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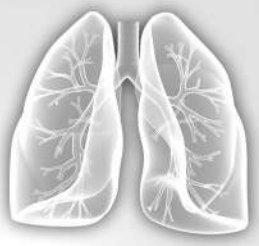

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Two Cases of Granulomatosis with Polyangiitis: Common Features with Tuberculosis and Differential Diagnosis

Granülomatöz Polianjitis Tanısı Alan İki Olgu: Tüberküloz ile Ortak Özellikler ve Ayırıcı Tanı

Zübeyde Gülce[1], Gülistan Karadeniz[2], Fatma Demirci Üçsular[2], Onur Karaman[2]

Abstract

Granulomatosis with polyangiitis is a form of vasculitis that affects the kidneys and the lower and upper respiratory tracts, and progresses with pathologically necrotizing granulomatous inflammation. Patients can present with such nonspecific symptoms as malaise, fever, weight loss and hemoptysis. Diagnosis is based on radiological, pathological and laboratory examinations. Lung involvement usually presents in the form of bilateral nodules, and cavitary lesions and pulmonary infiltrates may also be seen. Tuberculosis and granulomatosis with polyangiitis share common clinical symptoms, radiological findings and immunopathological features. In our country, where the incidence of tuberculosis (TB) is high, necrotizing granulomatous inflammation are often evaluated initially as TB. We present here two cases of nodular lung disease to draw attention to the need for careful differential diagnosis between granulomatosis with polyangiitis and tuberculosis.

Keywords: *Granulomatosis with Polyangiitis, necrotizing granulomatous inflammation, tuberculosis, c ANCA.*

Öz

Granülomatöz polianjiitis, böbrekleri, alt ve üst solunum yollarını etkileyen, patolojik olarak nekrotizan granülomatöz inflamasyonla seyreden bir vaskülittir. Hastalar, halsizlik, ateş, kilo kaybı ve hemoptizi gibi nonspesifik semptomlarla başvurur. Tanı kriterleri arasında, radyolojik, patolojik ve laboratuvar incelemeler yer almaktadır. Akciğer tutulumu genellikle bilateral nodüller olarak karşımıza çıkar. Bunun yanında kaviter lezyonlar ve pulmoner infiltrasyonlar da görülebilmektedir. Tüberküloz ve Granülomatöz polianjiitis klinik bulgular, akciğer görüntülemeleri, immünopatolojik olarak ortak özelliklere sahiptir. Tüberküloz insidansının yüksek olduğu ülkemizde nekrotizan granülomatöz inflamasyon ilk olarak tüberküloz lehine değerlendirilmektedir. Granülomatozis polianjiitis ve tüberküloz arasında dikkatli bir ayırıcı tanıya ihtiyaç duyulduğuna dikkat çekmek için burada, nodüler akciğer hastalığı olan iki olgu sunuyoruz.

Anahtar Kelimeler: *Granülomatöz polianjiitis, nekrotizan granülomatöz inflamasyon, tüberküloz, c ANCA.*

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Granulomatosis with polyangiitis (GPA), known formerly as Wegener's granulomatosis, is a rare autoimmune systemic disease characterized by small vessel vasculitis and pathologically necrotizing granulomatous inflammation affecting the kidneys and the lower and upper respiratory tracts. Mortality is as high as 90% in untreated cases (1). Patients mostly present to hospital with nonspecific symptoms, including malaise, fever, loss of appetite and weight loss (2,3). Diagnosis is based primarily on the evaluation of radiologic, pathologic, and laboratory findings, as the presence of granulomatous vasculitis in a biopsy alone is not sufficient for diagnosis. The similarity of the clinical, radiologic and even histopathologic features of GPA with those of tuberculosis make differential diagnosis difficult (2,4). We present here the cases of two GPA patients who were initially diagnosed with tuberculosis to highlight the potential difficulties encountered in the differential diagnosis of granulomatous diseases and tuberculosis, and the importance of early treatment.

CASE

Case-1: A 54-year-old woman diagnosed with diabetes mellitus and hypertension presented with complaints of loss of appetite, weight loss, weakness and pain in the knees. Thoracic computed tomography (CT) revealed nodular lesions in both lungs, after which a Tru-Cut biopsy was performed under CT guidance. The pathology result indicated "granulomatous inflammation with caseous necrosis", and recommended evaluation for miliary tuberculosis. The patient was duly diagnosed with smear negative tuberculosis and treatment was started. In the second month of treatment, urea and creatinine were found to be elevated by the health center to which she presented with respiratory distress. A diagnosis of acute kidney injury (AKI) was made, based on which, she was admitted and started on fluid therapy. No hemodialysis was performed as her urine output and urea and creatinine values had returned to normal. At this stage, she was referred to our center for re-evaluation of the tuberculosis diagnosis and for our opinion on the continuation or discontinuation of the anti-tuberculosis treatment.

A review of previous test results and the results of a positron emission tomography (PET CT) revealed bilateral multiple nodules and a lesion with a maximum diameter of 3 cm in the paravertebral area of the lower lobe of the left lung with SUV (Figure 1). The patient was a nonsmoker, and no lung malignancy was considered. The patient was evaluated for granulomatous diseases, especially GPA, and for ear, nose and throat (ENT) and ophthalmologic diseases. Paranasal sinus CT showed atrophy of the nasal turbinates and sinus mucosal thickening, while a nasal biopsy indicated nonspecific ulcerous inflammation. Proteins were detected in a urinalysis. Abdominal ultrasound was normal. The Tru-Cut biopsy samples obtained from the referring center were re-examined in the pathology unit of our hospital. Acid-fast bacillus (AFB) was negative, while findings compatible with GPA were identified, and the diffuse anti-neutrophil cytoplasmic antibody (c-ANCA) obtained from the patient was positive. The patient was referred to the rheumatology department and started on steroid and cyclophosphamide treatment based on the diagnosis of GPA. Upon clinical and radiological improvement, the patient was followed up and treated in the rheumatology outpatient clinic.

Case-2: A 38-year-old woman presented to the outpatient clinic with complaints of cough, chest pain, weakness, nausea, occasional vomiting and generalized arthralgia for 1 month. She had no known disease and did not smoke. The following test results were obtained: urea in blood biochemistry: 53 mg/dl; creatinine: 2.11 mg/dl; and sedimentation: 67 mm/h. A diagnostic CT-guided needle biopsy was performed on the diffuse bilateral nodular lesions identified on thorax CT, the largest of which was 2.1 cm in size (Figure 2). Pathological findings indicated necrotizing granulomatous inflammation. Her young age pointed to tuberculosis, however, her anamnesis suggested no contact with tuberculosis patients, and she reported no sputum production, night sweats or weight loss. A tuberculin skin test (TST) result was 0 mm, and a deep tracheal aspirate (DTA) smear was negative for AFB. The patient was subsequently examined for granulomatous lung diseases, especially GPA. Blood tests were positive for c-ANCA, but negative for myeloperoxidase (MPO) ANCA, antinuclear antibody (ANA) and rheumatoid factor (RF). Urine tests revealed protein 3(+) and erythrocyte 2(+). Her abdominal ultrasound was normal. Paranasal sinus CT revealed hypertrophy of the bilateral inferior nasal turbinates and a mucosal thickening of the walls of the maxillary and ethmoid sinuses. A subsequent examination by the ENT department revealed bilateral hearing loss and sinusitis. The patient was then referred to the rheumatology outpatient clinic where, based on her GPA diagnosis, she was started on steroid and rituximab treatment. Follow-up tuberculosis cultures showed no growth and thorax CT after treatment revealed regression in the lesions (Figure 3). The patient continues to be followed up by the rheumatology outpatient clinic.

DISCUSSION

GPA, known previously as Wegener's disease, was first described by Klinger in 1931 as a variant of polyarteritis nodosa. Godman and Churg determined the clinical and pathologic features of the condition in 1954 and coined the term GPA to indicate the presence of granuloma, necrotizing vasculitis and glomerulonephritis (known also as Wegener's triad) in the upper respiratory tract (3). According to the Chapel Hill Consensus criteria, the

presence of small- and medium-sized vasculitis and granulomatous inflammations involving the respiratory tract confirms a diagnosis of GPA, while ANCA positivity is excluded from the criteria (1). The American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) published the GPA classification criteria in 2020, which have high sensitivity and specificity in support of diagnosis. The criteria comprise a total of 10 items related to clinical, laboratory, histologic and radiologic findings, and a total of at least 5 points is required for a diagnosis of GPA. The ACR/EULAR classification criteria are presented in Table-1 (5).

The incidence rate between sexes is equal, and although it is most common in those aged 40–55 years, any age group can be affected (3,6). The incidence rate is estimated to be 2.1 per million with a reported 5-year survival rate of 74–91% (7,8). The mortality rate associated with untreated GPA is as high as 90% (1).

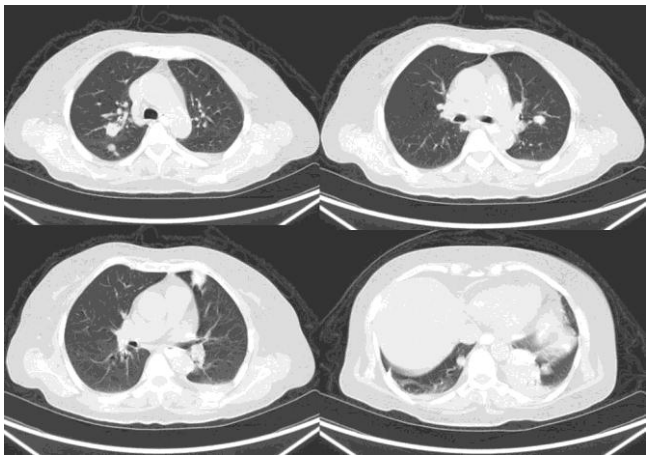

Figure 1: Bilateral multiple pulmonary nodules and a mass in the left lung

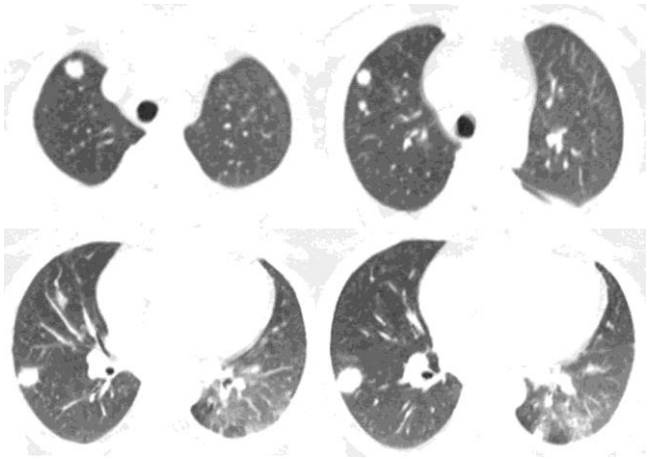

Figure 2: Pre-treatment thorax CT

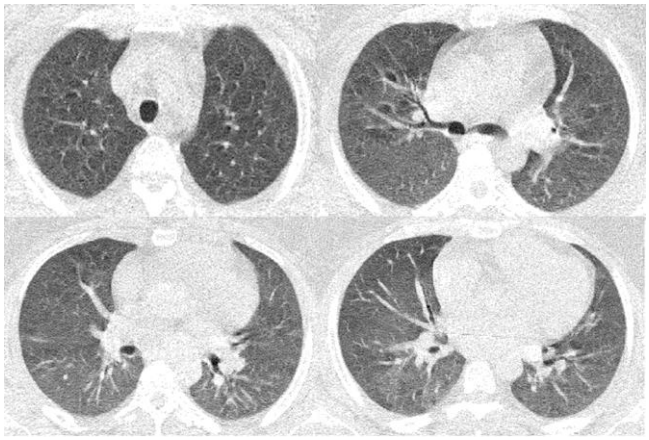

Figure 3: Post-treatment thorax CT

Table 1: 2022 ACR/EULAR Classification Criteria for Granulomatosis with Polyangiitis

Domain	Item	Points
Clinical	Nasal passage involvement (e.g., bloody discharge, ulcers, crusting, congestion, blockage, or septal defect/perforation)	+3
	Cartilaginous involvement (e.g., saddle-nose deformity, subglottic stenosis)	+2
	Conductive or sensorineural hearing loss	+1
Laboratory	PR3-ANCA (or C-ANCA) positivity	+5
	MPO-ANCA (or P-ANCA) positivity	-1
	Serum eosinophil count ≥1000/μL	-4
Histological	Granulomatous inflammation on biopsy	+2
	Pauci-immune glomerulonephritis	+1
Radiological	Nodules, cavities, or fixed infiltrates on chest imaging	+2
	Sinus opacification or bony destruction	+1

Patients usually present with such nonspecific symptoms as malaise, fever, loss of appetite and weight loss, although hemoptysis, nosebleeds and skin rashes may also be present. The upper and lower respiratory tract and kidneys are most common areas of involvement, although at the time of diagnosis, more than half of all patients have lung involvement, increasing to 85% in the more advanced cases (6,9). It usually appears as bilateral nodules measuring 2–3 cm and rarely as masses reaching 10 cm. Cavitary nodules, alveolar hemorrhage, and pulmonary infiltrations may also be observed among radiologic findings (6,10). The thorax CT findings of GPA may mimic those of several other diseases. Due to the similarity of radiologic findings – such as lung nodules, masses and cavities – differentiating between pulmonary tuberculosis, malignancy and bacterial, viral or fungal infections can be challenging (11). Li et al. (12) reported that 52% of patients diagnosed with GPA with thorax CT findings are

misdiagnosed, and suggested the need for biopsy for a definitive diagnosis.

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* that, similar to GPA, presents with symptoms such as fever, loss of appetite, weight loss and hemoptysis. Radiologically, the pulmonary infiltrations, nodules and cavitary lesions seen in the two conditions are similar. Tuberculosis, however, may present with different radiologic appearances (13). The upper lobe apical and posterior segments and the lower lobe superior segments of the lung are the most commonly involved regions, and any calcification in pulmonary nodules and lymph nodes is also useful in for diagnosis (14). In GPA, pulmonary involvement is mostly bilateral and there is no specific zone involvement (11).

GPA and tuberculosis have common histopathologic and immunologic features, and the release of cytokines and chemokines is the main mechanism of granuloma formation in both diseases. The lesions in cases with GPA may vary pathologically, from typical granulomatous vasculitis to such findings as nonspecific chronic inflammation (4). In cases with tuberculosis, caseous necrosis typically develops in the center of granulomas (13). In GPA, more than 90% of patients test positive for c-ANCA and pr3-ANCA (9). That said, ANCA positivity may also be observed in tuberculosis (4,15).

In Case-1 presented here, pathology indicated caseous inflammation, which initially pointed to tuberculosis due to its high incidence in this country. A subsequent paranasal CT of the patient, who had been identified with pulmonary nodules and a mass on imaging and granuloma on biopsy, was compatible with inflammation, indicating GPA based on ACR/EULARACR classification criteria. The second case was diagnosed based on the presence of nodular lesions, granulomatous inflammation on biopsy, and c-ANCA positivity.
It has been reported that reaching a concrete diagnosis can take up to a year as pulmonary and renal symptoms are faint at the time of first admission, and the disease has a slow course (16). The most important factor affecting prognosis is renal involvement. Rapid diagnosis in cases with GPA is crucial for prognosis due to the potential for rapid remission under immunosuppressive treatment regimens, thereby reducing the morbidity and mortality associated with the disease (17,18). Remission has been achieved through treatment in more than 90% of patients without renal damage (3). Treatment is generally rituximab, cyclophosphamide and methotrexate used in combination with steroids, and cyclophosphamide/rituximab has been reported to be effective in GPA patients with nodules, cavities and infiltration (9,19,20).
In conclusion, tuberculosis and GPA have common clinical findings, and their similar lung imaging, pathologic and even immunologic features can lead to misdiagnosis and inappropriate treatment, and cases of miliary tuberculosis due to misdiagnosis of GPA have been reported (21). Furthermore, delays in the diagnosis of GPA reduce the chance of dialysis-free survival (2). Although pathology is of great importance in the diagnosis of GPA, patients should always be subjected to a comprehensive evaluation.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - Z.G., G.K., F.D.Ü., O.K.; Planning and Design - Z.G., G.K., F.D.Ü., O.K.; Supervision - Z.G., G.K., F.D.Ü., O.K.; Funding - Z.G., G.K., F.D.Ü., O.K.; Materials - Z.G., G.K., F.D.Ü., O.K.; Data Collection and/or Processing - Z.G., G.K.; Analysis and/or Interpretation - Z.G., G.K.; Literature Review - Z.G., G.K.; Writing - Z.G., G.K.; Critical Review - Z.G., G.K., F.D.Ü., O.K.

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Microscopic Polyangiitis Presenting with Uncommon Reversed Halo Sign: A Case Report

Nadir Görülen Ters Halo İşareti ile Ortaya Çıkan Mikroskopik Polianjitis: Olgu Sunumu

Shengquan Wei, Huixia Wang, Gen Li, Tiantian Lv, Ruzhen Jia

Abstract

This case report presents an uncommon manifestation of microscopic polyangiitis (MPA) characterized by an initial reversed halo sign (RHS) on chest computed tomography (CT). A 49-year-old female patient with a history of sensorineural hearing loss presented with progressive respiratory symptoms. Comprehensive clinical investigations, including chest CT, laboratory tests and renal biopsy, confirmed a diagnosis of MPA, and targeted treatment with glucocorticoids and cyclophosphamide resulted in significant improvement in the lung lesions. This report aims to increase clinical awareness of atypical presentations of MPA and to reduce potential diagnostic challenges.

Keywords: *Microscopic polyangiitis, Reverse halo sign, tomography.*

Öz

Bu olgu sunumu, akciğer bilgisayarlı tomografisinde ilk olarak ters halo belirisi ile özdeşleşen, mikroskopik poliyanjitis (MPA)'nin nadir bir manifestasyonunu sunmaktadır. Sensorineural işitme kaybı geçmişi olan 49 yaşındaki bir kadın hasta, ilerleyici solunum sistemi semptomları nedeniyle kabul edildi. Akciğer tomografisi, laboratuvar testleri ve böbrek biopsisi dahil kapsamlı klinik tetkikler, MPA tanısını doğruladı. Glukokortikoidler ve siklofosfamid ile hedeflenmiş tedavi, akciğer lezyonlarındaki önemli bir iyileşmeye neden oldu. Bu yazı, klinisyenlerin MPA'nın atipik sunumuna olan duyarlılığını arttırmak ve potansiyel tanı zorluklarını azaltmak amacıyla hazırlanmıştır.

Anahtar Kelimeler: *Mikroskopik poliyanjitis, Ters halo belirisi, tomografi.*

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Microscopic polyangiitis (MPA) is an autoimmune disease that primarily affects small blood vessels and can cause damage to multiple organs, including the lungs and kidneys. The manifestation of the reversed halo sign on chest CT is commonly seen in various conditions, including both infectious and non-infectious diseases (1,2). To the best of our knowledge, the reversed halo sign is an uncommon manifestation in microscopic polyangiitis (MPA). This article reports a case of MPA with reversed halo sign as an initial manifestation to increase clinical awareness of the condition.

CASE

A 49-year-old housewife with sensorineural hearing loss was admitted to hospital with intermittent cough for 1 month, aggravated by expectoration for days. She had developed a mild cough 1 month earlier with occasional small amounts of white sputum after a cold that did not improve significantly with intermittent cephalosporins and levofloxacin. Her symptoms worsened over the 2 days prior to presentation with yellow sputum that was difficult to expectorate, and occasional chest tightness and shortness of breath after coughing and activity. On the day of admission she had a fever with a self-measured temperature of 38°C.

Blood routine: WBC; 7.2×10^9/L, N 81.8%, RBC; 3.7×10^{12}/L, HGB; 10.6g/L, PLT; 391×10^9/L.

Urine routine: WBC 70 cells/μL, RBC 353.7 cells/μL, urine protein (2+).

Blood gas analysis: pH 7.46, PaO_2 76 mmHg, $PaCO_2$ 32.5 mmHg, BE 0.2 mmol/L, SaO_2 96%.

Other: Liver and kidney function, myocardial enzymes, electrolytes, coagulation and blood lipids were normal. C-reactive protein was 67.60 mg/L, antistreptolysin O test was 35.0 IU/ml, rheumatoid factor was 36.3 IU/ml, erythrocyte sedimentation rate was 114 mm/h, D-dimer was 2.42 μg/ml, Widal and Weil-Felix tests were negative, and the nine components of the respiratory tract were normal. Sputum culture was negative for fungi.

Chest CT revealed multiple reversed halo signs in both lungs (Figure 1).

Painless bronchoscopy: The airway lumen remained patent, while a small amount of white and grey purulent discharge was observed (Figure 2). Transbronchial lung biopsies (TBLB), brushings and bronchoalveolar lavage (BAL) were performed in the posterior and anterior segments of the superior lobe of the right lung targeting the areas with relatively prominent lesions.

Lung bronchoscopic biopsy specimen pathology: Small tissue samples taken from the upper right and lower lung

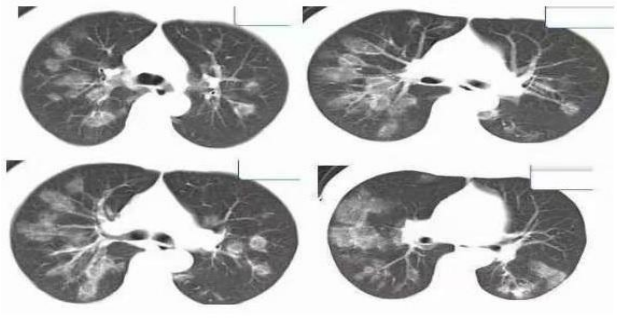

Figure 1: *Chest CT showing multiple RHS in both lungs*

Figure 2: *Bronchoscopic appearance*

bronchial mucosa were stained with hematoxylin and eosin (H&E) and sent for laboratory examination, revealing interstitial fibrous tissue hyperplasia, mild chronic inflammatory cell infiltration and a small amount of fibrinous exudation on the surface. CD56 (-), Ki67 (+ 2%), Napsin A (-), TTF-1 (-) Special staining: PAS negative (-) (Figure 3).

A microbiological examination of bronchoalveolar lavage fluid (BALF) revealed no bacteria, no acid-fast bacilli and no fungi and brush. BALF: Mycobacterium tuberculosis nucleic acid test < 500 copies/ml, GM test (-).

The patient was started initially on anti-infective treatment with moxifloxacin, with unsatisfactory results. Further pathological examinations of the lung biopsy specimen revealed mild hyperplastic interstitial fibrous tissue, a small amount of chronic inflammatory cell infiltration and a small amount of fibrinous exudation on the surface. A BALF pathogen test showed no evidence of bacteria, acid-fast bacilli or fungi, while serum anti-myeloperoxidase antibody (MPO-Ab), perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA) and anti-cardiolipin antibodies (ACA) tests were positive. A multidisciplinary panel could not exclude ANCA-associated vasculitis, and so a renal biopsy was performed, the resulting pathology of which was consistent with ANCA-associated vasculitis renal injury pointing to a final diagnosis of MPA (Table 1).

After the diagnosis was confirmed, the patient was started on oral prednisone 30mg qd, and chest CT 1 week later revealed a significant resorption of the lesions. Cyclophosphamide was added to the treatment protocol 2 weeks later (Figure 4). The patient was subsequently lost to follow-up.

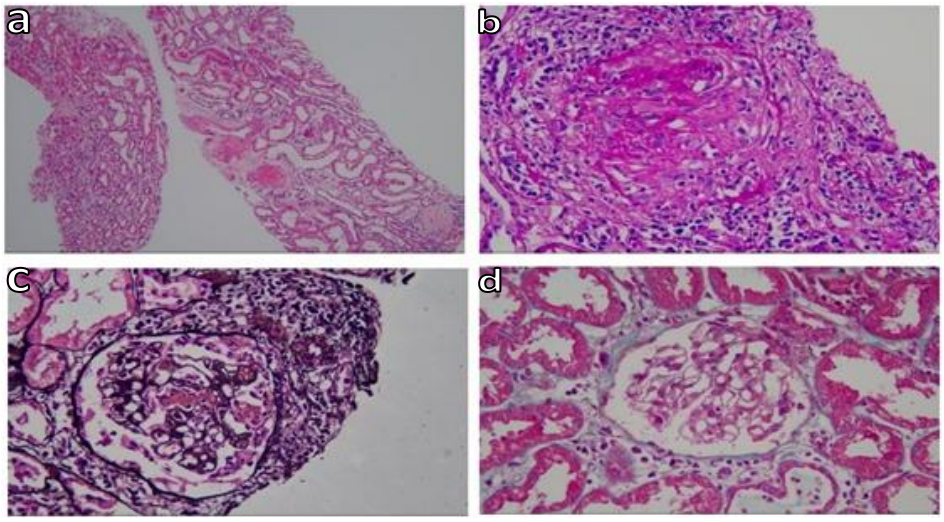

Figure 3: Dilation of some renal tubules with thickened basement membranes observed following H&E staining (a); cellular fibrous crescents identified under PAS staining (b); Small cellular crescents evident under PASM staining (c); no significant deposition of birefringent material within the glomeruli identifiable following Masson staining (d)

Table 1: Application of 2022 ACR/EULAR Classification Criteria for Microscopic Polyangiitis

Diseases	Details	Score
Criteria	**Nasal involvement:No symptoms reported**	**N/A**
Laboratory,Imaging, and Biopsy Criteria		
1. Positive test for perinuclear ANCA (pANCA) or anti-MPO antibodies	MPO-ANCA positive (1:320)	+6
2. Fibrosis or interstitial lung disease on chest imaging	Imaging shows UIP pattern indicating fibrosis	+3
3. Pauci-immune glomerulonephritis on biopsy	Proteinuria and elevated renal function consistent with pauci-immune GN	+3
4. Positive test for cytoplasmic ANCA (cANCA)	No results reported for cANCA	-1
5. Blood eosinophil count ≥ 1 x 109/L	No eosinophil count reported	-4
Total Score	**Sum of scores from above criteria**	**7**

Total Score: 7 points Diagnostic Threshold: ≥5 points

DISCUSSION

Microscopic polyangiitis (MPA) is a form of small-vessel necrotizing vasculitis that frequently affects multiple organ systems, particularly the lungs and kidneys (1,2). RHS is generally characterized by a central ground-glass opacity surrounded by a complete or partial ring of consolidation (3–5). The typical pulmonary manifestations of MPA include conventional HRCT patterns such as reticular opacities (75%) and traction bronchiectasis (38.3%) (2). To the best of our knowledge, its occurrence in MPA, as seen in our patient, is uncommon (6–8), being classically linked to cryptogenic organizing pneumonia (COP) and fungal infections (3–5,7).

In the presented case, histopathological correlation revealed a UIP-like pattern with perivascular inflammatory infiltrates and fibrosis, distinguishing it from the characteristic fibroblastic plugs seen in COP (4). This divergence underscores the critical role of histopathology in elucidating RHS's underlying etiology, especially when imaging findings overlap with COP (3–6,8).

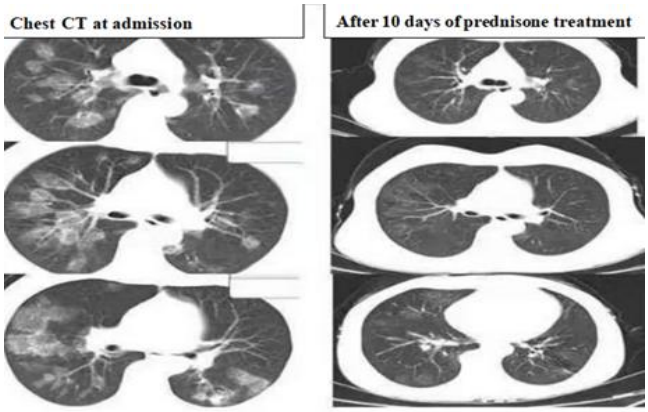

Figure 4: Chest CT at admission (first colon), and after 10 days of prednisolone treatment (second colon)

The pathogenic mechanisms underlying RHS in MPA differ fundamentally from COP's localized organizing pneumonia. ANCA-mediated vascular endothelial injuries likely trigger alveolar hemorrhage and the subsequent repair responses (9), resulting in the unique radiological-pathological discordance observed. This hypothesis aligns

with the patient's systemic manifestations and rapid treatment response to cyclophosphamide, which are atypical in classical COP management.

Renal biopsy confirmed the MPA diagnosis in the presented case (1,2), while hematuria and proteinuria further strengthened the diagnosis, along with the presence of anti-myeloperoxidase antibodies (MPO-ANCA) and perinuclear ANCA (p-ANCA), histopathological findings of interstitial fibrosis and inflammatory infiltrates (1,2), and the 2022 American College of Rheumatology/European Alliance of Associations rheumatology classification criteria for microscopic polyangiitis (10). The significant improvement noted in the pulmonary lesions following immunosuppressive therapy with glucocorticoids and cyclophosphamide corroborated the diagnosis and underscored the critical role of early therapeutic intervention (11). The lesions rapidly resolved following immunotherapy, which is atypical for infectious pulmonary pathology.

In conclusion, the identification of RHS in MPA is unusual, and so underscores the importance of expanding the differential diagnosis of RHS to include MPA, especially in cases of multi-organ involvement.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - S.W., H.W., R.J., T.L., G.L.; Planning and Design - S.W., H.W., R.J., T.L., G.L.; Supervision - S.W., H.W., R.J., T.L., G.L.; Funding -; Materials -; Data Collection and/or Processing - T.L., G.L., R.J.; Analysis and/or Interpretation - R.J., T.L., G.L.,S.W.; Literature Review - S.W., H.W.; Writing - S.W.; Critical Review - S.W., H.W.

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Multiple Pulmonary Nodules in a Patient with Sjögren's Syndrome: Extranodal Marginal Zone Lymphoma and Amyloidosis: A Case Report

Sjögren Sendromlu Olguda Multiple Pulmoner Nodüller: Ekstranodal Marjinal Zon Lenfoma ve Amiloidozis: Olgu Sunumu

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Abstract

Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by systemic involvement that primarily affects the exocrine glands. Although pulmonary involvement is often asymptomatic, it can present with interstitial lung disease, airway abnormalities and, in rare cases, pulmonary amyloidosis and lymphoma. A 69-year-old female with a history of SS and a previous diagnosis of extranodal marginal zone B-cell lymphoma (EMZBCL) following a parotidectomy presented with pleuritic chest pain and unintentional weight loss. Imaging revealed multiple pulmonary nodules and ground-glass opacities, and the nodules were assessed to be at high risk for malignancy. A biopsy and segmentectomy decision was made based on a multidisciplinary evaluation of PET-CT findings, and the resulting pathology revealed EMBCL and widespread AL amyloidosis. Chemotherapy was subsequently planned. This case highlights that pulmonary involvement in SS can remain hidden, requiring the careful monitoring of pulmonary symptoms in recognition of the high malignancy risk. A multidisciplinary approach can play a critical role in the management of such complex cases.

Keywords: *Sjögren's Syndrome, Nodule, Lymphoma, Pulmonary involvement, Multidisciplinary approach.*

Öz

Sjögren sendromu, ekzokrin bezleri etkileyen, sistemik tutulumla karakterize kronik otoimmün hastalıktır. Akciğer tutulumu genellikle asemptomatik olsa da, interstisyel akciğer hastalığı, hava yolu anormallikleri veya nadiren de pulmoner amiloidoz ve lenfoma gibi durumlarla ortaya çıkabilir. Sjögren sendromu tanılı 69 yaşındaki kadın hasta, plevral göğüs ağrısı ve kilo kaybı şikayetleriyle başvurdu. Görüntülemede çok sayıda pulmoner nodül ve buzlu cam opasiteleri tespit edildi. Daha önce parotidektomi sonra ekstranodal marjinal zon B hücreli lenfoma tanısı alan hastada nodul özellikleri malignite açısından yüksek riskli bulundu. PET-BT bulguları ve multidisipliner değerlendirme sonrası cerrahi biyopsi kararı alındı. Segmentektomi sonrası patoloji sonucu, ekstranodal marjinal zon B hücreli lenfoma ve yaygın AL amiloidoz olarak sonuçlandı. Hastaya kemoterapi planlandı. Bu olgu, Sjögren sendromlu hastalarda akciğer tutulumunun sessiz seyredebileceğini, akciğer bulgularının dikkatle izlenmesi gerektiğini ve malignite gelişme riskinin yüksek olduğunu göstermektedir. Multidisipliner yaklaşımın hastanın tedavisinde sağladığı faydalar, bu tür karmaşık olguların yönetiminde kritik bir rol oynamaktadır.

Anahtar Kelimeler: *Sjögren Sendromu, Nodül, Lenfoma, Akciğer tutulumu, Multidisipliner yaklaşım.*

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Sjögren's syndrome (SS) is a chronic autoimmune disorder that primarily affects the exocrine glands and is characterized by B-cell infiltration. The disease typically manifests with such symptoms as xerophthalmia (dry eyes) and xerostomia (dry mouth) (1). Systemic involvement develops in 30–40% of SS patients, with pulmonary manifestations ranging from airway abnormalities to interstitial lung disease, pulmonary embolism, hypertension, lymphomas, amyloidosis and pleural involvement (2).

Pulmonary involvement in SS is often asymptomatic, making early detection and diagnosis challenging (1). This case highlights the importance of evaluating pulmonary nodules for malignancy in patients with SS. The adopted diagnostic and therapeutic approach we present to literature contributes to clinical awareness, and emphasizes the importance of a multidisciplinary approach for the management of such complex cases.

CASE

A 69-year-old female patient presented to the pulmonology clinic with pleuritic chest pain. She had a history of chest trauma from a fall 3 weeks earlier, but denied any other pulmonary symptoms. Systemic questioning revealed a 5 kg weight loss (12% body weight) over the past 3 months. Vital signs were stable, and while a physical examination revealed no palpable lymphadenopathy or abnormal respiratory sounds. a suspicious callus formation was detected along the left eighth rib, prompting further imaging.

Chest X-ray and computed tomography (CT) of the patient, who had no smoking history, revealed peripheral ground-glass opacities and six randomly distributed nodules (~1 cm diameter) with regular margins (Figure 1). She had undergone parotidectomy seven years earlier to remove a parotid gland mass identified as extranodal marginal zone B-cell lymphoma, but did not continue treatment for SS or lymphoma and was lost to follow-up.

The patient was initially diagnosed with SS after presenting with dry eyes and dry mouth. A subsequent minor salivary gland biopsy revealed a focus score of 2, supporting the SS diagnosis, while serological tests revealed strongly positive SS-A (+++) and SS-B (+++) antibodies and a Schirmer test was negative. Based on these findings at the time of diagnosis, the patient was started on hydroxychloroquine, but opted to discontinue her treatment and follow-up due to social reasons. Given the absence of any other autoimmune disease, this case was classified as primary Sjögren's Syndrome (pSS).

Basedon the patient's history of extranodal marginal zone B-cell lymphoma, hematology was consulted and a bone marrow aspiration (BMA) was performed that revealed benign lymphoid aggregates. A comparison with imaging from 3 years earlier revealed little change in the peripheral ground-glass areas, while a previously identified ground-glass nodule in the superior segment of the left lower lobe now appeared solid (Figure 2).

PET-CT was performed to investigate the nature of the pulmonary findings, revealing bilateral upper lobe ground-glass opacities (~5x3 cm) with low FDG uptake (SUV max 1.9) and multiple nodules, the largest of which was in the left lower lobe, with an SUV max of 1.7. The case was discussed by a multidisciplinary panel of pulmonology, rheumatology, hematology, oncology, radiology and thoracic surgery specialists, who recommended VATS segmentectomy due to the increasing size and pronounced subsolid component of the left lower lobe nodule.

A histopathological analysis confirmed extranodal marginal zone B-cell lymphoma (CD20 and BCL2 positive) with widespread Amyloid Light Chain (AL) amyloidosis (kappa monoclonal) (Figure 3 A-E), for which hematology recommended systemic chemotherapy with an R-CHOP regimen (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone).

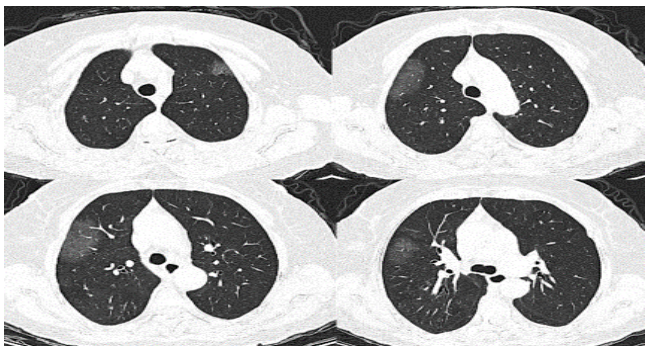

Figure 1: Peripheral ground-glass opacities (GGO) predominantly in the upper and middle lobes of both lungs

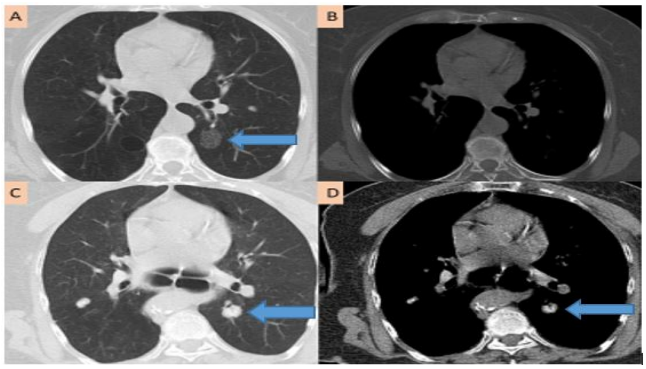

Figure 2: A nodule with an increasing solid component within the ground-glass opacity (blue arrow). Imaging from three years earlier, showing a well-defined ground-glass opacity (GGO) nodule (~1 cm in diameter) in the superior segment of the left lower lobe, and a regular lung cyst in the right lower lobe (A-B). In current imaging, a nodule (~1.5 cm) in the left lower lung lobe with an increased solid component can be seen. The previously noted right lower lobe lung cyst has disappeared, and a new solid nodular formation (~8 mm) can be observed peripherally (C-D)

DISCUSSION

Amyloidosis is a disorder characterized by the abnormal folding and accumulations of amyloid proteins in tissues, leading to organ dysfunction. Amyloidosis in the lungs may present as nodular lesions, and are often asymptomatic, but may in some cases cause such severe symptoms as respiratory distress, chest pain or hemoptysis. Diagnosis is established based on the identification of amyloid deposition through histopathological examinations and the exclusion of systemic amyloidosis (3).

Sjögren's syndrome is a recognized risk factor for amyloidosis due to the associated chronic inflammation, which promotes amyloid deposition. There are two major types of amyloid deposits seen in primary SS: Amyloid A (AA) deposits, which develop in patients with persistent inflammation, and Amyloid Light-Chain (AL) deposits, which are associated with amyloid-producing lymphoproliferative disorders such as mucosa-associated lymphoid tissue (MALT) lymphoma or plasmacytoma (4).

Sjögren's syndrome is an autoimmune disease with a predisposition for lymphoproliferative disorders. Pulmonary involvement in SS is often subclinical and may present as pulmonary nodules, interstitial lung disease, nonspecific interstitial pneumonia (NSIP) and airway abnormalities. Pulmonary nodules in patients with SS can be attributed to various malignancies, including non-Hodgkin lymphoma and lung carcinoma, among others, or such benign conditions as reactive lymphoid hyperplasia, organizing pneumonia, infection or amyloidosis (5). Studies suggest that a significant proportion of pulmonary nodules in SS patients are malignant, with lymphoma being the most frequently encountered type. A study by Maura et al. (6) reported that among 41 SS patients with pulmonary nodules, 15% had MALT lymphoma associated with amyloid deposition.

The overall prevalence of non-Hodgkin lymphoma (NHL) in SS patients was reported to be 9.2% in a long-term study of 584 patients who were followed for 30 years. The majorities of NHL cases are MALT, followed by nodal marginal zone lymphoma and diffuse large B-cell lymphoma (7). In another study, Nocturne et al. (8) reported the incidence of lymphoma to be 15–20 times greater in SS patients than in the general population.

Assessing the imaging characteristics of pulmonary nodules, Casal Moura et al. (6) examined biopsy-proven dominant pulmonary nodules in 38 patients and found no significant differences in nodule density, shape, margin characteristics or air bronchograms among patients, while PET-CT scans of patients with lung cancer exhibited significantly higher SUV values ($p = 0.056$). Similarly, a study of 60 SS patients conducted by Koyama et al. (9) reported "small" (<10 mm) or "large" (10–30 mm) pulmonary nodules in one-third of the sample, while none had lung masses (>30 mm). Among the remaining patients, 40 had no pulmonary nodules, although a histological diagnosis was available in only a few cases. In another study by Nocturne et al. (8), thoracic CT examinations of 24 SS patients revealed pulmonary nodules in half of the cases, although they were not histopathologically confirmed.

The laboratory findings of SS patients with NHL are often non-specific. However, serological markers such as lymphopenia, anemia, positive rheumatoid factor, elevated cryoglobulin levels, low C4 complement and monoclonal gammopathy are associated with an increased risk of NHL (10). Our case had no such serological markers.

18F-FDG PET/CT plays a critical role in the evaluation of pulmonary nodules. SUV max values greater than 3 on PET-CT are considered suspicious for malignancy (11). In our patient, the progressive increase in nodule size and the emergence of a distinct subsolid component raised concern for malignancy, although the SUV max values of the nodules remained relatively low, underscoring the need for histopathological confirmation.

MALT lymphoma treatment varies depending on disease stage. In early-stage cases, surgical resection or radiotherapy may suffice, whereas more advanced cases may require chemotherapy and immunotherapy. The R-CHOP regimen – comprising rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone – continues to be the standard approach to high-risk and advanced-stage MALT lymphoma cases, in which the Rituximab, a monoclonal anti-CD20 antibody, enhances chemotherapy efficacy through its immunomodulatory effects (12).

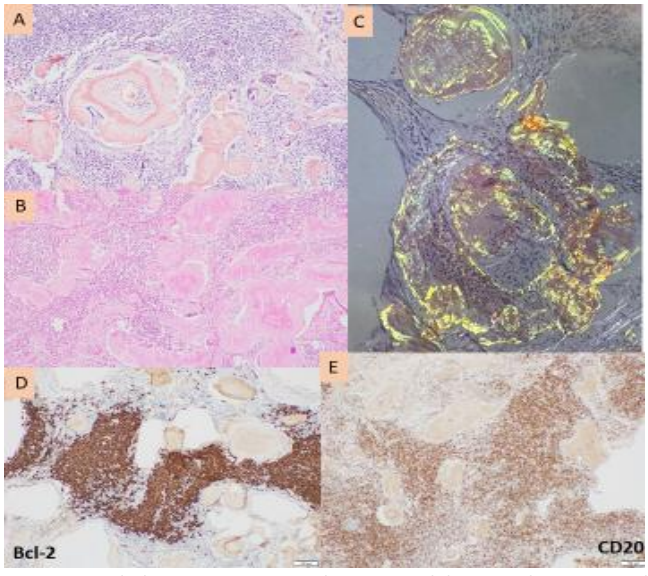

Figure 3: *Pathology specimen samples: Eosinophilic amorphous material identified as amyloid, showing salmon-colored staining with Congo red (100x)* ***(A)****; eosinophilic amorphous material deposition within the lymphoid cell infiltration (Hematoxylin and Eosin, 100x)* ***(B)****; under polarized light, amyloid deposition areas exhibiting apple-green birefringence (200x)* ***(C)****; Atypical lymphoid cells showing positive immunohistochemical staining for Bcl-2 (100x)* ***(D)****; Atypical lymphoid cells showing positive immunohistochemical staining for CD20 (100x)* ***(E)***

This case highlights the complex interplay between Sjögren's syndrome, lymphoma and pulmonary amyloidosis, and emphasizes the importance of recognizing the malignancy potential of pulmonary nodules in SS patients, as well as the adoption of a multidisciplinary approach to their evaluation. Regular follow-up and a comprehensive diagnostic strategy, including histopathological confirmation, are crucial for the optimization of patient outcomes. Further studies are warranted to provide a better understanding of such rare clinical presentations, and thus to support their management.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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RESPIRATORY CASE REPORTS

Unusual Presentation of Cryptogenic Organizing Pneumonia with Multiple Pulmonary Nodules Resembling Pulmonary Metastases: A Case Report

Kriptojenik Organize Pnömoni: Multipl Pulmoner Nodüller ile Akciğer Metastazını Taklit Eden Nadir Bir Olgu

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Abstract

Cryptogenic Organizing Pneumonia (COP) is a lung disease characterized by multiple areas of consolidation with a subpleural distribution or ground-glass opacities, various atypical presentations of which have been reported in the literature. A 47-year-old male who presented with a cough underwent thoracic computed tomography, revealing multiple bilateral pulmonary nodules, located predominantly in the upper lobes. The nodules, the largest of which measured 20 mm, had varying border characteristics and some had frosted-glass densities. Positron emission tomography/computed tomography revealed several small lymph nodes without mediastinal pathological FDG uptake. A large number of nodules were identified in both lung parenchyma, some of which were calcified and with mildly elevated FDG uptake (early SUV max: 2.18, late SUV max: 3.14). The patient presented with an unusual radiological pattern of bilateral pulmonary nodules mimicking pulmonary metastases, however, histopathological findings were consistent with COP. This case highlights how the radiological and nuclear imaging characteristics of COP can potentially lead to misdiagnosis, such as malignancy.

Keywords: *Cryptogenic organizing pneumonia, pulmonary nodules, pet-ct.*

Öz

Kriptojenik Organize Pnömoni (COP) genellikle akciğerlerdeki terminal bronşiyoller, alveoler kanallar ve alveollerde granülasyon dokusu proliferasyonunun görüldüğü, radyolojik olarak subplevral bölgelerde yerleşen çok sayıda konsolidasyon alanı ve buzlu cam opasiteleri ile karakterize edilen, çoğunlukla etyolojisi bilinmeyen bir hastalıktır. Kırk yedi yaşında erkek hasta, geçmeyen öksürük şikayetiyle polikliniğe başvurdu. Toraks bilgisayarlı tomografide, bilateral çoğunlukla üst loblarda yerleşen, en büyüğü 20 mm boyutunda, bazıları buzlu cam dansitesinde multipl pulmoner nodüller saptandı. Pozitron emisyon tomografisi/bilgisayarlı tomografide, mediastinal patolojik FDG tutulumunu göstermeyen birkaç küçük lenf nodu mevcuttu. Bilateral akciğer parankiminde hafif artmış FDG tutulumu olan (erken SUV max: 2.18, geç SUV max: 3.14) çok sayıda nodül gözlendi. Histopatolojik analiz, kriptojenik organize pnömoni tanısı olarak sonuçlandı. Radyolojik ve pozitron emisyon tomografisi görüntüleme özellikleri akciğer metastazını taklit eden bu olgu ışığında bilateral multipl pulmoner nodüllerin ayırıcı tanısında kriptojenik organize pnömoninin de göz önünde bulundurulması gerektiğini vurgulamak istiyoruz.

Anahtar Kelimeler: *Kriptojenik organize pnömoni, pulmoner nodül, pet-ct.*

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Cryptogenic organizing pneumonia (COP) is an interstitial lung disease characterized by proliferations of granulation tissue in the terminal airways, alveolar ducts and peribronchiolar alveoli. The etiology of COP can be either idiopathic or secondary, and known causes include chronic infections (e.g., Legionella, Mycoplasma, adenovirus), toxic inhalants (e.g., NO2), drugs, lung transplantation, radiation and collagen vascular diseases. In most cases, however, the causative agent remains unidentified, making the condition idiopathic (1,2).

The clinical and radiological findings of COP typically show dramatic improvement with corticosteroid therapy. Radiologically, COP is often characterized by multiple airspace consolidations with a peripheral, subpleural distribution, or areas of ground-glass opacity, although other, less common presentations have also been reported, making the diagnosis challenging (2,3). This case report describes a rare presentation of COP with a nodular pattern resembling miliary metastasis, highlighting the diagnostic complexity of the condition.

CASE

A 47-year-old male with a 35-year smoking history (10 cigarettes per day) presented with a persistent cough. His medical history included chronic obstructive pulmonary disease (COPD), diabetes mellitus and coronary artery disease. Upon physical examination, his vital signs were stable, but expiratory rhonchus was heard during respiratory examination. Other system examinations were unremarkable.

A chest X-ray revealed bilateral nodular opacities (Figure 1), prompting further imaging studies. A thoracic CT scan revealed multiple pulmonary nodules predominantly in the upper lobes, the largest of which measured 20 mm, and some with ground-glass densities. The scan also revealed some enlarged mediastinal (10 mm) and right suprahilar (15 mm) lymph nodes (Figure 2a).

Laboratory tests revealed the following values: leukocyte count 8.6 $\times$ $10^3/\mu$L (45% polymorphonuclear cells), C-reactive protein 1.61 mg/dL and antistreptolysin O 27.2 IU/mL. Renal and liver function tests and serologic tests for Brucella, hydatid cyst, toxoplasma, cytomegalovirus, hepatitis C and B viruses and HIV were all normal, and all autoimmune markers, including antinuclear antibody (ANA), perinuclear antineutrophil cytoplasmic antibody (p-ANCA) and cytoplasmic ANCA, were negative. A tuberculosis test was also negative.

Pulmonary function tests revealed FEV1: 1.54 L (55%), FVC: 2.59 L (75%) and FEV1/FVC ratio: 59.56%, consistent with a mixed obstructive and restrictive pattern, which could be attributable to the underlying COPD. Following initial treatment with broad-spectrum antibiotics, a follow-up CT scan revealed persistent nodules, although without any significant increase in size.

A positron emission tomography-computed tomography (PET-CT) scan revealed multiple millimetric pulmonary nodules with mildly elevated FDG uptake (early SUV max: 2.18, late SUV max: 3.14), some of which were calcified (Figure 2b). No pathological FDG uptake was detected in the mediastinal lymph nodes.

Given the suspicion of a malignancy due to the patient's smoking history and the characteristics of the nodules, a wedge resection of the lung was performed under video-assisted thoracoscopy (VATS), the histopathological examination of which revealed patchy fibroblastic plugs in the interstitium of alveoli consisting of spindled fibroblasts in a pale-staining matrix with a serpiginous or elongated shape (Figure 3a and b). Foamy macrophages, thickened alveolar septa, and rare neutrophils were also noted, confirming the diagnosis of COP.

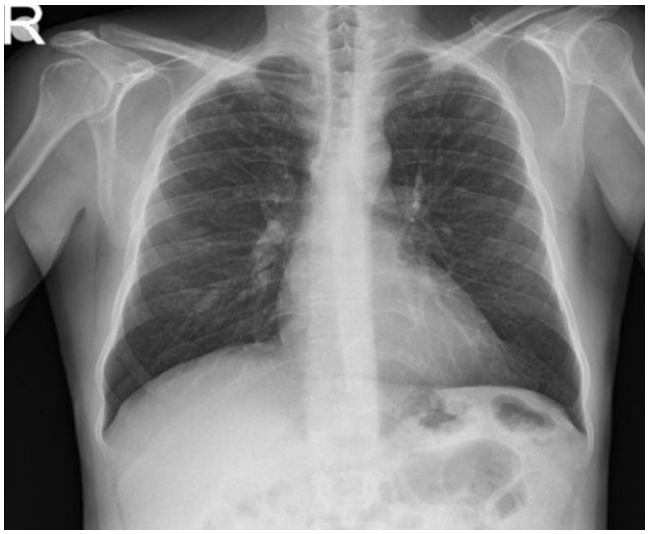

Figure 1: Chest X-ray showing bilateral nodular opacities

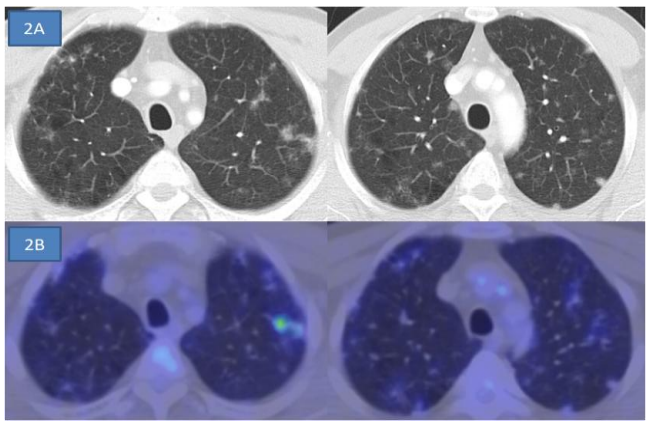

Figure 2: Thorax computed tomography. Multiple bilateral pulmonary nodules (the largest 20 mm) with variable border features detected predominantly in the upper lobe, some with opaque glass densities (A). Pet-CT: A large number of nodules observed in both lung parenchyma, with mildly elevated FDG uptake (early SUV max: 2.18, late SUV max: 3.14) (B)

The patient was started on corticosteroid therapy (48 mg/day), and a follow-up CT scan after 3 months revealed complete resolution of the pulmonary nodules (Figure 4).

The steroid treatment was discontinued at 4 months due to poorly controlled diabetes mellitus, and the patient was followed up for 5 years with no evidence of disease recurrence.

DISCUSSION

COP is a rare condition that can be challenging to diagnose due to its heterogeneous clinical and radiological features. It most commonly affects people between the ages of 50 and 60 years, with no significant predilection for either gender. Hallmark symptoms include dry cough, shortness of breath and, less commonly, fever, weight loss and crackles on auscultation (2). In the presented case, the patient exhibited a mixed pattern of lung function that was likely attributable to the concurrent COPD.

Radiologically, COP most often presents with airspace consolidation, ground-glass opacities and a peripheral distribution, particularly in the lower and middle lung zones (2–5). In the presented case, however, the patient presented with bilateral multifocal nodules predominantly in the upper lobes, which is an atypical finding for COP. This unusual presentation posed a diagnostic challenge, as the nodule pattern raised concern for metastatic disease.

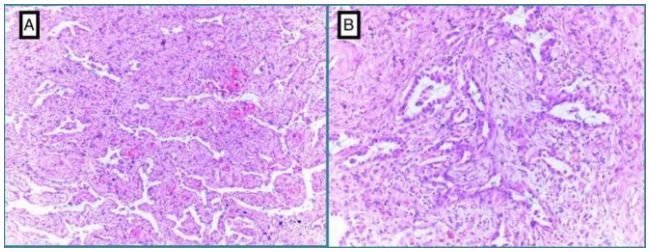

Figure 3: Thickened alveolar septa with fibroblatic plugs (x100, HE) (A); Elongated shaped spindled fibroblast in the alveolar septa (x200, HE)(B)

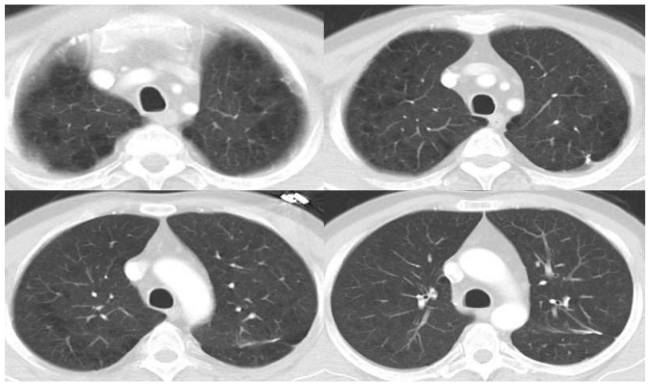

Figure 4: Post-treatment follow-up thorax computed tomography; bilateral nodular lesions completely regressed

Lymphadenopathy is not typically associated with COP. In the present case, however, mild mediastinal and suprahilar lymphadenopathy was noted that resolved completely after corticosteroid therapy. Such findings have not been widely reported in the literature, but should be highlighted as the resemblance to lymphoma or metastatic cancer can potentially complicate diagnosis.

The role of PET/CT in evaluating lung lesions is well-documented in malignancies, while its utility in COP is less clear. The mild FDG uptake in the pulmonary nodules observed in the present case could easily be mistaken for malignancy, underlining the importance of histopathological confirmation, as PET/CT findings in COP may overlap with those seen in cancer, particularly in patients with such risk factors as a smoking history.

Although there is evidence suggesting an association between COP and malignancy, particularly in patients with a history of smoking and chronic lung disease (6–8), our patient's response to corticosteroid therapy supported a diagnosis of COP rather than metastatic disease. The complete resolution of the nodules following treatment further strengthens this conclusion.

CONCLUSION

The presented case highlights the diagnostic challenge posed by COP, particularly when presenting with an unusual radiological pattern resembling pulmonary metastases, and the presence of mild lymphadenopathy and FDG uptake on PET/CT further complicated the diagnosis. Clinicians should be aware of these potential mimickers of malignancy and consider COP in the differential diagnosis when encountering patients with unexplained lung nodules. A prompt histopathological evaluation is crucial for appropriate management.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - D.P.Y., E.S.O., S.N., T.K., F.D.A., P.O.K.; Planning and Design - D.P.Y., E.S.O., S.N., T.K., F.D.A., P.O.K.; Supervision - D.P.Y., E.S.O., T.K., F.D.A., P.O.K., S.N..; Funding - D.P.Y., E.S.O., T.K., S.N., F.D.A., P.O.K.; Materials - E.S.O., T.K., F.D.A., P.O.K.; Data Collection and/or Processing - D.P.Y., S.N.; Analysis and/or Interpretation - D.P.Y., E.S.O., S.N., T.K., F.D.A., P.O.K.; Literature Review - D.P.Y., E.S.O., T.K.; Writing - D.P.Y., E.S.O., S.N., T.K., F.D.A., P.O.K.; Critical Review - D.P.Y., E.S.O., S.N., T.K., F.D.A., P.O.K.

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A Case of Aspergillosis Battling Thrombosis: Challenging Diagnosis and Treatment in an Immunocompetent Patient

Tromboz ile Mücadele Eden Aspergillozis Olgusu: İmmünokompetan bir Hastada Zorlu Tanı ve Tedavi Süreci

Nilüfer Yiğit[1], Hilal Argüner[1], Elifsu Özdil[2], Erhan Uğurlu[1]

Abstract

Invasive pulmonary aspergillosis (IPA) is typically seen in immunocompromised patients, but may also develop in immunocompetent individuals, and is associated with high mortality rates. We report here on the case of a 47-year-old male patiet with a history of asthma who presented with fever, cough and sputum production. He was initially diagnosed with hospital-acquired pneumonia and started on appropriate treatment, however, his symptoms persisted. Further investigations revealed Aspergillus spp., leading to a diagnosis of invasive aspergillosis. Radiological imaging revealed a lesion in the left upper lobe, and the diagnosis was confirmed through transthoracic needle biopsy. The patient was started on intravenous voriconazole, but developed thrombosis in the right cephalic vein. Anticoagulation therapy with enoxaparin was added to the protocol, however, balancing the treatment of thrombosis with the risk of bleeding presented a challenge. This case highlights the challenges that can be encountered in clinical diagnosis and treatment, and shows that aspergillosis should be considered even in immunocompetent patients. It further clarifies the need to find the optimum balance between thrombosis treatment and bleeding risk, as a critical aspect of the treatment process in cases of invasive aspergillosis.

Keywords: *Invasive pulmonary aspergillosis, immunocompetent individual, thrombosis, anticoagulant therapy.*

Öz

İnvaziv pulmoner aspergilloz (İPA), genellikle immünkompromize bireylerde görülen ve yüksek mortalite oranlarıyla ilişkilendirilen bir enfeksiyondur. Ancak nadiren immünkompetan bireylerde de ortaya çıkabilir. Bu olguda, astım öyküsü olan 47 yaşındaki erkek hasta ateş, öksürük ve balgam şikayetleri ile başvurdu. Başlangıçta hastane kaynaklı pnömoni tanısı konularak tedavi başlandı; ancak semptomları devam etti. Yapılan ileri tetkiklerde Aspergillus türleri tespit edilerek invaziv aspergilloz tanısı konuldu. Radyolojik incelemelerde sol üst lobda bir lezyon saptandı ve tanı transtorasik iğne biyopsisi ile doğrulandı. Hastaya intravenöz vorikonazol tedavisi başlandı, ancak sağ sefalik vende tromboz gelişti. Enoksaparin ile antikoagülan tedavi eklendi; ancak tromboz tedavisini kanama riski ile dengelemek önemli bir zorluk oluşturdu. İPA hastalarında tromboza yatkınlık ve tedavi sürecinde karşılaşılan zorluklar, terapötik kararlar alınırken dikkatli olunması gerektiğini vurgulamaktadır. Bu olgu, immünkompetan bireylerde dahi aspergillozun göz önünde bulundurulması gerektiğini göstermekte ve invaziv aspergilloz olgularında tromboz tedavisi ile kanama riski arasındaki dengenin sağlanmasının kritik bir önemi olduğunu ortaya koymaktadır.

Anahtar Kelimeler: *İnvaziv pulmoner aspergilloz, immünkompetan birey, tromboz, antikoagülan tedavi.*

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Invasive pulmonary aspergillosis (IPA) is a severe fungal infection caused by *Aspergillus* species, and is associated with high mortality rates. The main risk factors for IPA include neutropenia, hematopoietic stem cell transplantation (HSCT), solid organ transplantation, prolonged treatment with high-dose corticosteroids, hematological malignancies, cytotoxic therapy, advanced AIDS and chronic granulomatous disease, all of which can significantly impair the immune system (1). While IPA predominantly affects severely immunosuppressed hosts, immunocompetent patients may also be affected (2). The symptoms of IPA are nonspecific and may include antibiotic-resistant fever, cough, sputum production, dyspnea, and mild to severe hemoptysis (3).

The early diagnosis of IPA in severely immunosuppressed patients can be challenging, and high-resolution CT is the preferred imaging modality in cases with a high index of suspicion for invasive disease. Typical chest CT findings include multiple nodules and the halo sign appearing as a ground-glass opacity surrounding a pulmonary nodule, indicating hemorrhage, and typically observed during the early stages of infection (usually within the first week) in neutropenic patients. Another radiological feature is the air-crescent sign, which may be seen in the late stages due to necrosis, and appears as a crescent-shaped density in the primary nodule region (4). Bronchoscopy and bronchoalveolar lavage (BAL) can be useful for detecting *Aspergillus* antigens and ruling out other infections. In selected cases, though less frequently, CT-guided transthoracic biopsies, open lung biopsies, transbronchial biopsies or convex endobronchial ultrasound-guided transbronchial needle aspiration may be performed (5).

Voriconazole is a broad-spectrum triazole, available in both intravenous (IV) and oral, formulations that has been approved as the first-line treatment for invasive aspergillosis, and is currently among the preferred therapeutic options for patients with IPA. The recommended initial dose is 6 mg/kg IV every 12 hours on day 1, followed by a daily dose of 4 mg/kg IV. After 7 days, treatment can be switched to an oral regimen of 200 mg twice Daily (6,7).

CASE

A 47-year-old male patient with a 10-year history of asthma presented to our hospital with complaints of fever, cough and sputum. His medical history revealed that he had been treated for pneumonia at an external center, where he had spent 18 days in intensive care followed by 12 days in a regular ward, and had been discharged 5 days earlier. The patient was using an inhaler containing 500 micrograms of fluticasone propionate and 50 micrograms of salmeterol, had no chronic diseases other than asthma and had a smoking history of 25 pack-years. A posterior-anterior chest X-ray revealed densities (Figure 1A) and C-reactive protein (CRP) levels were found to be elevated at 116 mg/L (normal value <5 mg/L), prompting hospital admission. Routine biochemistry tests were performed, and Elisa tests were ordered, but no pathology was detected. The close monitoring of vital signs and blood sugar levels was initiated, and a sputum culture was requested.

The patient was referred to the infectious diseases department with a preliminary diagnosis of hospital-acquired pneumonia, and based on their recommendations, Brucella tests were ordered and empiric treatment with piperacillin-tazobactam (3x4.5 g) was initiated. The patient showed no expected clinical or laboratory response, the Brucella tests were negative and the sputum culture revealed normal upper respiratory flora. A respiratory PCR panel was subsequently performed, the empiric treatment was switched to tigecycline (2x100 mg), and the close monitoring of vital signs and CRP levels continued. Despite all efforts, the patient's fever persisted, and the piperacillin-tazobactam therapy was discontinued on the 5th day of hospitalization in favor of imipenem (4x500 mg).

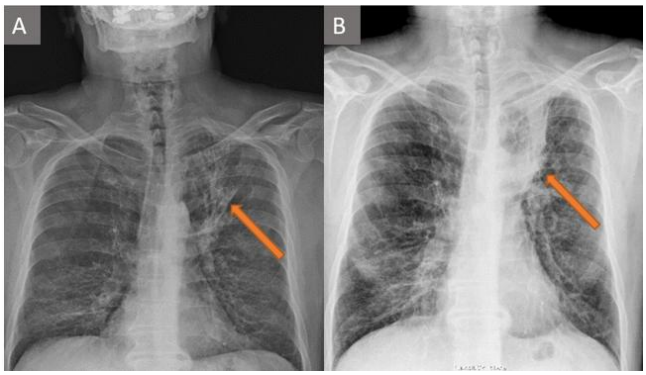

Figure 1: *In the initial chest X-ray, densities can be seen in the upper zone of the left lung and the lower zone of the right lung* ***(A)****. In a follow-up chest X-ray after discharge, a newly developed density can be seen in the upper zone of the left lung* ***(B)***

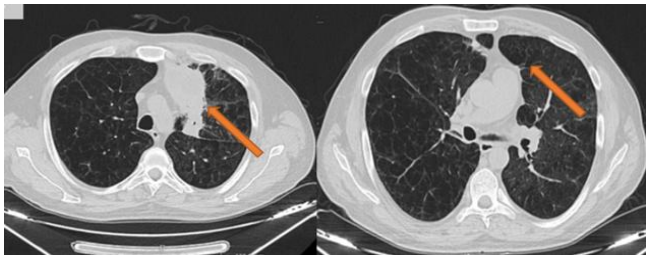

Figure 2: *Parenchymal sections of the chest CT revealing an irregularly contoured area of consolidation measuring 3.5x6.5 cm in the left upper lobe, extending into the paramediastinal area, with a centrally cystic area measuring 4x5.5 cm in the anterior part, and a subsolid nodule measuring approximately 5 mm in diameter in the right upper lobe*

Aspergillus spp. was detected in the fungal culture on the 12th day of hospitalization, but was dismissed as it was thought to be a result of contamination based on the patient's clinical, radiological and laboratory response to antibiotics and immunocompetence, and the absence of any abnormalities in blood glucose levels or vital signs.

During the 15-day hospitalization, the patient's symptoms improved and a decrease in CRP levels (9 mg/L) was noted, and the patient was duly discharged. However, the patient was readmitted 5 days later with similar symptoms, when a density was observed in the left upper lobe on posterior-anterior chest X-ray (Figure 1B), leading to a chest computed tomography (CT) scan (Figure 2). The CT scan revealed a soft tissue appearance in the left upper lobe, prompting a transthoracic fine needle aspiration biopsy to be performed under interventional radiology guidance.

The pathology report revealed invasive aspergillosis, and the patient was admitted to our service and started on IV voriconazole treatment. Following an evaluation of the patient's immunosuppressive status, the patient, who had no known comorbidities, underwent Elisa and rheumatological marker tests, which yielded no abnormalities. During hospitalization, the patient developed edema and numbness in the right forearm and Doppler ultrasonography was performed, revealing a non-compressible segment of the right cephalic vein in the proximal-middle forearm (~10 cm) with an appearance consistent with a hyperechoic thrombus in the lumen. The thrombus, the patient was duly started on subcutaneous enoxaparin sodium 2x1 for treatment. There was no history of any interventional procedure that could have contributed to thrombosis

Despite the IV voriconazole treatment, the patient's CRP levels and clinical condition did not improve significantly during inpatient follow-up, prompting a consultation with the infectious diseases department, and IV moxifloxacin (500 mg 2x1) was added to the treatment regimen. After a 24-day hospital stay, the patient's general condition improved and they were discharged with oral voriconazole and enoxaparin sodium. The patient was followed up by the cardiovascular surgery department for 3 months following the development of the thrombosis, and the thrombosis resolved after 3 months of treatment, after which the enoxaparin therapy was discontinued. Following 75 days of treatment, a thoracic CT scan revealed a regression of the lesions, and further improvement was observed on a 6-month follow-up thoracic CT (Figure 3).

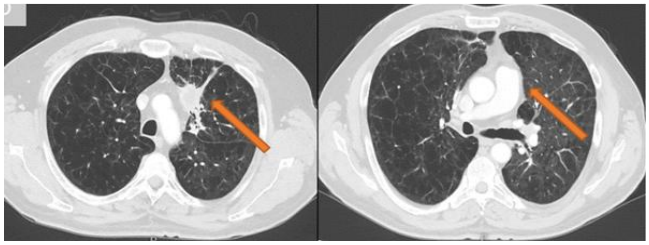

Figure 3: *Chest CT at 6-month follow-up in which the former nodular lesion in the right upper lobe is no longer visible and significant regression can be seen in the lesion in the left upper lobe*

DISCUSSION

IPA is a severe fungal infection with high morbidity and mortality, and predominantly affects the immunocompromised. *Aspergillus* species typically enter the body through the lungs but may disseminate to other organs.

The main risk factors for IPA include neutropenia, solid organ transplantation, hematologic malignancies, cytotoxic therapies and advanced-stage AIDS. The risk of developing IPA with systemic corticosteroid is supported by a number of case reports in the literature, even in immunocompetent patients (8,9). Furthermore, there is a growing body of studies reporting IPA in immunocompetent patients with severe chronic obstructive pulmonary disease (COPD), often associated with prolonged corticosteroid use (10). The use of inhaled corticosteroids (ICS) for the treatment of chronic lung diseases has been suggested in several studies to increase the risk of pneumonia. While this association is more clearly established in patients with COPD (11), there are also studies suggesting a greater risk of pneumonia in asthma patients using ICS when compared to those who do not (12). Although inhaled therapies are thought to increase the risk of pneumonia, there is currently a lack of evidence confirming the causative pathogens. That said, there is no strong evidence that inhaled corticosteroid use predisposes patients to Aspergillus infections, and so the long-term use of inhaled corticosteroids in our patient should be carefully considered as a potential contributing factor.

It has been well-documented that chronic pulmonary diseases predispose airways to colonization by *Aspergillus* species. Under specific conditions, such colonizations can progress to invasive diseases (13). In the presented case, IPA was observed despite the immunocompetent status of the patient, and this, along with the non-specific findings on thoracic CT, led to the initial dismissal of the growth in the sputum culture as a pathogenic cause. Advanced diagnostic measures were thus initiated due to the persistence of symptoms and the need to rule out malignancy. A diagnosis of invasive aspergillosis was finally arrived at based on the results of a transthoracic fine-needle biopsy. Concurring with similar cases reported in the literature, *Aspergillus* spp. was unexpectedly identified as the causative agent of invasive infection in our immunocompetent patient. This highlights the importance of maintaining a high index of suspicion for IPA, even in patients without classic immunosuppressive risk factors, and particularly when clinical and radiologic findings remain unresolved.

The findings of the present study underscore the diagnostic challenges associated with IPA. In patients with chronic

pulmonary diseases, *Aspergillus* spp. Isolated from lower respiratory tract samples should not be dismissed as mere colonization, as *Aspergillus* spp. should be considered a potential causative pathogen, even in immunocompetent patients. In cases where non-specific treatments fail to yield satisfactory results, evaluating *Aspergillus* spp. as an etiological agent can facilitate the implementation of early and accurate therapeutic strategies. Such an approach may prevent disease progression and circumvent the complications associated with invasive aspergillosis, ultimately improving patient outcomes.

The primary complications of IPA include the endothelial damage, local erosion and deep tissue invasion caused by fungal hyphae through angioinvasion (10). Specifically, galactosaminogalactan secreted by *Aspergillus fumigatus* and *Aspergillus flavus* accumulates on platelet surfaces, triggering platelet activation. This cascade leads to intravascular thrombosis and localized infarcts (10,14). Such pathophysiological mechanisms contribute to disease progression and increased mortality rates. These severe complications of IPA highlight the paramount importance of early diagnosis and aggressive treatment strategies. Timely therapeutic interventions can mitigate the progression of the disease and reduce the associated risks, thereby improving patient survival.

The surface-bound GAG produced by *Aspergillus fumigatus* and *Aspergillus flavus* binds to platelets, triggering their activation and activating the complement system. This process can lead to negative outcomes such as thrombosis, thrombocytopenia and excessive inflammation (10). The complement activation triggered against platelets by GAG plays a significant role in increasing the susceptibility to thrombosis in Aspergillus infections. Although this mechanism is understood, the current guidelines offer no adequate recommendations for the preventive treatment of thrombosis in Aspergillus infections (15). As seen in our case, the clinical outcomes of thrombosis can be observed, and managing potential complications during treatment can be challenging.

Platelets play a dual role in immune response by contributing to normal cell-mediated immunity, while also participating in fungal hyphal elongation and antifungal host defense. Platelets release procoagulant proteins upon stimulation by *Aspergillus*-derived factors, which in turn induce the excessive production of inflammatory mediators. This overproduction leads to tissue damage and thrombosis (10,16,17). In 2023, Vikhe et al. (2) reported a case of IPA complicated by portal vein thrombosis to highlight the challenges posed in patient management and treatment. In the same year, Yun et al. (18) described two pediatric cases of IPA under immunosuppression that developed intracardiac thrombi. Recent case reports underscore that IPA can lead to thrombosis not only in the vascular regions adjacent to the invasive fungal growth, but also in distant vascular areas under systemic effects. In the presented case, the thrombus was detected in the cephalic vein, and while rare, this aligns with previous findings and the suggested systemic thrombotic effects associated with IPA. Such a predisposition to thrombosis reinforces the need for further studies to evaluate the necessity and potential efficacy of antithrombotic prophylaxis strategies in patients diagnosed with IPA.

Lyu et al. (19) carried out a comprehensive cohort study between 2014 and 2020 in a pulmonary intensive care unit during which they analyzed the bleeding incidences and risk factors of patients receiving thromboprophylaxis. Of the 931 patients in the study, 26 were diagnosed with IPA, and 19 of these were identified as being at high risk of major bleeding. The authors reported IPA to be an independent risk factor for major bleeding, and suggested that *Aspergillus* infections could increase bleeding tendencies through vascular damage as a consequence of the infection's impact on vascular integrity, which they attributed to the systemic effects of the circulating infection. They further suggested that *Aspergillus* could contribute to localize bleeding through elastase production and the resulting damage to local tissues. These findings highlight the dual challenge posed by IPA, being the predisposition to thrombotic complications alongside the increased risk of bleeding, and underscore the importance of individualized patient management strategies that balance thromboprophylaxis and bleeding risk in cases with IPA.

The administration of anticoagulant therapy in patients diagnosed with IPA is a complex clinical scenario that requires careful assessment of both the thrombotic risk and bleeding potential. When planning anticoagulant therapy for these patients, it is, therefore, essential to consider not only the risk of thrombosis but also the potential for severe bleeding, to evaluate the clinical situation individually, and to make decisions based on a multidisciplinary approach. Prospective studies are needed to determine optimal management strategies.

CONCLUSION

IPA is a severe infection that can develop even in immunocompetent patients, making early diagnosis and appropriate treatment crucial. *Aspergillus* spp. should not be considered merely as colonizers, but also as potential pathogens, and vascular complications such as thrombosis and bleeding must be carefully managed during treatment. This highlights the importance of a multidisciplinary approach and the need for further studies of this condition.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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Lymphocytic Pleural Effusion Due to Crizotinib Usage

Krizotinib Kullanımına Sekonder Lenfositik Plevral Efüzyon

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Abstract

A 41-year-old woman with Anaplastic Lymphoma Kinase (ALK) gene positive adenocarcinoma of the lung presented with dyspnea in the 4th month of Crizotinib therapy with a prominent finding of bilateral mild pleural effusion. A comprehensive radiological and laboratory investigation discounted infection, rheumatological diseases and malignancies, while the symptoms and pleural effusion regressed after pausing Crizotinib medication. We present this unusual case of lymphocytic pleural effusion associated with Crizotinib, which is a novel tyrosine kinase inhibitor.

Keywords: *Crizotinib, lung cancer, pleural effusion.*

Öz

Anaplastik Lenfoma Kinaz (ALK) geni pozitif akciğer adenokarsinomu olan 41 yaşındaki bir kadın hasta, crizotinib tedavisinin dördüncü ayında nefes darlığı yakınması ile başvurdu. Radyolojik olarak bilateral hafif plevral efüzyonu olan hastada, kapsamlı radyolojik ve laboratuvar incelemelerinin ardından enfeksiyon, romatolojik hastalıklar, maligniteler gibi diğer yaygın nedenler dışlandı. Krizotinib ilacı kesildikten sonra semptomları ve plevral efüzyonunun gerilediği hatta steroid ile bu sürecin hızlandığı izlendi. Bu nedenle, bir tirozin kinaz inhibitörü olan krizotinib ile ilişkili alışılmadık bir lenfositik plevral efüzyon olgusunu sunmayı amaçladık.

Anahtar Kelimeler: *Krizotinib, akciğer kanseri, plevral efüzyon.*

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The echinoderm microtubule associated protein-like 4 (EML-4)-Anaplastic Lymphoma Kinase (ALK) oncogenic driver mutation appears in 2–7% of all cases of non–small-cell lung cancer (NSCLC) (1).

Crizotinib is an ALK inhibitor that was approved for the treatment of advanced-stage (IIIB and IV) lung adenocarcinoma patients with ALK (+) by the US Food and Drug Administration (FDA) in 2011, based on early phase clinical studies (2). Crizotinib is generally well tolerated even in older adult patients, with the most common side effects being gastrointestinal disorders and visual side effects, while peripheral edema, dizziness, tiredness, loss of appetite and interstitial pneumonia are less common (3,4).

Even it is seen rarely some drugs are one of the reasons of pleural effusion, and so for accurate diagnosis, the patients' drug history should be questioned in detail. Spontaneous recovery is generally observed after stopping treatment (4).

Diagnosis is based initially on a routine biochemical analysis of the pleural effusion to differentiate transudate/exudates, followed by a cytopathological and microbiological evaluation. Drug-induced pleural effusions are generally exudative with eosinophilic predominance in cell distribution.

Reports of pleural effusions associated with Crizotinib usage are rare in the literature. In one reported case, a 35-year-old woman with stage 4 ROS1-rearranged lung adenocarcinoma developed pleural effusion after four days of Crizotinib treatment. Examinations, including surgical thoracoscopy, pointed to no specific diagnosis, however, the effusion regressed after discontinuing Crizotinib (5). We present here the case of an ALK-positive lung adenocarcinoma patient with bilateral pleural effusion associated with Crizotinib treatment.

CASE

A 41-year-old female admitted with chest pain on right side was identified with a right hilar lesion and pleural effusion on right hemithorax (Figure 1A). Chest computed tomography revealed a 5 cm mass in right middle lobe, and pathology from a subsequent transthoracic needle aspiration biopsy confirmed lung adenocarcinoma. A FISH (Fluorescence in-situ hybridization) analysis of the tumor tissue was positive for an ALK rearrangement, and so Crizotinib therapy was initiated. Bilateral pleural effusion developed in the 3rd month that was more prominent on the right side (Figure 1B and 1C) that, when drained, revealed a regression of the primary lesion (Figure 1D). Ultrasound-guided thoracentesis was first performed on the left hemithorax, revealing the fluid to be serous and exudative, with no malignant cells observed on cytological examination. The effusion in the right hemithorax was drained using a pleural catheter, and the procedure was completed with talc pleurodesis. However, effusion in the right lung persisted, any malign cells were observed on cytoblock investigation for three times. The effusion on both sides contained a predominance of lymphocytic cells (Figure 2) that were negative for tuberculosis bacillus or any other microbiological agent. The patient's left ventricular function was normal on echocardiography, and antinuclear antibody testing was negative in fluid. Transdiaphragmatic fluid passage was excluded based on abdominal ultrasonography. Finally, the patient's drug usage was questioned, and she has stopped using diltiazem at first but effusion was persisted. Crizotinib treatment was suspended secondly, and a decrease in the amount of fluid was noted 15 days later. Methylprednisolone 40 mg/day was added to the treatment protocol to increase the patient's recovery rate. Her general medical condition improved, and she was started on Crizotinib again with frequent clinical and radiological follow-ups under steroid treatment. The amount of fluid did not increase as the steroid dose was tapered. While patient takes methylprednisolone 16 mg/day Crizotinib, left pleural fluid disappeared and right pleural thickening appeared due to talc pleurodesis (Figure 1E and 1F).

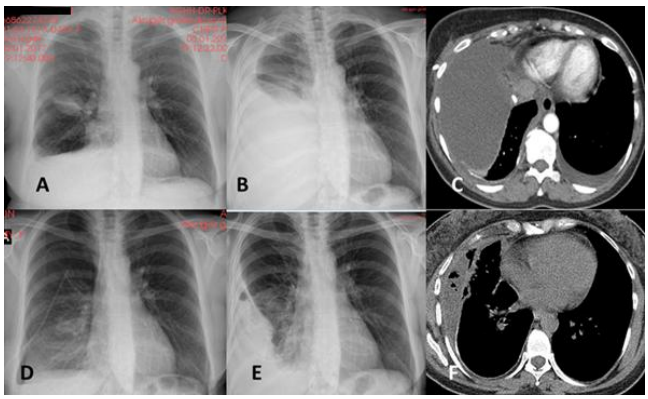

Figure 1: Chest X-ray on admission (A), Bilateral pleural effusion on Chest X-ray (B), Bilateral pleural effusion on CTT (C), Regression of primary lesion after effusion drainage (D), Complete response of pleural effusion on the left side and organized effusion on the right side (E), Regression of pleural effusion on CTT (F)

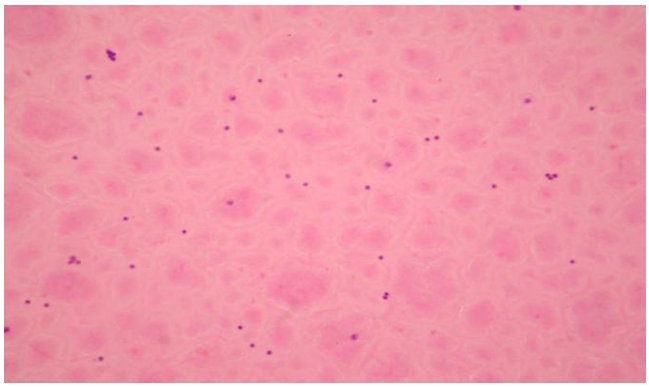

Figure 2: Cytological analyses of pleural liquid demonstrating lymphocyte infiltration (H&E X400)

DISCUSSION

Patients with lung cancer may develop increased pleural fluid as a side effect of chemotherapeutic agents (6). Drug related pulmonary toxicity is a common condition, in contrast to pleural effusion, which is more rare (7). As a result, drug-related sources of pleural effusion are largely overlooked.

Previous studies have reported varying times between the first dose of the suspected drug to the occurrence of pleural effusions, ranging from days to a decade (8). Drug dependent pleural effusions may be unilateral or bilateral, and may be accompanied by parenchymal lesions, fluid and/or systemic eosinophilia. If drug-dependent pleural effusion can be ruled out, the patient may be treated under a diagnosis of idiopathic pleural effusion (9).

On the 120th day of Crizotinib treatment, the patient's complained of shortness of breath. After eliminating such etiologies as infection, tuberculosis, malignant pleural effusion and collagen vascular disease, the lymphocytic predominance in the fluid led us to question the medication protocol.

Pleural effusion has been reported to occur due to the tyrosine kinase inhibitor (TKI) Desatinib. The underlying cause of pleural effusion related to Desatinib is immune response, for which the short term discontinuation of the drug, diuretic and steroid treatments is suggested (10). Other causes of lymphoplasmacytic pleural effusion include tuberculosis, viral pleurisy, rheumatoid diseases, cancer, chylothorax and asbestos exposure (9).

We attributed the increased pleural effusion in our patient to inflammatory response, supported by such findings as inflammatory cells in the pleural liquid, an absence of malignant cells in the pleural effusion, and the absence of clinical evidence of infection. In contrast to drug dependent interstitial lung diseases, drug-related pleural effusions are usually not life-threatening. In our case, the reinitiation of Crizotinib along with steroid treatment suppressed the patient's inflammatory process, preventing recurrence, and even initiating a rapid decrease. Literature contains several studies assessing Desatinib, from tyrosine kinase family, but none investigating Crizotinib (11).

The importance of the presented case lies in its identification of the relationship between the ALK inhibitor and pleural effusion. Pleural effusions associated with TKIs should be evaluated carefully, with considering possible drug reaction and "disease progression decision" should be made after careful cytological evolution.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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RESPIRATORY CASE REPORTS

Solitary Fibrous Tumors: Analysis of 5 Cases and Literature Review

Soliter Fibröz Tümörler: 5 Olgunun Analizi ve Literatür İncelemesi

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Abstract

The solitary fibrous tumor (SFT) is a rare mesenchymal neoplasm derived from CD34+ dendritic stromal cells, primarily found in the pleura but also occurring in other sites like the lung and peritoneum. It accounts for approximately 5% of pleural tumors. Respiratory symptoms, such as cough and dyspnea, typically result from the compression of adjacent structures. The treatment of choice remains surgical, involving complete excision of the tumor, often requiring extensive resections. The prognosis is generally favorable for benign forms, although postoperative monitoring is crucial due to a risk of recurrence, particularly in more aggressive cases; surgery should also be considered in the event of local recurrence, if technically feasible. This study aims to analyze the clinical presentation, pathological findings, and outcomes of five patients diagnosed with SFT, emphasizing the importance of early diagnosis and effective management.

Keywords: *Solitary Fibrous Tumor, mesenchymal, surgery.*

Öz

Soliter fibröz tümör (SFT), CD34+ dendritik stromal hücrelerden türetilen nadir bir mezenkimal neoplazmdır ve öncelikli olarak plevrada bulunur, ancak akciğer ve periton gibi diğer bölgelerde de görülür. Plevral tümörlerin yaklaşık %5'ini oluşturur. Öksürük ve dispne gibi solunum semptomları tümörün genellikle komşu dokulara basısından kaynaklanır. Tercih edilen tedavi cerrahidir ve tümörün tamamen çıkarılmasını içerir ve genellikle kapsamlı rezeksiyonlar gerektirir. Prognoz genellikle benign formlar için iyidir, ancak özellikle daha agresif olgularda tekrarlama riski nedeniyle postoperatif takip çok önemlidir; teknik olarak mümkünse lokal tekrarlama durumunda da cerrahi düşünülmelidir. Bu çalışma, SFT tanısı konulan beş hastanın klinik sunumunu, patolojik bulgularını ve sonuçlarını analiz etmeyi ve erken tanı ve etkili tedavinin önemini vurgulamayı amaçlamaktadır.

Anahtar Kelimeler: *Soliter fibröz tümör, mezenkimal tümör, cerrahi.*

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Solitary fibrous tumors (SFTs) are rare neoplasms located primarily in the pleura, although they may also develop in other regions, such as the lungs and peritoneum. SFTs account for approximately 5% of all pleural tumors (1). While they can occur at any age, peak incidence is typically observed in those aged 50–70 years. While sex is generally not considered a risk factor, previous studies have reported a slight predominance in females (2,3). Although the majority of pleural solitary fibrous tumors are classified as benign, 10–20% are found to be malignant, characterized by rapid growth, local invasion, and a high rate of recurrence and metastasis (4). Historically, such tumors have often been misdiagnosed as benign pleural mesothelioma, although advances in the approach to classification have improved the delineation of their biological behaviors (3).

The clinical manifestations of SFTs can vary widely, ranging from asymptomatic presentations to respiratory symptoms such as dyspnea and chest pain. Such symptoms are frequently associated with tumor size, which can reach significant dimensions without apparent clinical effects (2). Surgical intervention remains the treatment of choice, typically involving radical resection (R0). Preoperative planning with detailed imaging is crucial for assessing the extent of the disease. While multiple thoracotomies may be necessary to ensure complete resection, a minimally invasive approach may also be considered. Recurrence is often linked to incomplete resection, and repeat operations can enhance prognosis (5).

CASE

Case 1: A 64-year-old female non-smoker with no significant medical history presented with dyspnea and a decline in her overall condition. Upon examination, her ECOG performance status was 0, with a peripheral oxygen saturation of 92% in ambient air. A pleuropulmonary examination revealed no particular abnormalities, while a chest CT scan revealed a tumor mass located in the left lower lobe, accompanied by mediastinal and axillary lymphadenopathy (Figure 1).

Bronchoscopic examination revealed extrinsic compression of the lingula, while a histopathological analysis of an ultrasound-guided biopsy of the mass confirmed a diagnosis of solitary fibrous tumor. A multidisciplinary oncology panel recommended surgical intervention, but the patient was later lost to follow-up.

Case 2: A 62-year-old patient who had been a chronic smoker for 20 years but abstinent for the past 15 years presented with an isolated productive cough. Clinical examination indicated an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and a peripheral oxygen saturation of 93% in ambient air, with dullness noted in the lower two-thirds of the right thoracic hemithorax. Thoracic computed tomography revealed a large mass in the parietal pleura measuring 175 mm on its longest axis, with homogeneous enhancement (Figure 2).

A percutaneous ultrasound-guided biopsy confirmed the presence of a solitary fibrous tumor, which tested positive for CD34 and STAT6, and exhibited a diffuse overexpression of P53, indicating an aggressive nature. The patient underwent a complete en bloc tumor resection, and the subsequent histopathological analysis classified the tumor as high risk, with tumor necrosis foci assessed at 10% and four mitoses per 2 mm^2. The patient was subsequently referred for adjuvant chemotherapy for further management, but was lost to follow-up.

Case 3: A 79-year-old female non-smoker patient with a history of hypertension managed for 12 years who was taking aspirin for the treatment of ischemic heart disease and insulin for the control of diabetes presented with stage II dyspnea, dry cough that was occasionally productive and unquantified weight loss over the past year. Her general condition was stable upon examination, with a saturation of 98% and dullness noted in the left basis thorax. Thoracic computed tomography revealed a circumscribed mass in the left lower lobe that was causing a mass effect on the mediastinum (Figure 3).

Bronchoscopic examination revealed compression of the lingula with an inflammatory appearance, while a bronchial biopsy revealed necrosis and hemorrhage without viable cells. Ultrasound-guided biopsy confirmed the diagnosis of a solitary fibrous tumor, and surgical intervention was recommended by a multidisciplinary panel; however, the patient was subsequently lost to follow-up.

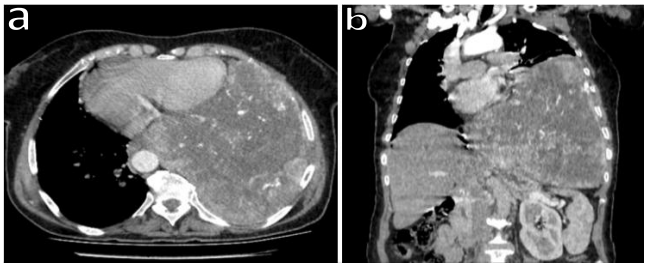

Figure 1: Axial (A) and sagittal (B) thoracic CT images revealing a large tumor mass in the left lower lung lobe

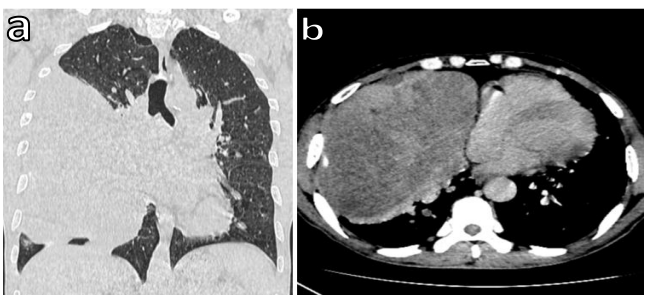

Figure 2: Thoracic CT in parenchymal (A) and mediastinal (B) windows showing a diffuse right pleural tumor mass compressing the right lung and mediastinal structures

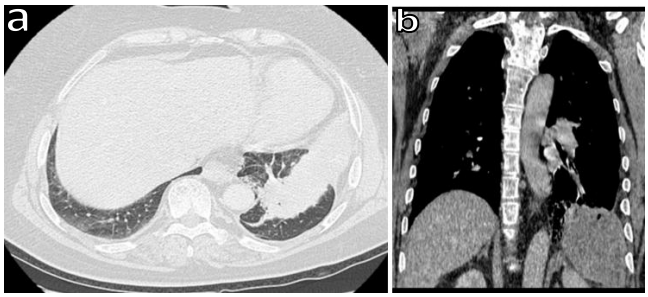

Figure 3: Thoracic computed tomography in parenchymal window (A) and mediastinal window (B) showing a well-defined tumor mass in the left lower lobe with clear margins against the lung parenchyma, suggesting a pleural origin

Case 4: A 32-year-old female non-smoker with no notable medical history presented with progressive dyspnea and a deterioration of her general condition over the past 7 months, accompanied by the emergence of a parietal swelling. Clinical examination revealed an adherent, indurated and painful mass located on the left parietal region measuring nearly 20 cm, while thoracic computed tomography showed a left pleural effusion and a hypodense nodular mass measuring 133 mm in the left lower lobe that was compressing the adjacent structures. Thoracic magnetic resonance imaging suggested the presence of a left parietal thoracic tissue mass (Figures 4 and 5).

Ultrasound-guided biopsy confirmed the diagnosis of a solitary fibrous tumor. Following a staging workup that revealed no distant metastases, the patient underwent surgery for the complete excision of the tumor with negative surgical margins, and she was subsequently referred for Imatinib-based chemotherapy. Post-operative monitoring for 3 months indicated a favorable evolution of the patient's condition, with no signs of recurrence or associated complications.

Case 5: A 32-year-old male non-smoker presented with stage III dyspnea for 1 month, accompanied by a productive cough with hemoptysis and left-sided chest pain. An examination revealed an oxygen saturation of 95% in ambient air. Auscultation revealed an absence of vesicular breath sounds on the left, as well as dullness to percussion, and a subsequent thoracic computed tomography revealed a posterior thoracic mass measuring 133 x 107 x 80 mm that was predominantly cystic, along with another adjacent mass measuring 98 x 97 x 81 mm that was enhanced after contrast injection. Unilateral pleural thickening associated with the multifocal basis thoracic masses was also noted.

The patient underwent tumor excision and decortication, and the subsequent morphological examination and immunohistochemistry confirmed the diagnosis of a solitary fibrous tumor. The patient presented again 3 months later with stage III dyspnea, a productive cough with hemoptysis and 7 kg weight loss of. An examination revealed desaturation to 40% in ambient air, which was improved to 96% by non-invasive ventilation. Computed tomography confirmed the persistence of the left nodular pleural thickening primarily within the lower lobe, revealing it to have become diffuse and heterogeneous, measuring 106 mm in the anterobasal region (Figure 6).

The patient ultimately died following cardiorespiratory arrest, despite resuscitation efforts. The cause of death was attributed to respiratory distress and severe hypoxia secondary to a pulmonary infection.

The characteristic features of all our cases are shown in Table 1.

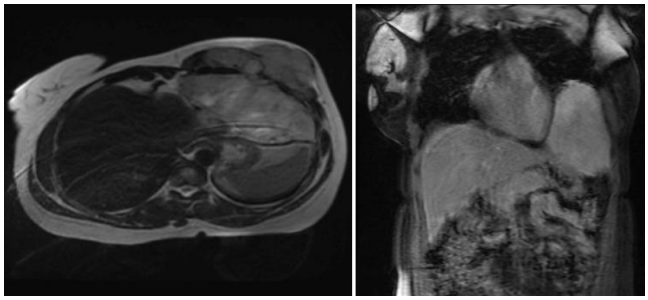

Figure 4: Thoracic magnetic resonance imaging (MRI) T1 sequence showing a tissue mass measuring 146 x 121 x 124 mm on the left anterior thoracic wall enveloping the anterior arches of the 6th, 7th and 8th left ribs, described as hypointense on T1 with heterogeneous enhancement after contrast injection

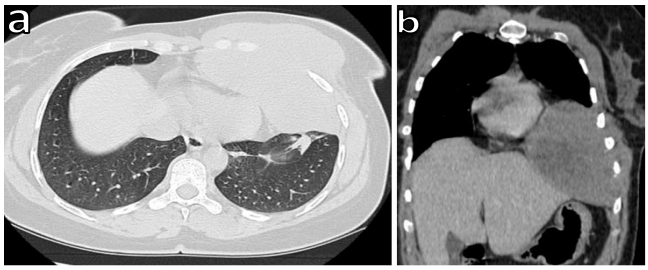

Figure 5: Thoracic computed tomography in parenchymal window (A) and mediastinal window (B) showing a tumor mass of the left thoracic wall measuring 15 cm along its longest axis eroding the anterior arches of the 7th and 8th left ribs, and displacing the diaphragm and pericardium without signs of infiltration

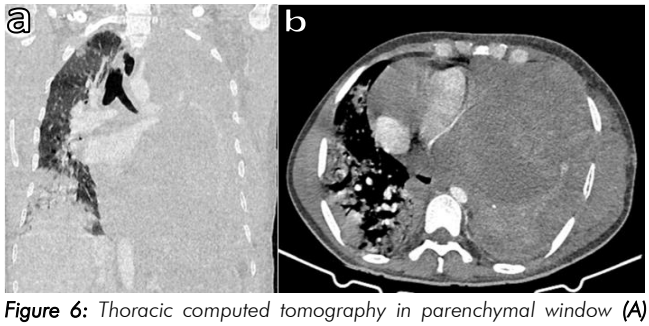

Figure 6: Thoracic computed tomography in parenchymal window (A) and mediastinal window (B) showing a tumor mass in the left posterior basis thoracic region that is predominantly cystic, measuring 133 x 107 x 80 mm, as well as a second lobulated adjacent posterior basis thoracic mass, measuring 98 x 97 x 81 mm enhanced after contrast injection. Also revealed is unilateral pleural thickening associated with the multifocal basis thoracic masses, likely indicative of local recurrence

Table 1: Characteristics of Solitary fibrous tumor cases

Case Number	Patient Age (years)	Patient Sex	Smoking History	Initial Symptoms	Clinical Findings	Imaging Results	Diagnosis	Treatment	Surgical Details	Outcome
Case 1	64	Female	No	Dyspnea	WHO performance status 0, oxygen saturation 92%	Tumor mass in left lower lobe, mediastinal and axillary lymphadenopathy	Solitary fibrous tumor	Recommended surgery; lost to follow-up		Lost to follow-up
Case 2	62	Male	Yes	Isolated productive cough	WHO performance status 0, oxygen saturation 93%	Large mass in right pleura, 175 mm, homogeneous enhancement	Solitary fibrous tumor	Recommended surgery; and adjuvant chemotherapy	Complete en bloc tumor resection	Lost to follow-up
Case 3	79	Female	No	Stage II dyspnea, dry cough, unquantified weight loss	WHO performance status 0, oxygen saturation 98%	Circumscribed mass in left lower lobe, mass effect on mediastinum	Solitary fibrous tumor	Recommended surgery; lost to follow-up		Lost to follow-up
Case 4	32	Male	No	Stage III dyspnea, productive cough, hemoptysis	Oxygen saturation 95%, absence of breath sounds on left	Cystic mass 133 x 107 x 80 mm, pleural thickening	Solitary fibrous tumor	Surgery	Tumor excision and decortication	Died following cardiorespiratory arrest
Case 5	32	Female	No	Progressive dyspnea, parietal swelling	WHO performance status 3, large left chest mass Indurated, painful mass on left parietal region	Left pleural effusion, hypodense nodular mass, 133 mm	Solitary fibrous tumor	Recommended surgery; and adjuvant chemotherapy	Complete excision of the tumor, Negative surgical margins	favorable evolution no recurrence or complications

DISCUSSION

Solitary fibrous tumors (SFT) are rare mesenchymal neoplasms that are localized primarily in the pleura, but that may also occur in other areas, such as the lungs and peritoneum. SFTs account for approximately 5% of all pleural tumors, with an estimated malignancy risk of 10–20% (1). Around 900 cases have been documented in the literature since 1931. While most SFTs exhibit benign histological features and show no tendency for recurrence following complete surgical resection, their biological behavior can vary widely, and SFTs that are at first benign may transform into malignant solitary fibrous tumors (MSFTs) over time (6).

Pleural tumors are predominantly secondary lesions, with adenocarcinomas, squamous cell carcinomas and melanomas being the most common types. Primary tumors of the pleura can differ considerably in terms of their morphology, histology, clinical presentation and radiological features. WHO (2021) categorizes such tumors into three main groups: mesothelial tumors, lymphoproliferative tumors and mesenchymal tumors. Among the mesenchymal tumors, SFTs belong to the fibroblastic tumor subset, and typically occur in patients aged 40 years and older with a sex ratio of 1:1. Their etiology remains unknown, with no established association with tobacco or asbestos exposure (7).

Benign solitary fibrous tumors (SFTs) typically develop slowly and often remain asymptomatic, often being discovered incidentally during imaging examinations. Possible symptoms include chest pain, chronic cough and dyspnea, with chest pain being the most common complaint. (8).

In contrast, malignant solitary fibrous tumors (MSFTs) tend to present earlier with severe symptoms related to their rapid growth and invasive nature, such as exacerbated chest pain, hemoptysis and respiratory failure. Studies report symptoms to be present in 58–75% of patients with MSFTs. (8)

Computed tomography (CT) with contrast enhancement remains the optimal reference examination for the characterization of the nature of the lesion. A standard CT scan can determine the size and location of the tumor, while multi-slice CT can be used for three-dimensional reconstruction, aiding in the better characterization of the internal structure and boundaries of the lesion. This information is essential for the differentiation of benign and malignant tumors, and for the creation of treatment plans. Enhanced CT can also identify the feeding arteries of the tumor, thus facilitating diagnosis and guiding surgical procedures (1).

Magnetic resonance imaging (MRI) is a valuable tool for distinguishing between solitary fibrous tumors (SFTs) and pleural effusions, and for assessing their relationships with adjacent structures. SFTs exhibit mixed intensity signals with low to intermediate intensity on T1-weighted images (T1WI) and heterogeneous hyperintensities on T2-weighted images (T2WI) in necrotic areas. Under contrast, there is marked and uneven enhancement, however, past studies have suggested that MRI cannot reliably distinguish malignant solitary fibrous tumors (MSFTs) from

benign lesions, except in cases with obvious signs of invasion (1).

Solitary fibrous tumors of the pleura (SFTP) are diagnosed based on anatomopathological examinations. Macroscopically, these tumors can reach sizes of up to 30 cm and are classified as giant when they measure at least 15 cm or occupy more than 40% of a hemithorax (9).

Histologically, SFTs exhibit hypo- and hypercellular areas with spindle-shaped cells and branching capillaries, and a low number of mitoses is typically observed (< 3 mitoses/mm^2) without atypia or necrosis. Immunohistochemistry, particularly positive staining for STAT6, is essential for the confirmation of diagnosis (10).

Patients with SFTs should be managed in specialized centers with experience in oncological thoracic surgery (9). Surgery remains as the only validated and recommended treatment, and may be combined with postoperative radiotherapy.

In inoperable cases, treatments such as radiotherapy, chemotherapy, targeted therapy and immunotherapy may be considered on a case-by-case basis, while asymptomatic tumors in patients with significant comorbidities or advanced age may benefit from therapeutic abstention.

The surgical treatment of solitary fibrous tumors of the pleura (SFTPs) and their malignant forms (MSFTs) relies on complete tumor resection, being the primary factor influencing prognosis. The goal is to achieve a negative margin while preserving pulmonary parenchyma. The choice of procedure depends on the size, location, the relationship of the tumor with adjacent tissues, and the overall health of the patient.

Pedunculated tumors are generally treated with wedge resections, while sessile or large tumors may require lobectomy or pneumonectomy. Video-assisted thoracoscopic surgery (VATS) is recommended for pedunculated tumors smaller than 5 cm due to its postoperative advantages, however, thoracotomy remains the standard approach to MSFTs or invasive tumors.

Preoperative preparation, including tumor embolization or ligation of the vascular pedicle, is recommended for highly vascularized tumors to reduce the risk of bleeding. Reconstruction of the thoracic wall may be necessary after resection to restore thoracic morphology (11).

Adjuvant radiotherapy is recommended for patients with close surgical margins (R1/R2) or those with high-risk SFTPs, allowing for better local control of the disease, although its benefit on overall survival has yet to be clarified. In the event of local recurrence, surgical resection is preferred if the patient is eligible, or if R0 resection is not possible, adjuvant radiotherapy can be considered as an alternative (5,12).

Neoadjuvant chemotherapy based on anthracyclines is an option for locally advanced tumors when R0 resection is not feasible. In cases of synchronous pulmonary metastases or extra-pulmonary disease, systemic treatment has been proposed, although supporting data are limited and past results have often been contradictory.

Adjuvant chemotherapy with anthracyclines as a first-line treatment offers an objective response rate of 0–20%, with disease stability achieved in 26–65% of cases (6).

SFTPs, being highly vascularized, exhibit strong expressions of the proteins involved in angiogenic pathways such as PDGFR and VEGFR. Anti-angiogenic agents such as Sunitinib, Sorafenib and Pazopanib have shown prolonged disease control in case studies, leading to their use to be recommended following chemotherapy failure (14).

Immunotherapy for the treatment of high-grade solitary fibrous tumors of the pleura (SFTPs) has shown promise, with several cases of partial responses reported following anti-PD1 or PD-L1 treatments. A phase III trial is currently underway comparing Nivolumab/Ipilimumab with Pazopanib in patients with advanced sarcomas, including SFTPs.

Surgical resection remains the primary treatment modality, often combined with postoperative radiotherapy, as the only validated treatment, confirming the prognostic benefit of R0 resection.

In cases in which resection is not feasible, treatments such as radiotherapy, chemotherapy, targeted therapy and immunotherapy may be considered on a case-by-case basis, although these alternatives should be considered only after surgical resection has been ruled out. This approach reflects the complexity of managing SFTs and underscores the importance of tailoring the treatment to the individual patient characteristics.

The prognosis for benign SFTs is generally favorable, with a 5-year overall survival rate of 100% among patients with benign tumors (13). It should be noted, however, that local recurrences and malignant transformations can occur with a 10-year recurrence rate of between 10% and 25% that can generally be attributed to incomplete resection (14). For MSFTs, the survival rate is significantly lower, with disease-free survival and overall survival rates at 5 years of 58.3% and 66.7% reported, respectively. The surgical approach also affects outcomes, with VATS yielding a 10-year overall survival rate of 96.3% compared to 78.4% for thoracotomy. Tumors of the visceral pleura typically have better survival rates than those of the parietal pleura (15).

SFTPs are generally localized masses, and are often benign, however, a subset (10% to 30%) exhibits aggressive behavior, with local or systemic recurrences.

The risk of recurrence in solitary fibrous tumors of the pleura (SFTPs) is associated with several factors:

• Histological Factors: Hypercellularity, high mitotic figures, nuclear pleomorphism, as well as hemorrhage or tumor necrosis increase the risk of recurrence.

• Macroscopic Characteristics: Tumors with a sessile morphology, size greater than 10 cm, and a parietal pleural origin are also implicated.
• Clinical Factors: Symptomatic presentation, the presence of pleural effusion, incomplete resection and advanced age are among the aggravating factors.
• Immunohistochemical Criteria: High Ki67 proliferation index and overexpression of p53 contribute to assessments.
• Genetic Factors: Specific NAB2-STAT6 fusions are relevant when evaluating recurrence risk (6).

Follow-up for the identification of solitary fibrous tumors of the pleura (SFTPs) is crucial, especially for malignant forms, which have a recurrence rate of up to 54%. Recurrences primarily occur within the first 2 years, although such cases have been reported 17 years after surgery. Metastases mainly affect the liver, central nervous system and other organs (16).

There are currently no specific treatment recommendations, however, the National Comprehensive Cancer Network (NCCN) advises the strict follow-up of cases of malignant SFTP. Rigorous follow-up is essential for the adaptation of treatments and the improvement of clinical outcomes (17). Unfortunately, three of the five cases presented here were lost to follow-up, while of the remaining cases that were added to a follow up program, one died due to a pulmonary infection.

CONCLUSION

Our findings reinforce the importance of long-term surveillance, as recurrence can occur even years after the initial resection, particularly in aggressive cases. Among the five presented cases, three were lost to follow-up limiting our ability to assess their long-term outcomes. However, the aggressive nature of some cases, particularly Case 5, aligns with previous studies reporting a 10–25% recurrence rate, despite complete resection, underlining the need for clinicians to remain vigilant and proactive post-treatment.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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Oral Nosocomial Myiasis in an Intensive Care Unit: A Case Report

Yoğun Bakım Ünitesinde Oral Nozokomiyal Miyazis: Olgu Sunumu

Ayşe Çapar[1], Derya Özyiğitoğlu[2], Şeyma Başlılar[3]

Abstract

Myiasis has been more frequently studied as an animal disease caused by fly larvae, although it may also affect humans. Bacteria and viruses are the most common nosocomial pathogens in intensive care units, although it is necessary to be aware of the potential for nosocomial parasitic infections. We present here a case of oral myiasis in a 96-year-old patient with Alzheimer's disease who was intubated while being treated for aspiration pneumonia. Our intention in this regard is to clarify the specific clinical features of the disease, especially hospital-acquired myiasis, and to raise awareness of the potential for nosocomial parasitic infections among physicians, as preventable and treatable diseases.

Keywords: *Musco domestica (housefly), Nosocomial infections, Oral myiasis.*

Öz

Miyazis genellikle sinek larvalarının neden olduğu bir hayvan hastalığı olarak bilinir, ancak insanlarda da enfeksiyonlara neden olabilir. Bakteriler ve virüsler yoğun bakım ünitelerinde en sık görülen nozokomiyal patojenlerdir. Ancak nozokomiyal paraziter enfeksiyonlar için uyanık olmak önemlidir. Bu çalışmada, aspirasyon pnömonisi nedeniyle entübe edilen 96 yaşındaki Alzheimer hastasında oral miyazis olgusu sunulmuştur. Amaç, özellikle hastane kaynaklı miyaziste hastalığın spesifik klinik özelliklerini ortaya koymak ve hekimler arasında nozokomiyal parazit enfeksiyonları hakkında şüphe uyandırmaktır. Çünkü parazit enfeksiyonları önlenebilir ve tedavi edilebilir hastalıklardır.

Anahtar Kelimeler: *Musco domestica (karasinek), Nozokomiyal enfeksiyonlar, Oral miyazis.*

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Myiasis is a parasitic infestation of Dipteran insect larvae that can affect humans and other vertebrates (1). The word "Myia" means specifically "invasion of tissues by fly larvae". The first case of human myiasis involving dipterous larvae was reported by Hope in 1840, while Fritz Zumpt expanded the definition in 1965, referring to "the invasion of Diptera larvae that feed on living and deceased host tissues, body fluids or ingested food products, at least for a while" (2).

Human myiasis can take various forms, but the most common is cutaneous myiasis, given the need of pathogens for easily accessible parts of the body for oviposition and larval development (3). Oral myiasis, on the other hand, is the rarest form due to the limited contact of the oral cavity with the external environment (4).

Dipteran flies may also cause hospital-acquired myiasis, although such incidences are rarely reported. Musca domestica, known more commonly as houseflies, live close to humans, breed in garbage and animal feces, and contaminate food, and cases of nosocomial myiasis attributable to this species have been reported (3).

We present here the case of a 96-year-old patient with myiasis admitted to the ICU to emphasize the potential development of nosocomial infections from parasitic infestations in the critically ill.

CASE

A 96-year-old woman with Alzheimer's disease who applied to our center with shortness of breath was identified with consolidation in the lower zone of the right lung in imaging studies consistent with aspiration pneumonia. The patient, who had a Glascow coma scale score of 7, was subsequently transferred to the ICU following intubation. The lack of adequate coughing and swallowing functions led to unsuccessful extubation trials. Oral care was provided 3 times a day using a chlorhexidine oral care solution, and the patient was followed up in the ICU for 40 days. A single fly larva was detected in the oral cavity during routine oral care approximately 1 month after ICU admission (Figure 1), although no other larvae were identified by a careful examination of the oronasal cavity. The cavity was cleaned with a 70% alcohol solution. No ulcerated lesions were identified in the cavity and mucosal integrity was intact. The patient was started on broad spectrum antibiotherapy but died on the 40th day of hospitalization due to pneumosepsis and septic shock. The larva obtained from the patient was thought to be a housefly larva. Despite preventative measures, houseflies had previously been detected in the ICU.

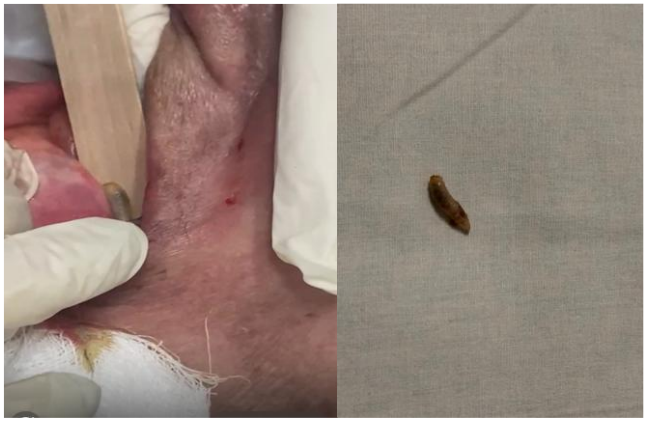

Figure 1: *Oral nosocomial myiasis*

DISCUSSION

Myiasis refers to the opportunistic parasitic invasion of fly larvae, occurring especially in tropical and subtropical regions. Black fly larvae are associated primarily with facultative myiasis. The transmission of maggots to humans can follow two routes, the most common of which is via the direct inoculation of eggs into living tissues and body cavities, while less common is through the ingestion of food infected with larvae (3,5). Black flies can also cause pseudomyiasis, in which flies that do not need any host to develop and lay eggs accidentally (6). The presented case had developed cavitary myiasis (oral myiasis), and the causative pathogens were thought to be black flies (Musco domestica), having been previously encountered in the ICU. The hospital is located on the seafront, surrounded by trees and in a location with high humidity, and the patient was hospitalized in July, in the height of summer. Despite the preventative measures taken in the institution, including fly screens, electric insect traps and environmental spraying, the patient developed a myaisis infection.

Nosocomial myiasis is a rarely reported condition that occurs most frequently in immobile and debilitated patients. The oral cavity is rarely affected by parasitic infestation, however, poor oral hygiene and a constant open mouth posture can predispose a person to oral myiasis (7).

In the presented case, the patient was a 96-year-old immobile female with Alzheimer's disease whose lack of adequate swallowing and poor coughing reflex were risk factors for myiasis, exacerbated by her prolonged ICU stay while intubated and her persistent open mouth posture. Consistent with the literature, the patient presented with oral myiasis in the head and neck region (7,8).

Intensive care guidelines offer recommendations for the prevention of nosocomial infections, including fly screens on the windows in the social areas of ICUs, and electric fly traps on the walls in high-risk areas. Open wounds and bodily cavities should be kept clean and closed to reduce the likelihood of myiasis. Treatments of diseases that can cause halitosis, especially sinusitis and pneumonia, can reduce the risk of myiasis. Furthermore, nursing care can be improved by increasing the number of nurses, encouraging vigilance, raising awareness and providing training in infestations and pest control, all of which can reduce the risk of myiasis. Nosocomial infections can have a detrimental effect on the reputation of the hospital and ICU, as well as psychological effects on patients and their families (9,10).

Training programs targeting the prevention of such parasitic infections should include basic information about the classification and spread of infestations, signs indicating the presence of infestations, the role of hygiene rules, and the chemical and the biological control methods, and should be provided by the infection control unit to ICU staff every 6–12 months.

No specific treatment has been identified for nosocomial myiasis, however, the most common approach involved the mechanical removal of the larvae with the help of a clamp. It has been reported that irrigation with ether forces the maggots out, while wounds can be debrided by washing with antiseptic solutions such as normal saline or 0.2% chlorhexidine. Ivermectin is often used due to its larvicidal action (2). Maggot therapy has also been proposed, involving the inoculation of sterile fly larvae into chronic wounds to provide tissue debritment and to induce therapeutic myiasis (8). In the presented case, the patient's oronasal cavity was carefully explored and her mouth was disinfected with 70% ethyl alcohol. No wound, ulcerated lesion or necrotic tissue was found in the oral cavity, and no additional treatment other than oral sanitization was deemed necessary.

CONCLUSION

Nosocomial parasitic infestations are rare but may be fatal in advanced stages, and so appropriate attention should be paid to the prevention and detection of fly larvae in ICUs. Although most cases to date have been reported in tropical regions, non-tropical areas may come to be affected as a result of climate change. For this reason, the awareness of this crucial issue among health care providers should be raised.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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A Case Requiring a Multidisciplinary Approach: Birt-Hogg-Dube Syndrome

Multidisipliner Yaklaşım Gerektiren Bir Olgu: Birt-Hogg-Dube Sendromu

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Abstract

Birt-Hogg-Dubé Syndrome (BHDS) is characterized by benign cutaneous lesions in the head and neck region, pulmonary cysts or spontaneous pneumothorax. It is a rare disorder associated with a mutation in the folliculin (FLCN) gene. A 53-year-old male patient who presented with exertional dyspnea was identified with multiple cystic lesions in a computed tomography (CT) scan, as well as pneumothorax in the right lung. The patient presented again 2 years later complaining of left-side chest pain, and left-sided pneumothorax was identified on imaging. The patient had 2–3 mm papules on his shoulders, cheeks and forehead, and a pathological examination confirmed a diagnosis of trichodiscoma. The patient, who had bullous lung disease, trichodiscoma and a positive FLCN gene sequencing result, was diagnosed with BHDS. We share this case to emphasize the need to consider BHDS in the differential diagnosis of rare cystic lung diseases in patients presenting with recurrent pneumothorax and distinctive cutaneous findings.

Keywords: *Birt-Hogg-Dube Syndrome, Trichodiskoma, Pulmonary Cyst.*

Öz

Birt-Hogg-Dube Sendromu (BHDS); baş ve boyun bölgesi hamartomları, pulmoner kistler veya spontan pnömotoraks ile karakterizedir. Otozomal dominant geçiş gösteren nadir bir hastalıktır. Follikülin (FLCN) gen mutasyonu mevcuttur. Bizim olgumuz 53 yaşında erkek hasta efor dispnesi ile başvurdu. Görüntülemesinde sağ akciğerde pnömotoraks ve bilgisayarlı tomografide multipl kistik lezyonlar görüldü. İki yıl sonra, hasta sol göğüs ağrısı ile başvurdu. Sol akciğerde pnömotoraks görüldü. Hastada omuz, çene ve alın bölgesinde 2-3 mm papül saptandı. Lezyonların patolojisi trichodiscoma olarak sonuçlandı. Büllöz akciğer, trichodiscoma ve pozitif FLCN gen dizilimi olan hastaya BHDS tanısı konuldu. Bu olgu, tekrarlayan pnömotoraks ve belirgin kutanöz bulgularla gelen hastalarda nadir kistik akciğer hastalıklarının ayırıcı tanısında BDHS'nin düşünülmesinin gerekliliğini vurgulamak için paylaşıldı.

Anahtar Kelimeler: *Birt-Hogg-Dube Sendromu, Trichodiskoma, Pulmoner Kist.*

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Birt-Hogg-Dubé Syndrome (BHDS) is characterized by benign cutaneous lesions in the head and neck region, pulmonary cysts or spontaneous pneumothorax. It is a rare disorder with an autosomal dominant inheritance pattern that can be traced to a mutation in the folliculin (FLCN) gene (1,2). Pulmonary manifestations include multiple, irregularly shaped, thin-walled cysts located predominantly in the lower lobes and subpleural regions, along with secondary spontaneous pneumothorax (3). Fibrofolliculoma and trichodiscoma are among the specific cutaneous manifestations (4). Diagnosis is established based on clinical suspicion, imaging, skin biopsy and genetic testing. While BHDS is a rare condition, it should be considered in patients with recurrent spontaneous pneumothorax and characteristic cutaneous findings, as early diagnosis may help prevent complications. Given the potential complications associated with BHDS, clinicians should maintain a high index of suspicion in such patients. We share this case to emphasize the need to consider BHDS in the differential diagnosis of rare cystic lung diseases, particularly in patients presenting with recurrent pneumothorax and distinctive cutaneous findings.

CASE

A 53-year-old male patient presented with exertional dyspnea persisting for 2–3 days. His medical history included hypertension and undifferentiated spondyloarthritis, and he was an active smoker with a 20 pack-year smoking history. A physical examination revealed an absence of breathing sounds in the right lung. His general condition was moderate to good, his SpO_2 was measured at 91% in room air and other vital signs were within normal limits. Laboratory findings revealed pathological values of WBC: 12,310 $\times$ $10^3/\mu$L and CRP: 35.1 mg/L. Imaging revealed pneumothorax in the right lung (Figure 1), and so a tube thoracostomy was performed.

Follow-up computed tomography (CT) scans revealed multiple cystic lesions of varying sizes, predominantly in the subpleural regions of both lungs, with a greater distribution in the lower lobes (Figures 2). After a 2-year lapse in follow-up, the patient returned with new-onset left-sided chest pain, at which time, imaging confirmed a left-sided pneumothorax (Figure 3). A further tube thoracostomy was performed, followed by video-assisted thoracoscopic surgery (VATS). Pathological examination revealed a bullous formation, minimal congestion and inflammation, along with focal mesothelial hyperplasia on the pleural surface. Due to the recurrent pneumothorax and bullous lung involvement, pulmonary function tests (PFTs) were performed for differential diagnosis, revealing a restrictive pattern, and decreased diffusing capacity for carbon monoxide (DLCO) (FVC: 78%, FEV1: 80%, FEV1/FVC: 98%, DLCO: 68%). Alpha-1 antitrypsin levels were measured and found to be within the normal range (1.30 g/L, reference range: 0.9-2).

A physical examination revealed 2–3 mm papules on the shoulders, cheeks and forehead (Figure 4), and a pathological examination of the biopsied material confirmed the diagnosis of trichodiscoma. A FLCN gene analysis was then performed and found to be positive. As a result, the patient, who had bullous lung disease, cutaneous lesions diagnosed as trichodiscoma and a positive FLCN gene sequencing was diagnosed with BHDS. Due to the increased risk of renal malignancies, a renal ultrasound was performed, with normal results. The patient was placed under regular follow-up.

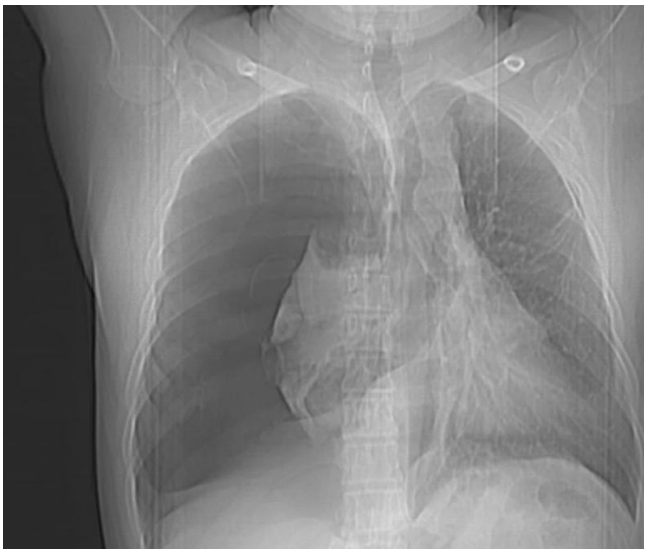

Figure 1: Posteroanterior (PA) chest radiograph showing right-sided pneumothorax

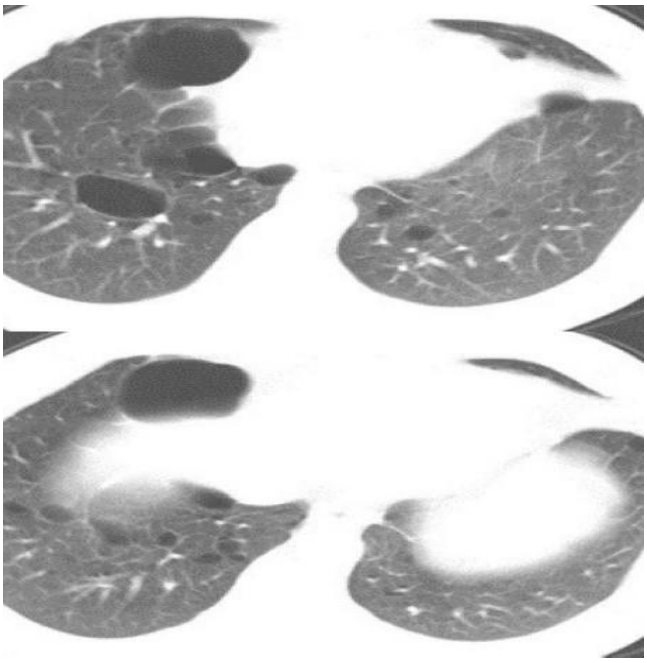

Figure 2: Chest CT demonstrating bilateral pulmonary cysts

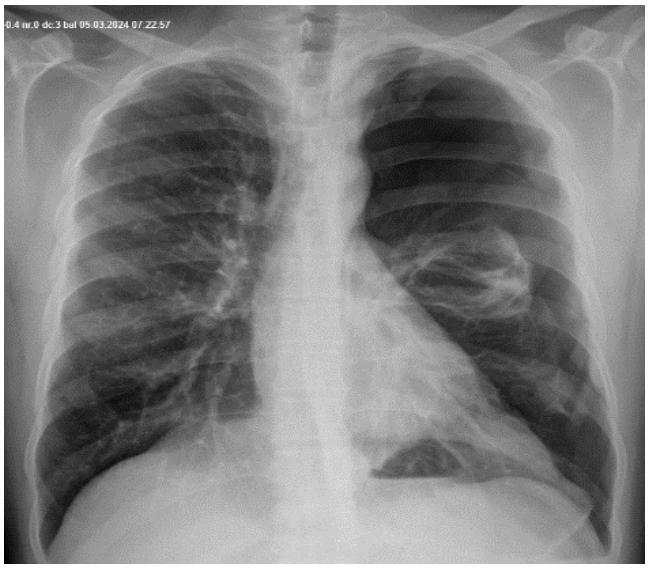

Figure 3: Posteroanterior (PA) chest radiograph showing left-sided pneumothorax

DISCUSSION

BHDS is a rare autosomal dominant disorder characterized by benign cutaneous lesions in the head and neck region, pulmonary cysts or spontaneous pneumothorax, and an increased risk of renal malignancies. A folliculin (FLCN) gene mutation is present in BHDS (1,2). Our patient was found to have trichodiscomas in the head and neck region, along with pulmonary cysts. The FLCN gene mutation was detected as positive. Among the pulmonary manifestations, multiple, irregularly shaped, thin-walled cysts located predominantly in the lower lobes and subpleural regions may be observed, along with secondary spontaneous pneumothorax (3). In our case, bilateral diffuse multiple thin-walled cysts were identified predominantly in the lower lobes, and recurrent pneumothorax episodes were also noted.

BHDS should be considered in the differential diagnosis of cases where pneumothorax is accompanied by bullae, predominantly in the lower lobes and subpleural regions. Patients should be informed about the potential risk of new pneumothorax episodes, and should be advised to avoid activities that involve pressure changes, such as scuba diving and air travel. The presented case highlights the importance of considering BHDS in patients who present with recurrent spontaneous pneumothorax.

Fibrofolliculoma and trichodiscoma are among the specific cutaneous manifestations of BHDS, and in the presented case the pathological diagnosis was confirmed as trichodiscoma. Acrochordons are common skin lesions observed in both the general population and BHDS (1). Acrochordons are not specific for BHDS, and their high prevalence in the general population may lead to delayed diagnosis in the affected. Patients should thus be evaluated for additional symptoms, and further investigations should be carried out when necessary.

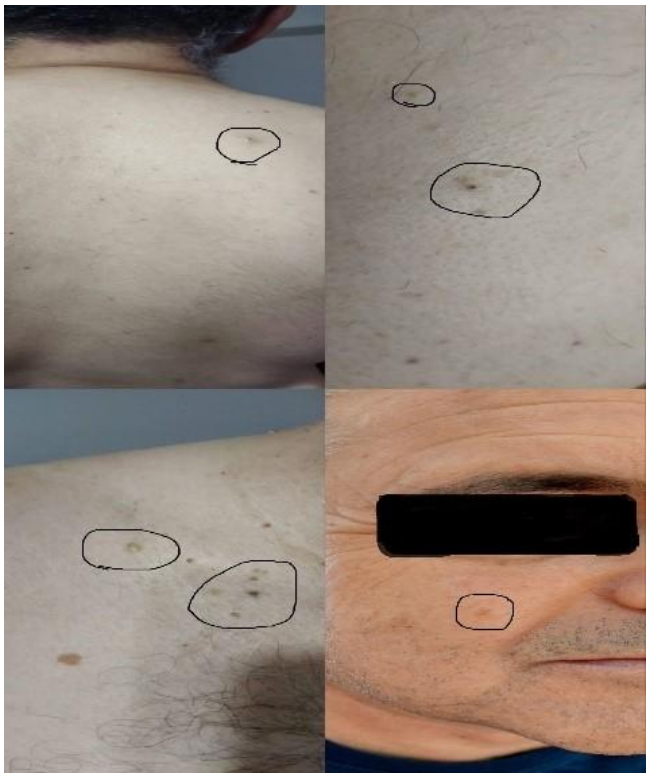

Figure 4: Clinical image showing 2–3 mm papules on the patient's shoulders, cheeks and forehead. The diagnosis of trichodiscoma was confirmed by a histopathological examination

Table 1: Diagnostic criteria of BHDS

BHDS Diagnostic Criteria
For a diagnosis of Birt-Hogg-Dubé Syndrome (BHDS), patients must meet either one major criterion or two minor criteria
Major Criteria
1. Presence of five or more fibrofolliculomas or trichodiscomas, at least one of which is confirmed by histopathology, developing in adulthood.
2. Presence of a pathogenic folliculin (FLCN) gene mutation.
Minor Criteria
1. Presence of multiple, bilateral, and basally located lung cysts, with or without spontaneous pneumothorax.
2. Diagnosis of renal cancer, characterized by early onset (before age 50), multifocal or bilateral presentation, or a mixed chromophobe and oncocytic histopathology.
3. Family history of BHDS in a first-degree relative

The clinical manifestation of greatest concern in BHDS is renal tumors. BHDS is commonly associated with chromophobe and hybrid chromophobe/oncocytic tumors (4). It has also been associated, albeit less frequently, with intestinal polyps, thyroid cysts and nodules, parathyroid adenomas, oncocytomas and melanomas (5). Given the potential presence of malignancies, screening tests were performed in the present case. Patients with BHDS should undergo periodic evaluations for malignancy risk. Diagnoses of BHDS are established based on clinical suspicion, imaging, skin biopsy and genetic testing. The diagnostic criteria determined by the European BHD Consortium are presented in Table 1. In the presented case, the

patient met two major criteria and one minor criterion, and since the diagnostic criteria were fulfilled, the patient was diagnosed with BHDS.

Given the potential complications associated with BHDS, clinicians should maintain a high index of suspicion in patients presenting with recurrent spontaneous pneumothorax and characteristic dermatological findings. Early diagnosis and long-term surveillance are crucial for the prevention of morbidity and appropriate management. BHDS should be considered in patients with cystic lung disease, especially those with a family history or those reporting skin lesions. Recognizing BHDS early can facilitate timely interventions and reduce the risk of severe complications, including renal malignancies, and close follow-up and periodic evaluations are recommended for optimal patient care.

CONCLUSION

BHDS should be considered in a differential diagnosis of rare cystic lung diseases in patients with recurrent pneumothorax and prominent skin findings. Recognizing BHDS early can facilitate timely interventions and reduce the risk of severe complications, including renal malignancies, and close follow-up and periodic evaluations are recommended for optimal patient care.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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