic diameter over 5 cm, the presence of a dilatation of 1.5 mm per year, the presence of a dilatation beyond sinus valsalva or aortic dissection in the family history are interpreted in favor of risk factor for aortic dissection. Prophylactic aortic root surgery should be considered if aortic diameter reaches over 4 cm in the sinus valsalva. The risk for aortic dissection increases in pregnancy, close cardiovascular monitoring is needed in the pregnancy and postpartum period (11).

It would be considerable to avoid activities that may induce stress in the joints to prevent joint injuries in the patients with MFS. Heart beat rate, systolic blood pressure and cardiac output increases during both dynamic exercise (e.g. running) and static exercise (e.g. weightlifting). Peripheral vascular resistance and diastolic blood pressure tend to decrease during dynamic exercise; however, they increase during static exercise. Therefore, the patients with Marfan syndrome should avoid intense static exercises; however, they should be encouraged to participate in low intensity dynamic exercises. It is recommended to avoid contact sports to protect aorta and eye-lens and also scuba-diving increasing risk for pneumothorax (5).

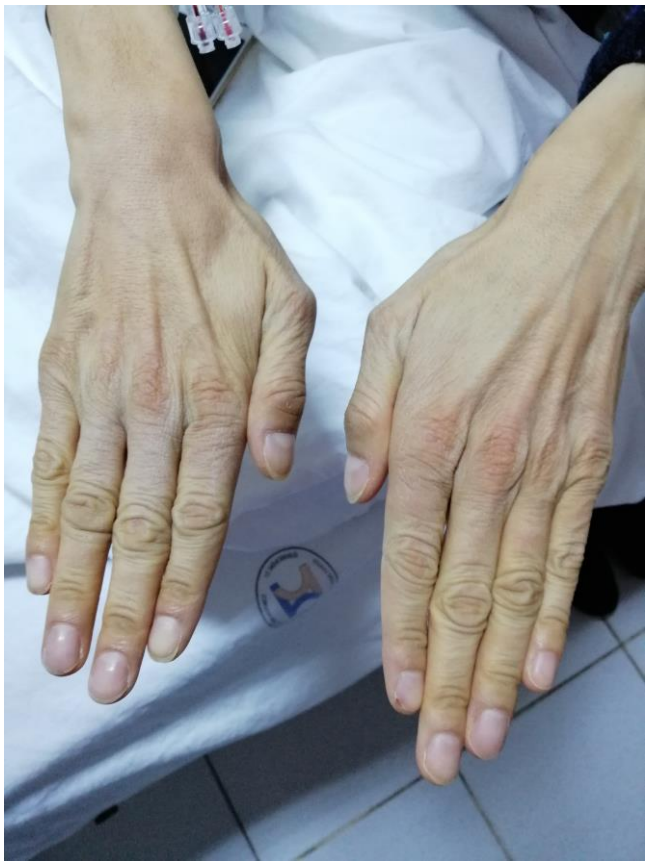

Figure 7: *Long-thin spider digits (arachnodactyly)*

Pectus excavatum is encountered in approximately two third of the patients with MFS, that entity may lead to serious restrictive respiratory insufficiency and also nay complicate the implementation of the cardiac surgical procedures (12). Spontaneous pneumothorax is found in 4-11% of the patients, it is associated with apical bullae and its recurrence is frequent (13). Upper airway tends to collapse during sleep in the adult patients with MFS and that condition leads to development of obstructive sleep apnea syndrome (OSAS). The anomalies of craniofacial structures also contribute to this entity.

A small number of cases have been reported in our country as associated with this syndrome with a general incidence of approximately 1:9,800 births (14,15). It is noticeable that diagnosis of MFS was not considered although our case was hospitalized in the department of Chest Diseases for several times and undergone surgery for scoliosis. This fact suggests that diagnosis of MFS is not considered in such cases. Although it is untreatable, diagnosis of MFS has a critical importance since early diagnosis; regular follow-up and appropriate life style involving the required precautions provide a good prognosis.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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