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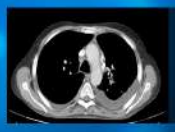

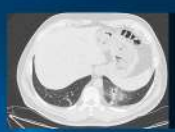

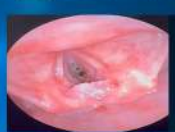

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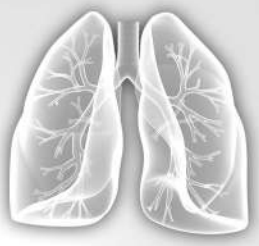

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Rare Coexistence of Kartagener Syndrome and Granulomatous Polyangiitis: A Compelling Case Report

Granülomatöz Polianjit ve Kartagener Sendromunun Nadir Birlikteliği: İlginç Bir Olgu Sunumu

Gülce Cansu Serin, Fatma Arslan, Elif Selçuk, Miraç Öz, Aslıhan Gürün Kaya, Serhat Erol, Aydın Çiledağ, Akın Kaya

Abstract

Primary ciliary dyskinesia (PCD) is predominantly an autosomal recessive disorder that is characterized by recurrent respiratory infections stemming from impaired ciliary motility. Granulomatous polyangiitis is a necrotizing vasculitic disease marked by granulomatous inflammation in the vascular wall that often manifests in the lungs with cavitating nodules, masses and consolidations. A 24-year-old female patient presented to our clinic complaining of dyspnea, productive cough and pleuritic chest pain, and was diagnosed with Kartagener Syndrome based on her situs inversus, bronchiectasis and sinusitis. Subsequent genetic tests and further clinical evaluations, including thoracic CT, revealed findings of cavitating nodules, PR3-ANCA positivity and leukocytic vasculitis from a skin biopsy pathology, confirming the coexistence of PCD and granulomatous polyangiitis.

Keywords: *Granulomatosis with polyangiitis, Kartagener's Syndrome, Primary ciliary.*

Öz

Primer siliyer diskinezi (PSD), yetersiz siliyer motilite kaynaklı tekrarlayan solunum yolu enfeksiyonları ile karakterize çoğunlukla otozomal resesif geçişli bir bozukluktur. Granülamatöz polianjit, sıklıkla akciğerlerde kaviter nodüller tutulumlar, kitleler ve konsolidasyonlar yapan damar duvarında granülamatöz inflamasyon ile seyreden nekrotizan bir vaskülittir. Yirmi dört yaşında kadın hasta, kliniğimize dispne, prodüktif öksürük ve plöretik göğüs ağrısı ile başvurdu. Hastanın situs inversus, bronşektazi ve sinüzit bulguları göz önüne alınarak, genetik testler ile Kartagener Sendromu tanısı konuldu. Toraks tomografisinde kaviteleşen nodüllerinin olması, PR3-ANCA pozitifliği ve cilt biyopisi sonucunda lökositik vaskülit saptanması üzerine PSD ve granülamatöz polianjit tanısı doğrulandı.

Anahtar Kelimeler: *Granülomatöz Polianjit, Kartagener Sendromu, Primer Siliyer Diskinezi.*

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Primary ciliary dyskinesia (PCD) is a predominantly autosomal recessive disease characterized by frequent respiratory system infections resulting from dysfunction in ciliary motility. Its reported incidence in the population is in the range of 1 in 15,000–20,000 live births. Patients may present with chronic rhinosinusitis, infertility and bronchiectasis caused by upper and lower respiratory tract infections (1). PCD accompanied by situs inversus totalis, bronchiectasis and recurrent sinusitis is referred to as Kartagener Syndrome (2). Although PCD is diagnosed in childhood and adolescence, it may also be detected rarely in adulthood. Differential diagnoses in suspected cases are ruled out based on advanced genetic examinations, evaluations of cilia structures by electron microscope and nasal nitrite oxide tests. The mutations most commonly associated with PCD are those of the dynein axonemal heavy chain 5 (DNAH5) and dynein axonemal medium chain 1 (DNA I1) (3). Given the lack of any curative treatment, the primary approach to bronchiectasis secondary to PCD is preventive education to reduce the risk of infections in the patient, and such precautions as frequent routine follow-ups and regular pneumococcal and influenza vaccines. In cases that develop an acute infection, an appropriate antibiotic treatment is applied based on sputum culture results (4).

Granulomatous polyangiitis is a rare necrotizing systemic vasculitis that progresses to granulomatous inflammation in the vessel wall, and can be fatal if left untreated. The prevalence of the disease is in the region of 3/100,000. Patients are usually diagnosed between the ages of 45 and 60 years (5). For a diagnosis of the disease, two of the following criteria must be met: involvement in the sinuses; involvement on chest X-ray or cavitary lesions; presence of hematuria or erythrocytes, along with urinary sediment; and histopathological detection of granulation in the perivascular area around the artery or arteriole, or in the artery itself. Lung involvement may be observed in 50–90% of cases. Patients may be asymptomatic or may present with such symptoms as dyspnea, cough, chest pain and hemoptysis (6,7). Alveolar hemorrhage, single or multiple nodules in the parenchyma, and tracheal or subglottic stenosis may be observed (5). Nodular involvement is observed in 50% of patients. Such nodules can turn into necrotic cavities (7). c-ANCA is detected positive at a rate of 90% in patients with systemic involvement. PR3-ANCA positivity is more specific for disease involvement, and so its diagnostic value is quite high. The disease is treated with corticosteroids in combination with such immunosuppressive agents as cyclophosphamide and rituximab, with reported remission rates of up to 80% (6).

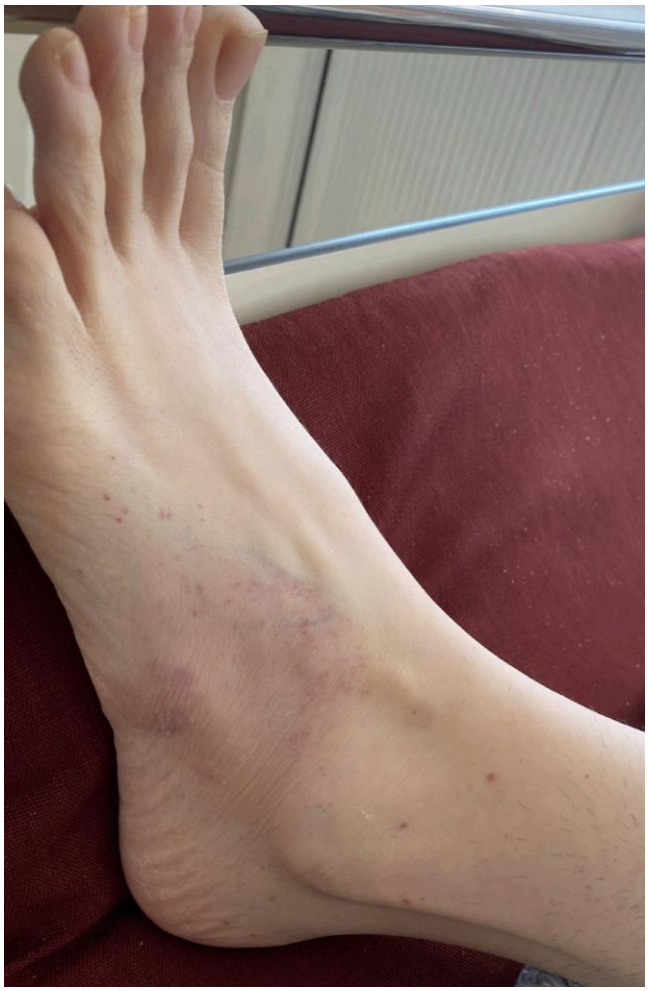

Figure 1: Maculopapular rashes on the lower extremities, unresponsive to pressure

CASE

A 24-year-old female nurse presented to our clinic with complaints of grade 4 dyspnea on the mMRC scale, cough, sputum, pleuritic pain, weight loss and fever, leading to an initial diagnosis of bronchiectasis exacerbation. A review of her medical history revealed a pattern of frequent lung infections, prior hospitalizations and Pseudomonas aeruginosa colonization in recent sputum cultures. The patient had been recently hospitalized for parenteral antibiotic treatments.

Her family history revealed no significant features, other than an aunt with a history of bronchiectasis. A physical examination revealed situs inversus totalis, along with widespread rales and rhonchi in the lungs. Maculopapular rashes on the lower extremities that were unresponsive to pressure were also observed (Figure 1).

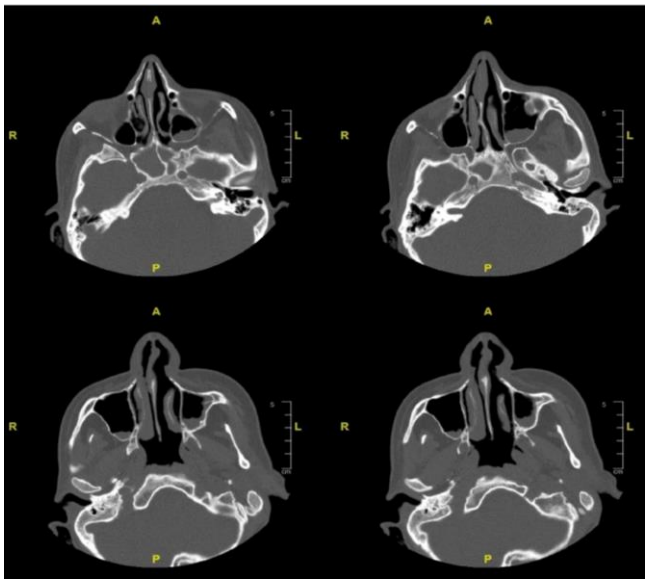

Figure 2: *Paranasal sinus CT-demonstrated sinusitis*

Laboratory tests revealed elevated CRP (290 mg/L), an increased sedimentation rate (57 mm/h), proteinuria (2268 mg/24 hours), albuminuria (980 mg/24 hours) and microscopic hematuria (349 erythrocytes in spot urine). The patient started on empirical parenteral antibiotic treatment with meropenem.

Paranasal CT scans revealed sinusitis, turbinate hypertrophy (Figure 2) and thoracoabdominal situs inversus totalis, as well as thick-walled cavitary lesions with air-fluid levels in the middle-lower zones of both lungs, bronchiectasis, mucus plugs, and nodules with a tree-in-bud pattern (Figure 3).

Systolic pulmonary artery pressure was measured through transthoracic echocardiography at 30 mmHg, and slight tissue thickening in the anterior mitral valve and a mild systolic collapse, not extending beyond the annulus level at its tip, were observed. Abnormal movement of the interventricular septum was noted, while no significant abnormalities were detected in other wall movements. The interatrial septum was found to have an aneurysmatic structure.

Various tests were conducted on the immunosuppressed patient, including sputum culture, sputum acid-resistant bacteria (ARB) screening test, sputum culture for tuberculosis, serum galactomannan level, beta-D-glucan antigen test and CMV-DNA screening. Immune biomarkers were also assessed due to the preliminary diagnosis of vasculitis, given the presence of cavitary nodules on thoracic CT, along with skin rash and sinusitis. Bronchoalveolar lavage was performed using fiberoptic bronchoscopy and Pseudomonas growth was identified in the sputum culture, leading to the initiation of broad-spectrum antibiotic treatment based on the antibiogram.

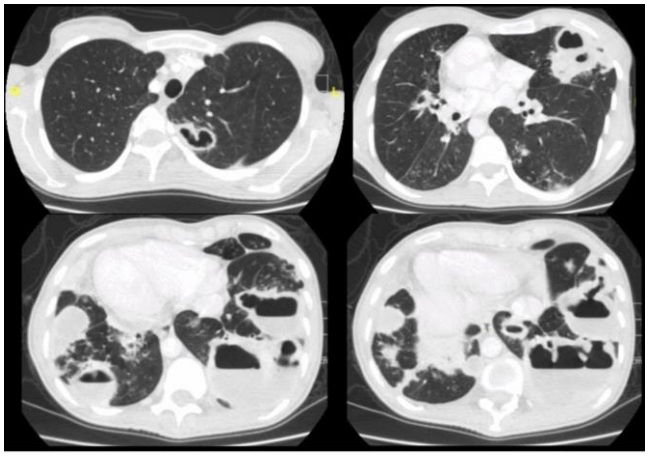

Figure 3: *Thorax CT revealing thick-walled cavitary lesions with air-fluid levels, widespread in the upper-middle-lower zones of both lungs, bronchiectasis and mucus plugs*

The PCD diagnosis was confirmed by genetic tests, which identified mutations in DNAI1 associated with defects in both the outer and inner dynein arms. Additionally, the patient was identified with positive ANCA and PR3 antibodies, proteinuria and hematuria were observed during follow-up, and vascular C3 positivity was detected in the dermal papillae, consistent with leukocytic vasculitis.

Considering the findings, long-term inhaler tobramycin treatment was initiated for P. aeruginosa colonization, and the patient was also placed on systemic steroid and rituximab treatment, leading ultimately to the diagnosis of Granulomatous Polyangiitis. A significant improvement in the patient's clinical condition was noted during follow-up, and an almost complete regression of symptoms. The patient returned to work, and a thorax CT scan at the 8th-month follow-up revealed a reduction in the cavitary lesions (Figure 4).

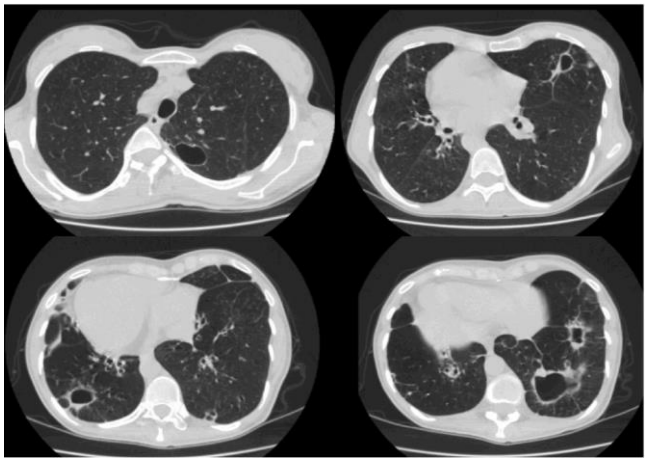

Figure 4: *Regression in the cavitary lesions revealed on thorax CT at 8th month follow-up*

DISCUSSION

PCD is typically diagnosed in childhood and adolescence, but may on rare occasions be diagnosed in adulthood. Characterized by frequent respiratory infections resulting from the impairment in ciliary motility, patients with chronic lung infections in PCD face the risk of lung function loss and structural deterioration in lung parenchyma (1). Controlling chronic infections with appropriate antibiotic treatments is thus crucial. Antibiotic therapy is tailored to previous culture results and sensitivities identified in upper and lower respiratory tract secretions (8).

Tsubouchi et al. (9) reported on a case with PCD and simultaneous intralobar pulmonary sequestration who was started on clarithromycin treatment upon the identification of a Staphylococcus aureus growth in a bronchoalveolar lavage culture for the effective management of the chronic lower respiratory tract infection prior to a surgical intervention. In the presented case, suitable antibiotic therapy was initiated upon the detection of pseudomonas in the sputum culture, and clinically significant improvement and a marked reduction in secretions were achieved.

Ciftci et al. (10) commented on the potential difficulties in diagnosing PCD due to the nonspecific and overlapping of symptoms with those seen in other chronic respiratory conditions, including refractory asthma, atypical cystic fibrosis, pulmonary sequestration, yellow nail syndrome and middle-lobe/lingula syndrome, potentially leading to delayed or misdiagnoses.

While studies in literature reporting concurrent or overlapping systemic vasculitis such as PCD and Granulomatous Polyangiitis are scarce, such systemic diseases should be considered in the differential diagnosis of patients presenting with cavitary and nodular lesions on thorax CT. A review of cases in literature suggests that granulomatous polyangiitis may often be confused with such conditions as lung malignancy, metastasis, sarcoidosis and tuberculosis due to its progression with nodular lesions and granulomatous inflammation in the lungs. Isolated lung involvement can lead to misdiagnosis, and tissue diagnosis and immunological markers should guide the differential diagnosis (11-13). Granulomatous polyangiitis can be fatal if left untreated. In the study by Arunsurat et al. (14) of two cases with systemic organ involvement and pulmonary nodular lesions, one case had nodular involvement accompanied by a cavitary lesion, and despite the initiation of methylprednisolone and cyclophosphamide, the patient yielded to infection after the third course of immunosuppressive treatment. The second case, treated with methylprednisolone and azathioprine, showed significant improvement in lung lesions after 6 months of treatment. Due to the nephrotic-level proteinuria in our patient, methylprednisolone and rituximab treatments were initiated based on rheumatology recommendations. Simultaneously, inhaler tobramycin was started due to persistent Pseudomonas growth in sputum cultures, and both clinical and radiological improvements were observed in the patient.

Recent studies have reported decreased NO levels in the airways of PCD patients. NO plays a role in immune system defense, bronchomotor tonus regulation, ciliary activity and airway clearance. Reduced NO levels may be linked to the neutrophilic inflammation response (15). Although the pathophysiology of granulomatous polyangiitis is as yet not fully understood, antineutrophil antibodies against neutrophilic proteinase 3 and myeloperoxidase enzymes have been associated with disease development (16). This may contribute to an increase in the frequency of coexistence of such rare diseases as PCD and granulomatous vasculitis. Given the rarity of the two diseases, however, it is no surprise that no detailed case studies of the issue were found in literature.

CONCLUSION

Lower respiratory system infections are more prevalent in patients with Kartagener Syndrome due to bronchiectasis and reduced mucociliary clearance. In cases with newly developed cavitary lesions, however, the potential for underlying systemic diseases should be considered. In our case, in which two rare diseases coexisted, significant improvement was achieved with the diagnosis and treatment of vasculitis.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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Necrotising Sarcoid Granulomatosis with Rares Localisations: Skin, Nose and Lung

Nadir Lokalizasyonlu Nekrotizan Sarkoid Granülomatoz: Deri, Burun ve Akciğerler

Lamiyae Senhaji, Mariem Karhate Andaloussi, Bouchra Amara, Mounia Serraj

Abstract

Necrotizing sarcoid granulomatosis (NSG) is a rare disease with non-specific clinical symptoms that may be confused with other conditions, leading potentially to delayed diagnosis. It is characterized histopathologically by sarcoid-like granulomas, vasculitis and varying degrees of necrosis. We present here the case of a 52-year-old male who presented with NSG in rare locations (the skin and nose), discussing not only the clinical, radiological and histopathological features of this rare disease, but also the treatment and prognosis.

Keywords: *Necrotizing sarcoid granulomatosis (NSG), skin, nose, lung.*

Öz

Nekrotizan sarkoid granülomatozis (NSG), nonspesifik klinik semptomlarından dolayı fazlaca ayırıcı tanı veya tanının gecikmesine yol açan nadir bir hastalıktır. Histopatolojik olarak sarkoid benzeri granülomlar, vaskülit ve değişken derecelerde nekroz ile karakterizedir. Nadir görülen NSG lokalizasyonları (deri ve burun) ile başvuran 52 yaşında bir erkek hastayı bildiriyoruz ve bu nadir hastalığın klinik, radyolojik ve histopatolojik özelliklerinin yanı sıra tedavi ve prognozunu da bu yazıda tartışacağız.

Anahtar Kelimeler: *Nekrotizan sarkoid granülomatozis, deri, burun, akciğer.*

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Granulomatous lung diseases have been broadly studied by pathologists, while NSG has attracted less attention among both pathologists and pneumologists. The histopathology pattern is between sarcoidosis and Wegener disease, while clinical and radiological features are non-specific. The present study investigates this little-known pathology, presenting the case of a patient diagnosed with NSG who developed rare extra-pulmonary symptoms.

CASE

A 52-year-old male with a history of pulmonary tuberculosis in 1999 and lymph node tuberculosis in 2018 (histology: granulomatosis without caseous necrosis) presented in 2019 with symptoms that had emerged 6 years earlier, including dyspnea and dry cough, and facial lesions that had appeared 2 months ago. A physical exam revealed crackles on auscultation and erythematous plaque on the face.

Thoracic CT revealed consolidation in the right Fowler segment and multiple bilateral nodules of different diameters that were associated with pleural effusion and mediastinal lymphadenopathy.

A pleural puncture revealed exudate and 2 biopsies carrying out an inflammatory charge without granuloma or caseous necrosis. The biopsy culture and Xpert MTB were both negative.

The endobronchial appearance was found to be normal on bronchoscopy, and the tracheobronchial secretions sent for bacterial and fungal analysis produced negative results. The patient underwent bronchoalveolar lavage, and the fluid was found to be paucicellular and to have a mixed cell population.

A biopsy of the skin lesions revealed a histological appearance suggestive of necrotizing and granulomatous vasculitis, compatible with Wegener disease.

A lesion in the nasal mucosa and perforation of the nasal septum was identified during an ENT examination, and the subsequent biopsy revealed necrotizing vasculitis with granulomatous lesions but an absence of caseating necrosis, suggestive of Wegener disease. The case was ANCA negative.

No treatment was started, and the patient was subsequently lost to follow-up, but presented again in 2023 due to the worsening of his dyspnea.

At the thoracic level, multiple perihilar consolidations crossed by air bronchograms (Figure 1) were identified, associated with multiple nodules and micronodules in the subpleural and peribronchovascular arrangement (Figure 2) associated with calcified mediastinal adenomegaly (Figure 3), a bilateral pleural effusion of moderate abundance and low abundance pericardial effusion, along with Celio mesenteric adenomegaly at the abdominal level. Bronchoscopy and subsequent biopsies revealed granulomatosis with epithelial cells, but with neither giant cells nor caseous necrosis. The pleural liquid was transudative, and an ENT exam revealed the continued existence of the nasal septum perforation. A pulmonary function test revealed low FVC at 1.54 L (36%).

Cranial, cervical, thoracic and abdominal CT scans revealed mucosal thickening in the left maxillary sinus at the facia cervical level associated with the mucosal filling of the left ethmoidal cells and the left sphenoidal hemisinus without adjacent bone lysis (Figure 4).

Echocardiography revealed a medium pericardial effusion with no signs of constriction, while the results of a cardiac MRI were normal.

A laboratory exam revealed all ANA (-), soluble antigen (-), ANCA (-), rheumatoid factor and all bacterial and mucosal specimen findings to be negative.

The case was discussed at a multidisciplinary meeting, and after ruling out a diagnosis of tuberculosis, sarcoidosis and Wegener disease, the patient was diagnosed with necrotizing sarcoid granulomatosis with systemic localizations in the lung (consolidations and nodules on CT), bronchi (biopsy on bronchoscopy revealing a granulomatosis without caseous necrosis), pleura (exudative pleural effusion), heart (pericardial effusion), ENT (perforation to the nasal septum at the ENT examen with a CT showing mucosal thickening in the left maxillary sinus associated with mucosal filling of the left ethmoidal cells and the left sphenoidal hemisinus), lymph nodes (mediastinal lymphadenopathy and celio mesenteric adenomegaly) and skin (rheumatous plaque with a biopsy revealing necrotizing and granulomatous vasculitis). The patient started corticotherapy at a dose of 1mg/kg/day (60mg/day) for 6 weeks, after which degression was begun. During follow-up, the patient improved clinically (he is now asymptomatic and has gained 9 kg in weight), radiologically (disappearance of the pleural effusion, but persistence of the right paracardiac consolidation) and functionally (increased FVC, from 1.54 L before treatment to 2.08 L). The patient's follow-up is continuing due to the risk of relapse.

DISCUSSION

Granulomatous pulmonary conditions can develop alongside many diseases, and while they are most commonly associated with infectious diseases (tuberculosis, fungal diseases) and sarcoidosis, they may also develop alongside such other conditions as hypersensitivity pneumonitis, berylliosis, vasculitic granulomatous disease (GEP, GEPA), rheumatoid polyarthritis, bronchocentric granulomatosis, immunodeficiency (CVID, cancer), iatrogenic (foreign body, drugs) and, of course, necrotizing sarcoid granulomatosis (NSG) (1,2).

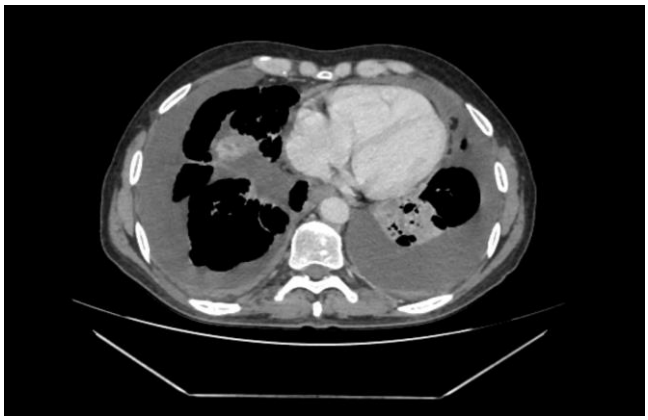

Figure 1: Thoracic CT, mediastinal section showing a moderately large bilateral pleural effusion with perihilar condensation focus

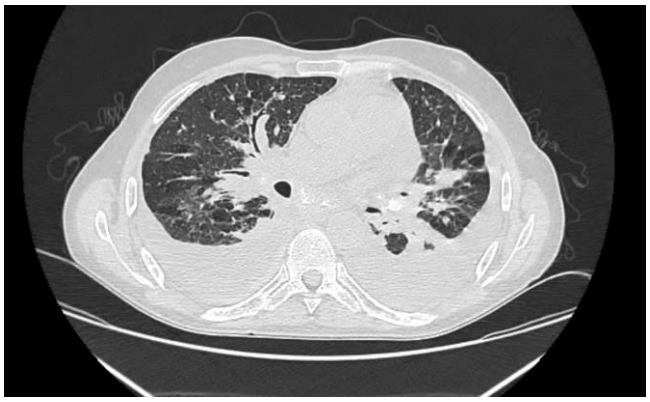

Figure 2: Thoracic CT, parenchymal section of multiple pulmonary nodules and micronodules

NSG was first described by Liebow in 1973 in a study detailing 11 young adults who were presented with respiratory symptoms, all of whom were identified with nodular lesions by a CT scan and histological findings of granulomas, necrosis and vasculitis. He described three criteria for the diagnosis of the condition:

1. Histologically, a background of sarcoid-like granulomatous with marked granulomatous angiitis and varying degrees of necrosis,
2. Radiologically, multiple pulmonary nodules or ill-defined infiltrates but no enlarged hilar nodes, and
3. Clinically, symptoms of cough, fever, sweat, malaise, dyspnea and pleuritic pain, suggest a possible underlying infection but with minimal physical signs (3).

Today, however, there is considerable polemic questioning whether NSG is a disease in its own right, or merely a form of sarcoidosis, specifically a developed form of nodular sarcoidosis (NS). Those who concur with this train of thought claim that there is a degree of overlap between NSG and NS in clinical, radiological and also histopathological terms, as both present with pulmonary and systemic symptoms, as well as nodules, masses, cavitations and pleural effusion among their radiological features. Histopathology, necrosis occurs in classical sarcoidosis, with incidences of 6–35% reported in different studies. The necrosis is minute, spotty and involves a small central portion of granulomas. Granulomatous vasculitis is common in cases of sarcoidosis, and can involve arteries, veins or both. Many studies to date confirm it with reported incidences in the range of 42–69% (4). Therefore, some authors favor the term "sarcoidosis with NSG pattern" over NSG (4,5).

The etiology and pathogenesis of the condition remain unclear, although some authors suggest that certain infections and post-infection immune disorders are involved in the pathogenesis of NSG. Huang et al. (6) reported a reduced peripheral blood CD4/CD8 T cell ratio and increased lesion ratio indicating that the cells migrate from the blood to the organs, especially the lungs due to their large blood content, leading to their more frequent involvement, more frequent disorders and the subsequent formation of granulomas and vasculitis (3,6).

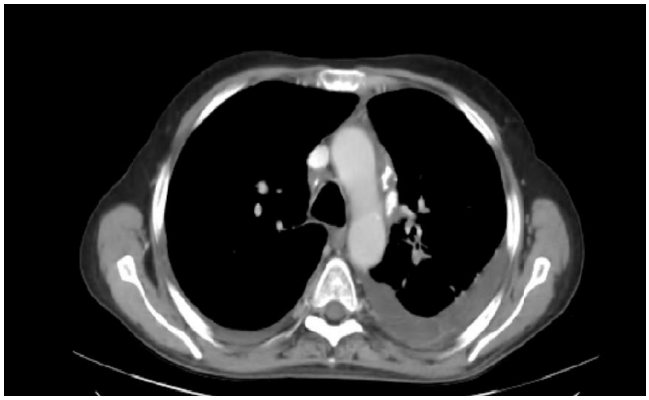

Figure 3: Thoracic CT, mediastinal section showing mediastinal lymphadenopathy

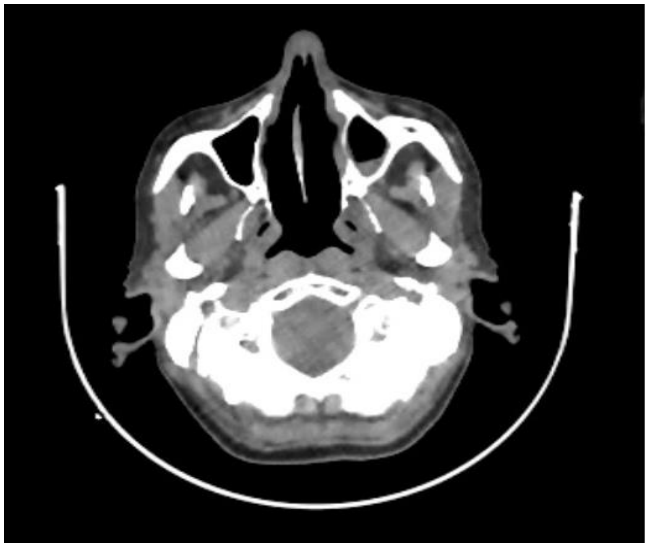

Figure 4: Cervical facia CT showing mucosal thickening in the left maxillary sinus with filling of the left ethmoidal cells, but without adjacent bone lysis

A 2016 metanalysis by Karpathiou et al. (7) including all cases of NSG reported in the English language over the last 43 years (130 reported cases) revealed a median age of 42 years (range 8–68) at the time of diagnosis, a predominance among females (62%), and presentations with cough, dyspnea, fever, chest pain or weight loss. In a case presented by Huang et al. (6), hemoptysis was the main symptom. In other cases, the patients have been asymptomatic, with the discovery of a mass in the lung leading to an investigation, resulting in the NSG diagnosis. The condition may also be associated with such extrapulmonary manifestations as skin erythema nodosum, uveitis and central nervous system (CNS) involvement. Liver, stomach, kidney, heart, nose and spleen involvement are rarely reported (8,9). The case described herein presented with pulmonary symptoms, as well as skin and nose involvement, and actually lymphadenopathy because of the misdiagnosis of lymph node tuberculosis even if the histopathology didn't show caseous necrosis. This fact has been reported in several studies in which patients were started on TB treatment but were subsequently reassessed due to a lack of response, and diagnosed with NSG (10). Our patient underwent antibacillary treatment with clinical stabilization for 1 year.

Radiographic imaging (CT scan) revealed multiple nodules with peribronchial and subpleural distributions in the mid or lower lung fields, while other radiographical manifestations included solitary nodules or masses mimicking lung tumors, leading to an FD/ PET scan in some cases and a surgical biopsy to confirm the diagnosis (5,11,12). Diffuse infiltrates, cavitations, some mediastinal lymphadenopathy (less than sarcoidosis), and pleural effusion or diffuse pleural thickening may also be seen in some cases (13). The pulmonary lesions match our patients'. Our patient also had lesions in the sinus, which are a very rare manifestation.

NSG is diagnosed based on the identification of histopathologically confirmed non-caseating epithelial cell granulomas, granulomatous vasculitis and necrosis. Diagnosis can be difficult in small specimens and mostly requires a surgical biopsy, or assessment of a surgically removed mass. That said, culture, bacteriological and mucosal tests should be carried out to exclude differential diagnoses, especially infections, as well as laboratory exams to eliminate vasculitis granulomatosis diseases, autoimmune diseases, DCIV and other possible candidates (ANA, ANCA, RF, dosage of immunoglobulin) (14). Several specimens showing granulomatous and necrotizing vasculitis were identified in the presented case, while infections in the bronchoalveolar lavage and vasculitis granulomatosis and autoimmune diseases were excluded based on the patient's ANA and ANCA negativity.

The pulmonary function test results reported in several studies include reports of normal pulmonary function, while others mention obstructive–restrictive ventilation deficits, commonly restrictive ventilatory deficits, and frequently, reduced DLCO. All of these conditions improve with treatment. Our patient had a restrictive ventilatory defect that improved after 6 weeks of corticotherapy.

NSG is a disease that can resolve with or without treatment (8). Patients are usually started on corticotherapy at a dose of 1mg per kg per day for an average of 6 months, and usually have a very good response within 2 to 4 weeks. Relapses have been reported upon dose reduction, spurring increased doses or the addition of immunosuppressors such as methotrexate to the protocol to counter the reduction (13). Immunosuppressants may also be needed in some systemic forms of the condition, or in cases that do not respond to corticotherapy. Such situations have been described in a few cases in literature (pulmonary NSG, ocular or neural location) in which the adjunction of cyclophosphamids or similar therapies was required to improve symptoms or to allow a reduction in corticotherapy doses. One described case required cerebral radiation (9). Our patient responded very well to the corticotherapy, but a long follow-up is needed to confirm full resolution or to identify any relapses.

In general, the prognosis of patients with NSG is favorable, and the patient in the present study was no exception. Patients can get better with or without any treatment, although a few may develop complications and die. Studies have reported a poor prognosis, especially in cases with an extended follow-up. A multicentric follow-up study assessing patients followed up for 18–114 months reported the death of one patient due to central nervous system infection, two patients due to lung cancer and four patients due to relapse (6). Other reported deaths are attributed to pneumonia or hemoptysis (9). As such, long-term follow-up is recommended, with further examinations whenever a new pulmonary consolidation, nodule or cavitation appears along with a worsening of symptoms, along with a biopsy (14).

CONCLUSION

NSG is a rare disease that is usually benign but may sometimes have a mortal course. Many organs can be involved, and several features are shared with sarcoidosis. More data-driven studies are required in the future to provide a better understanding of etiology and the associated risk factors for recurrence.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - L.S., M.K.A., B.A., M.S.; Planning and Design - L.S., M.K.A., B.A., M.S.; Supervision - L.S., M.K.A., B.A.,

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

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Hydatid Cyst Mimicking High-Risk Pulmonary Embolism: A Case Report

Yüksek Riskli Pulmoner Emboliyi Taklit Eden Kist Hidatik: Olgu Sunumu

Merve Nur Şahin, Melike Yüksel Yavuz, Ceyda Anar, Onur Turan, Bünyamin Sertoğullarından

Abstract

Pulmonary embolisms take two forms, depending on whether the cause is thrombotic or non-thrombotic. Although emboli with non-thrombotic causes are rare, they should not be ignored during diagnosis. In such cases, a detailed anamnesis should be taken, existing risk factors should be inquired, and additional tests should be made before making a firm diagnosis. In our case, a hydatid cyst embolism that occluded a large part of the pulmonary artery had been identified as a medium–high-risk pulmonary thromboembolism during hospitalization in an external center and thrombolytic treatment had been started. As the patient's symptoms were identified as unresolved during an outpatient clinic check-up, a hydatid cyst was diagnosed based on the results of a transthoracic fine needle aspiration biopsy and treatment was started.

Keywords: *Hydatid cyst, pulmonary embolism, pulmonary artery.*

Öz

Pulmoner emboliler, trombotik ve nontrombotik nedenlere bağlı olarak iki gruba ayrılır. Nontrombotik nedenlere bağlı emboliler nadir görülen nedenler olmakla birlikte tanı sırasında gözden kaçırılmamalıdır. Bu gibi durumlarda detaylı anamnez alınmalı, mevcut risk faktörleri sorgulanmalı ve ek tetkikler ile esas tanı konulmalıdır. Pulmoner arterin büyük bir kısmını tıkayan hidatik kist embolisi olan olgumuzda, dış merkezde yatışı sırasında orta-yüksek riskli pulmoner tromboemboli olarak değerlendirilmiş ve trombolitik tedavi verilmiştir. Poliklinik kontrolünde semptomlarının devam etmesi üzerine transtorasik ince iğne aspirasyon biyopsisi ile hidatik kist tanısı konulmuş ve patolojik tanıya göre tedavi verilmiştir.

Anahtar Kelimeler: *Kist hidatik, pulmoner emboli, pulmoner arter.*

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A pulmonary embolism is a life-threatening cardiovascular emergency in which an obstruction occurs in the pulmonary arterial area. Emboli can take three forms based on their physical structure: solid, liquid (fat embolism) and gas emboli (air embolism). Included within the solid emboli group are thrombi, tumoral formations and cystic formations (1). Hydatid cysts are cystic formations that are mostly found in the liver (70%) and lungs (20%), with the remainder developing in such organs as the spleen and kidneys (10–15%) (2). Literature contains a few reports of hydatid cyst embolisms with intramural involvement of the pulmonary artery in cysts which affect the lung and latter obstructive symptoms like chronic exertional dyspnea. Although rare, this type of pulmonary arterial involvement is life threatening and so should not be overlooked (3).

CASE

A 74-year-old female patient was admitted to our emergency department with fatigue and pain on her left side that had been continuing for 1 week. A physical examination revealed minimal rales on auscultation while other systemic features were normal. Tests revealed blood pressure: 110/80 mm/Hg; pulse: 85/min; and oxygen saturation: 77% in room air. A radiological examination of the patient revealed a lesion that had filled the lumen in the left main pulmonary artery (Figure 1 and 2), which was observed to be completely occluded. An examination of the upper and lower lobes of the left lung revealed 7x5 cm cystic lesions in the left lower lobe posterobasal, and several multiloculated cystic lesions in the apical upper lobe of the right lung that tended to merge peribronchovascularly (Figure 3)

The patient was planned to be hospitalized with a preliminary diagnosis of pulmonary embolism, at which time her medical history was accessed revealing her admission to the emergency department of an external center 1 year earlier due to progressively increasing shortness of breath for 3 months. She had been admitted to the coronary intensive care unit at that time with a preliminary diagnosis of pulmonary thromboembolism completely occluding the left main pulmonary artery. The patient, based on her preliminary diagnosis of massive pulmonary embolism, started on thrombolytics after obtaining her consent and that of her relatives. It was further noted that she had been discharged, and follow-up and treatment were arranged. Her shortness of breath persisted, and a cuticular membrane was observed in a cross-section of the transthoracic fine needle aspiration biopsy cell block taken from the parenchymal lesions with findings compatible with hydatid cyst (Figure 4). An Immune hemagglutination (IHA) test was positive and echocardiography was normal, however, surgery was contraindicated due to her multiple lesions, widespread parenchymal involvement and poor medical condition. The medical treatment of the patient was arranged after taking the opinion of the infectious diseases department, resulting in the prescription of 2x400 mg of albendazole for 3 weeks, followed by a 1-week break, and then the reintroduction of the treatment for 3 weeks. The patient was provided with a home oxygen concentrator due to her continued oxygen requirement, and her discharge was planned.

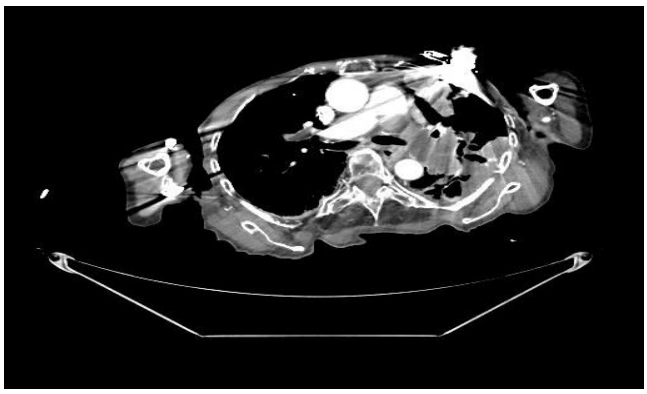

Figure 1: Irregular density increases on axial section consistent with hydatid cyst, causing left pulmonary artery occlusion

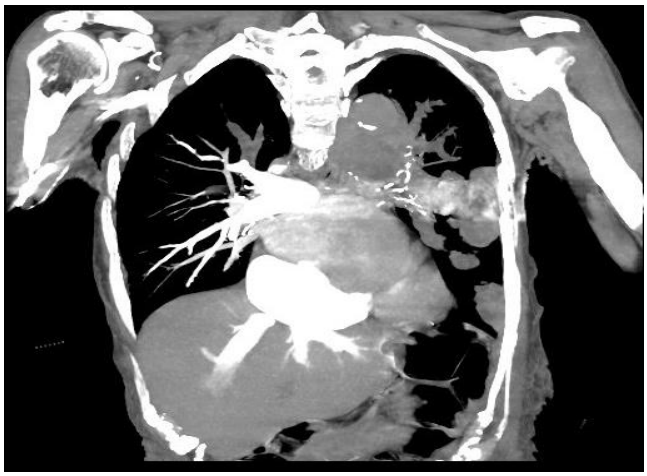

Figure 2: Irregular density increases on coronal section consistent with hydatid cyst, causing left pulmonary artery occlusion

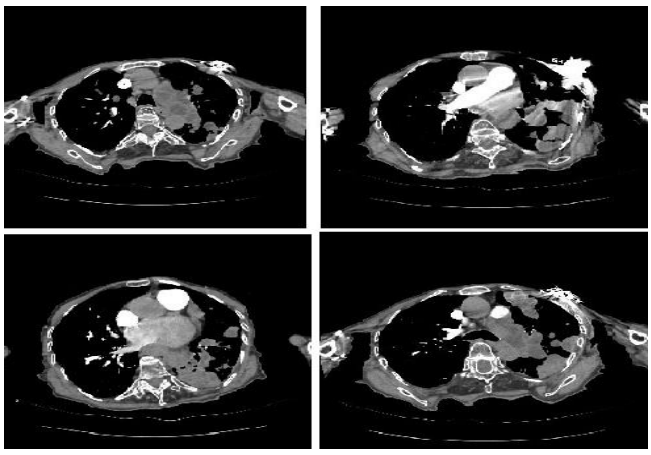

Figure 3: Multiloculated cystic lesion filling the lumen of the left main pulmonary artery, and a peribronchovascular diffuse lesion with a tendency to merge in the upper and lower lobes of the left lung

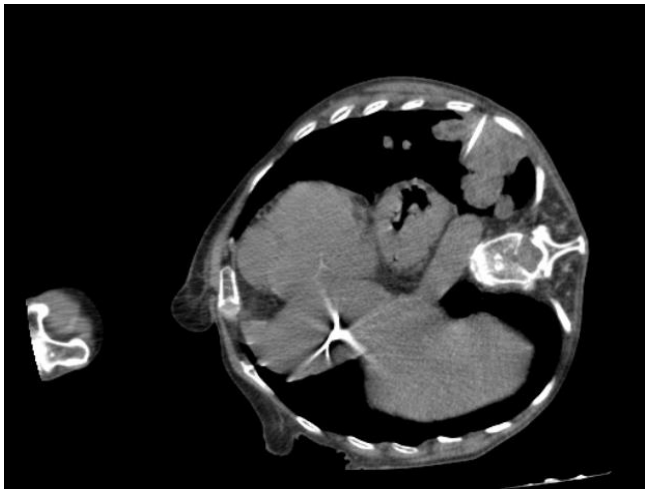

Figure 4: CT-guided transthoracic fine needle biopsy

DISCUSSION

Hydatid cysts involving the pulmonary artery may resemble a pulmonary thromboembolism, and so the differential diagnosis must be made precisely. In the presented case, the erroneous initiation of thrombolytic treatment after the patient's condition was mistaken for thromboembolism may have led to thrombolytic side effects. In such embolism cases, therefore, rare causes such as septic embolism, tumor embolism, cotton wool embolism and hydatid cyst embolism, as non-thrombotic causes of pulmonary embolism, should not be forgotten. A 63-year-old male patient started on heparin and thrombolytic therapy for pulmonary thromboembolism at an external center was identified with a hydatid cyst during follow-up. In that case, the appearance of a 1.5 cm cystic structure adhered to the wall of the intraventricular septum was also found to be compatible with hydatid cyst (4). Hydatid cysts should, therefore, be kept in mind during differential diagnoses to protect the patient from the side effects of incorrect treatments. In cases with hydatid cyst embolisms, as in our case, the primary treatment is surgery, followed by medical treatment. Terminating the life cycle of parasites is the most important step in preventing disease. In the initial period of cyst formation, the patient is usually asymptomatic, and no symptoms develop until the cyst reaches a diameter of 5 cm (5). Symptoms develop due to pressure on the neighboring structures or the development of complications. In our case, the hypoxia and dyspnea that occurred due to the complete occlusion of the pulmonary artery by the cyst were the stimulus. If any suspicions are raised based on the patient's anamnesis and radiological findings, immunological methods such as ELISA, IHA, and latex agglutination and immunoblot tests may be of benefit. Immunological diagnostic approaches are used not only for primary diagnosis, but also for follow-up following surgical and/or medical treatments (5). The positive IHA result following the hospitalization of our patient supported our diagnosis. Lung hydatid cysts grow faster than hydatid cysts in other organs due to the constant intrathoracic negative pressure and the high elasticity of the lung, and the resulting cyst begins to grow, and may perforate spontaneously or in the event of intrathoracic pressure increases, such as coughing (6). Peripherally located cysts that rupture into the pleural cavity can lead to a more serious clinical picture, such as pneumothorax, empyema or pyopneumothorax (7). In the presented case a centrally located cyst invaded the pulmonary artery, and aside from shortness of breath, there were no other obvious clinical findings that would contribute to the diagnosis. It should not be forgotten that the pulmonary artery invasion of a hydatid cyst can occur in all age groups. Çetin et al. (8) reported hydatid cyst involvement in both pulmonary arteries of a 14-year-old female. In the presented case, the 74-year-old female patient had been keeping cats and dogs in her garden for years. Şentürk et al. (3) detected a cystic formation within the left pulmonary artery on Doppler ultrasonography that caused a vascular filling defect and included a pulmonary artery hydatid cyst. In our case, the preliminary diagnosis of hydatid cyst was made based on a pulmonary CT angiography taken while the patient was hospitalized, but after greater knowledge of the patient's history was obtained, a pathological diagnosis was made based on a biopsy of the area in which the cyst was located. Aili et al. (9) reported on a case who was diagnosed with a non-thrombotic pulmonary embolism due to hepatic hydatid disease. The primary treatment for hydatid cysts involves the surgical resection of the area using parenchyma-preserving procedures as much as possible, with the initiation of medical treatment after surgery (10). In the presented case, the patient was considered unresectable due to extensive parenchymal involvement and so was limited to medical treatments. Previous studies have reported oral mebendazole or albendazole therapy to effective treatments for pulmonary hydatid cyst (11,12). Studies show that approximately 70% of patients with pulmonary hydatid disease respond to medical treatment to some extent (12,13).

In conclusion, pulmonary hydatid cyst is a benign pathology that can develop in all age groups and is a non-thrombotic embolus with strong associations with morbidity and mortality if the diagnosis is delayed. The diagnosis and treatment of the condition are thus important, and it should not be forgotten that radiologically, hydatid cysts in the lung can mimic many pathologies, especially malignancies and pulmonary thromboembolisms..

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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Alveolar Hemorrhage and Traumatic Pneumatoceles Following Breath-Hold Diving in Shallow Water

Sığ Suya Serbest Dalış Sonrası Gelişen Bir Alveoler Kanama ve Travmatik Pnömatosel Olgusu

Ece Kaptan[1], Raif Can Yarol[2], Aylin Ozgen Alpaydin[1], Naciye Sinem Gezer[2]

Abstract

Breath-hold diving, known also as freediving, is a form of underwater diving in which one holds their breath, making use of no breathing equipment. The complications associated with breath-hold diving have not been well studied in literature, in contrast to scuba diving. Hemoptysis risk is known to be correlated with deep diving. We present here the computed tomography findings of a breath-hold diver who presented with hemoptysis following a dive to 4 meters, which can be considered shallow in the sport. The patient's chest computed tomography revealed multiple pneumatoceles within the areas of pulmonary hemorrhage. To the best of our knowledge, there have been only a few cases reported to date in which pneumatoceles were identified associated with free diving.

Keywords: *Alveolar hemorrhage, barotrauma, breath hold diving, computed tomography, pneumatocele.*

Öz

Serbest dalış, nefes tutmaya dayalı ve herhangi bir solunum ekipmanı kullanılmadan yapılan bir su altı dalış şeklidir. Tüplü dalışın aksine, serbest dalışın komplikasyonları literatürde yeterince araştırılmamıştır. Hemoptizi riskinin dalış derinliğiyle ilişkili olduğu bilinmektedir. Dört metrelik sığ derinliğe dalmaya sonucu hemoptizi ile başvuran bir serbest dalgıç olgusunu ve bilgisayarlı tomografi bulgularını sunmayı amaçladık. Toraks bilgisayarlı tomografisinde pulmoner kanama alanlarında çok sayıda pnömatosel görülmüştür. Bildiğimiz üzere literatürde daha önce serbest dalışa sekonder pnömatosel gelişen az sayıda olgu bulunmaktadır.

Anahtar Kelimeler: *Alveolar kanama, barotravma, serbest dalış, bilgisayarlı tomografi, pnömatosel.*

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Breath-hold diving (BHD), known also as freediving, is an underwater sport requiring one to hold one's breath without using any breathing equipment. In contrast to scuba diving, studies of the complications of breath-hold diving are few and far between in literature. We report here on the case of a breath-hold diver who developed hemoptysis despite only diving to a shallow depth, and who developed multiple pneumatoceles within the areas of pulmonary hemorrhage. There are only a few studies in literature reporting on the development of pneumatoceles as a result of freediving (1).

CASE

A 46-year-old male freediver was admitted to the emergency room of our university hospital with hemoptysis occurring after a free dive to a depth of 3–4 meters deep. After swimming rapidly 40–50 meters out into the sea from the shore, he quickly dived to the sea floor without resting, holding his breath for longer than any previous attempt, and returned to the surface after feeling pressure on his body. He didn't lose consciousness or swallow any seawater, and there was no cough, chest pain or shortness of breath upon reaching the surface. After taking a deep breath he initially brought up around 100 ml of blood and continued to produce further 5 ml quantities of blood at a time until he swam to shore.

Upon admission to the hospital, his chest was clear on auscultation, and there were no rhonchi or rales. He was not febrile, with a temperature of 36°C and respiration was recorded at 20 breaths/minute. His oxygen saturation was 96% in air, blood pressure was 143/95 mmHg and heart rate was 60 beats/minute. blood tests values were C-reactive protein (CRP) 1.1 mg/L; high sensitivity Troponin-T (HS-TROP) at 7.2 ng/L; creatine kinase MB (CK-MB) 1.3 ng/mL; activated partial thromboplastin time (APTT) 28.86 s; International Normalized Ratio (INR) 1.02; partial thromboplastin time (PT) 11.31 s; white blood cell count (WBC) 7.5 × 103/μL; lymphocyte count 1.2 × 103/μL; neutrophil count 4.4 × 103/μL; hemoglobin 14.9 g/dL; hematocrit 43.0%; and platelet count 242 × 103/μL. A Polymerase chain reaction (PCR) test for COVID-19 was negative.

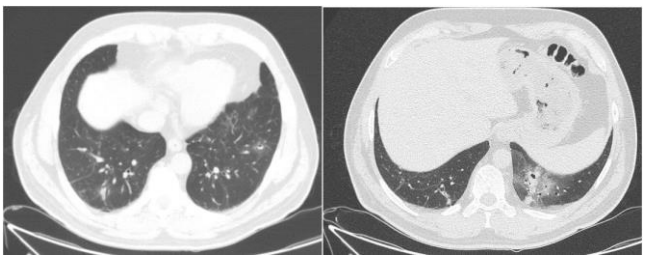

Figure 1: Axial chest CT images revealing pulmonary hemorrhage, presenting as patchy areas of ground glass opacity and consolidation in both lower lobes, and multiple pneumatoceles 3–9 mm in size within the areas of pulmonary hemorrhage

Chest CT images revealed pulmonary hemorrhage, presenting as patchy areas of ground glass opacity, consolidation and multiple pneumatoceles, as can be seen in Figure 1, contrasting a CT scan taken 2 years ago the patient was fitted with a stent following coronary artery disease which showed no consolidations, infiltration or pneumatoceles.

The patient was hospitalized for 3 days, during which there was no hemoptysis, no shortness of breath or cough, and no requirement for oxygen therapy. He was treated with intravenous ampicillin 4 g/sulbactam 2 g per day during his stay and peroral amoxicillin 1700 mg /clavulanate 250 mg per day for a week after being discharged.

The patient had experienced a myocardial infarction 2 years earlier for which he was fitted with a coronary stent and had been treated with acetylsalicylic acid 100mg/d and ezetimibe 10 mg/d since then. Vasculitis markers of anti-extractable nuclear antigen antibodies (ENA), anti-smooth muscle antibodies (ASMA), anti-parietal cell antibodies (APCA), anti-neutrophil cytoplasmic antibodies (ANCA), anti- cyclic citrullinated peptide (Anti-CCP), anti-smooth muscle antibodies (ASMA), anti-mitochondrial antibodies (AMA) and anti-liver-kidney microsome antibodies (LKM) were negative in a blood test, although only the anti-nuclear antibody (ANA) test result was at the lower limit of positivity (with 1/100 titer, stained colored).

A bronchoscopy examination identified no abnormalities in the bronchi of all lobes and segments, other than in the right intermediate bronchus that was identified as aspirated coagulum. There were no endobronchial lesions nor active bleeding during the procedure. A histopathological examination of bronchial washings from all bilateral segmental bronchi was negative for malignancy. Globular iron accumulations were detected in alveolar macrophages with Prussian blue staining, suggesting alveolar hemorrhage.

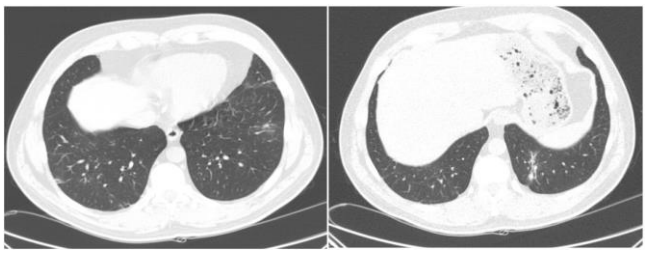

Figure 2: Control chest CT revealing regression of pulmonary hemorrhage and shrinkage of the pneumatoceles 24 days after the initial admission to hospital

The patient was clinically well and had no hemoptysis, shortness of breath or cough 12 days after being discharged from the hospital, and his chest was clear on auscultation. A control chest CT carried out 24 days after the initial presentation revealed a regression of the pulmonary hemorrhage and the pneumatoceles, as shown in Figure 2.

DISCUSSION

BHD is a form of underwater diving that requires the practitioner to hold their breath with no mechanical support. According to Cialoni et al. (2), 26.4% of breath-hold divers develop pulmonary symptoms such as hemoptysis, cough and dyspnea. Other reported complications of BHD are arterial gas embolism (3), orbital emphysema (4) and Taravana syndrome (5), and repeated BHD has been shown to cause brain damage (6).

As divers reach greater depths, the water pressure compresses the lungs and chest. Changes in lung air volume lead to pulmonary barotrauma. Pulmonary edema and hemoptysis result from fluid extravasations into the alveoli secondary to increased transcapillary pressure (7). Hemoptysis risk is known to be correlated with water pressure, and is directly proportional to the depth.

Although hemoptysis is rare when diving in shallow water, it has been found to occur at depths as low as 4 meters. To the best of our knowledge literature contains only one reported case in which hemoptysis occurred following a 3-meter BHD. In that study, the patient was a regular cannabis user and the pathophysiology was attributed to cannabis-induced lung damage (8). Although there was no such history in our case, we believe anticoagulants may have facilitated the bleeding. The fact that we cannot be certain the diver used the correct technique during the dive can be considered a limitation of the study.

Pneumatoceles are intrapulmonary gas-filled cystic spaces that can develop with various sizes and appearances. Traumatic pneumatoceles are pneumatoceles that vary in size, shape, wall thickness and number, and that occur secondary to a traumatic event. They may not be seen until a few hours or even several days after the trauma, being initially obscured by surrounding contusions. They should not be mistaken for cystic lung disease since they are typically asymptomatic and resolve in time, as was the case in our patient. The anti-nuclear antibody (ANA) test result of our patient was at the lower limit of positivity (with 1/100 titer, stained colored), although the patient had no history of chronic constitutional symptoms such as fever, fatigue, joint swelling, pain or hemoptysis that would indicate a rheumatic disease before the traumatic event. As the condition developed immediately after a traumatic event and there were no prior symptoms or radiological indicators, other cystic lung diseases were not considered in a differential diagnosis. Since the PCR test was negative, COVID-19 pneumonia was not considered.

CONCLUSION

Pulmonary hemorrhage is a common complication in breath-hold divers, and is known to be associated with water pressure. The risk of pulmonary hemorrhage rises directly proportional to depth, although it must be kept in mind that shallow diving may also lead to hemorrhage, as in our case.

Traumatic pneumatoceles may be seen on chest CT as a rare complication of BHD, and should not be mistaken for cystic lung disease since they are typically asymptomatic and resolve in time.

Main points:

- Reported complications of BHD are pulmonary hemorrhage, arterial gas embolism, orbital emphysema, Taravana syndrome and brain damage.
- Pulmonary hemorrhage risk is known to be correlated with water pressure, and the risk is directly proportional with depth, although it should be kept in mind that hemorrhage can occur even during shallow dives.
- Traumatic pneumatoceles may be seen on chest CT as a complication of BHD, and should not be mistaken for cystic lung disease since they are typically asymptomatic and resolve in time..

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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Subglottic Stenosis due to Sjögren's Syndrome

Sjögren Sendromuna Bağlı Subglottik Darlık

Görkem Berna Koyun[1], Serdar Berk[1], Şule Karadayı[2]

Abstract

A 36-year-old female patient diagnosed with asthma at an external center was referred to us after her complaints did not improve, at which point, hoarseness was added to the complaints. Stridor was identified in a respiratory system examination. Tracheal stenosis was seen in a postero-anterior chest X-ray and a fixed airway obstruction in a respiratory function test, upon which, the patient was referred to the ear, nose and throat department. Subglottic stenosis was detected on a neck computerized tomography and a bronchoscopy evaluation. The etiology of subglottic stenosis was evaluated, collagen tissue markers were positive, and the patient was asked to undergo a rheumatology consultation. The patient was subsequently diagnosed with Sjögren syndrome based on a salivary gland biopsy result. This rare case is presented to underline the need to keep Sjögren syndrome in mind as an etiology of subglottic stenosis.

Keywords: *Sjögren's syndrome, subglottic stenosis, chest disease.*

Öz

Otuz altı yaşında kadın hasta dış merkezde astım tanısı almış olup şikayetlerinin düzelmemesi üzerine tarafımıza başvurmuştur. Bu süreçte şikayetlerine ses kısıklığı da eklendi. Hastanın solunum sistemi muayenesinde stridor mevcuttu. Postero-anterior akciğer grafisinde trakeal darlık görüldü ve solunum fonksiyon testinde sabit hava yolu obstrüksiyonu mevcuttu. Bu neden ile hasta kulak burun boğaz konsülte edildi. Boyun bilgisayarlı tomografisi ve bronkoskopi değerlendirme sonucunda subglottik stenoz tespit edildi. Subglottik stenozun etiyolojisi açısından değerlendirildi ve kollajen doku belirteçlerinin pozitifti ve hastaya romatoloji konsültasyonu istendi. Tükürük bezi biyopsi sonucu ile hastaya Sjögren sendromu tanısı konuldu. Bu olgu, çok nadir de olsa, subglottik stenozun etiyolojisinden Sjögren sendromu akılda tutulması açısından sunulmuştur.

Anahtar Kelimeler: *Sjögren sendromu, subglottik stenoz, göğüs hastalıkları.*

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Connective tissue diseases are a heterogeneous spectrum of diseases with multiple organ involvement. Laryngeal involvement can be expected in connective tissue diseases, with the most commonly affected area being the cricoarytenoid joint. Failure to recognize laryngeal involvement due to connective tissue may be life-threatening due to the disruption of the airway (1).

Sjögren's syndrome is a chronic inflammatory, autoimmune disease characterized by lymphocytic infiltration of exocrine glands, affecting especially the salivary and lacrimal glands (1). The symptomatic findings of Sjögren's syndrome are diverse, as in addition to glandular findings there are also systemic clinical and extra-glandular findings (2). Dry eyes and mouth are the most common symptoms, caused by lymphocyte infiltration and dysfunction of the exocrine glands (3).

Although lung involvement is common in Sjögren's syndrome, the clinical symptoms are rarely important. The most common form of involvement is diffuse interstitial lung disease. Findings regarding pulmonary involvement in Sjögren's syndrome; It can manifest as interstitial lung disease, obstructive airway disease, pulmonary lymphoma and tracheobronchial dryness (4). The incidence of bronchitis, bronchiectasis, pneumonia and bronchiolitis increases due to the disruption of the secretion clearing mechanism and the drying of secretions (5). Wheezing and dry cough may develop due to the absence of secretions in the larynx, trachea and central bronchial branch points in cases with Sjögren's syndrome (6).

Subglottic stenosis was detected in the examination of the patient in the present study who presented to our clinic with complaints of hoarseness, dry cough and wheezing after being followed-up with a diagnosis of asthma and treatment at an external center. Examinations and consultations to clarify the etiology of the condition led the patient to be diagnosed with Sjögren's syndrome. We present this case of Sjögren's syndrome, a connective tissue disease, to highlight its ability to cause tracheal stenosis and particularly asthma, and due to the rareness of reports covering this condition in literature.

CASE

A 36-year-old female patient, whose consent was obtained for her detailing in this case report. presented to the chest diseases clinic of an external center with a 1-year history of shortness of breath and was subsequently diagnosed with asthma. The patient's complaints did not subside with medical treatment and hoarseness was added to the previously identified shortness of breath upon being hospitalized in our center for further diagnostic tests.

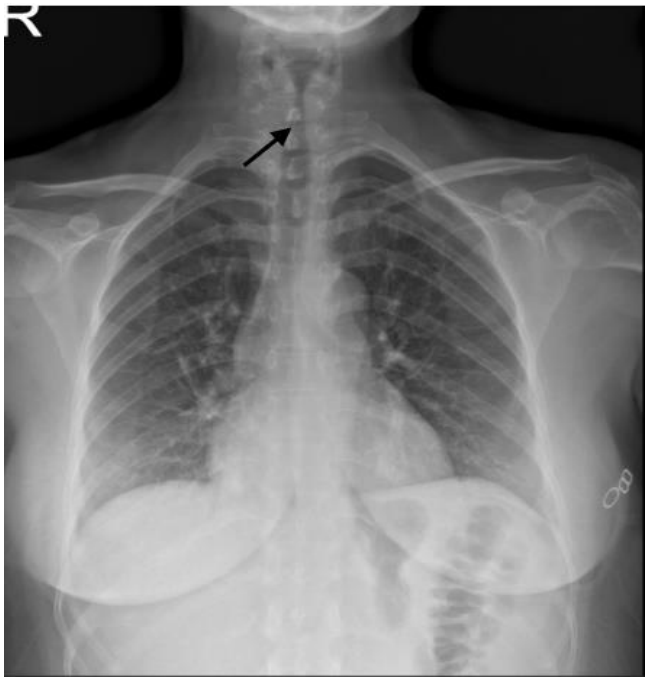

Figure 1: Narrowed lumen opening in the proximal trachea (Black arrow)

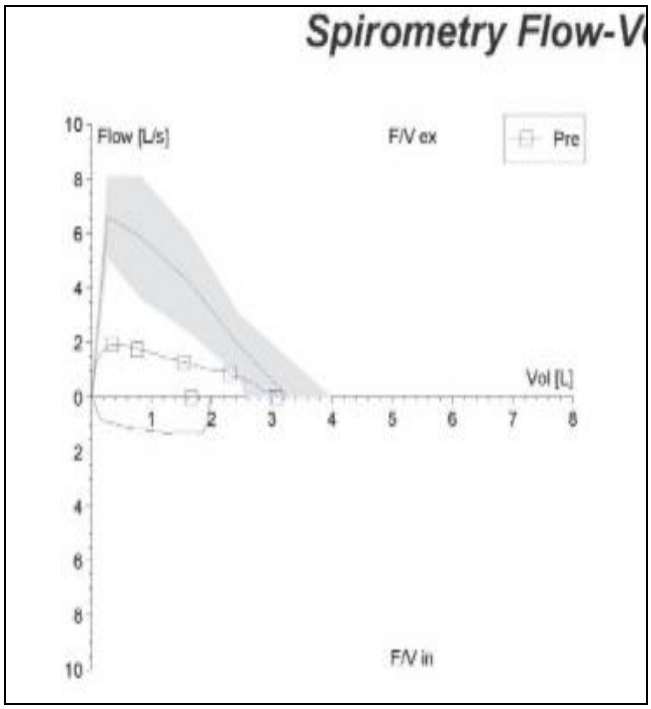

Figure 2: Plateau appearance in inspiration and expiration on spirogram

The patient had a history of hypothyroidism and was using levothyroxine sodium. She had no history of smoking and no history of recent surgery but had given birth to a cesarean delivery under spinal anesthesia 1 year earlier.

Here vital signs on admission were fever 36°C; Ta: 120/85 mmHg; pulse: 75/min; and respiratory rate: 19/min. Inspiratory stridor was identified during an examination of her respiratory system. Other system examination findings were normal, and her routine hemogram and biochemistry results were within normal limits.

A posteroanterior chest radiography was normal other than a suspicious calibration decrease identified in the upper sections of the trachea (Figure 1). In a respiratory function test, although the patient was unable to comply fully with the protocol, a flattening-plateau appearance was noted in both the inspiration and expiration loops in the flow-volume curve (compatible with fixed airway obstruction) (Figure 2).

The patient was asked to undergo an ear, nose and throat (ENT) consultation to identify the etiology of the stridor and hoarseness. A laryngoscopy performed by the ENT revealed stenosis in the subglottic area, and a neck CT was performed on the patient and neck CT interpretation: It was reported that the calibration of the tracheal diameter at the infraglottic level in the larynx decreased and was measured as 7 mm (stenosis?).

Based on the preliminary diagnosis of subglottic stenosis, we conducted a fiberoptic bronchoscopy (FOB) was performed ahead of surgical planning, revealing lesions in the form of mucosal swellings, starting at the vocal cord level, with 2–3 cm involvement proximal to the trachea, narrowing the lumen by 50%, and could not be progressed with bronchoscopy (Figure 3).

Lavage and biopsy were taken from the patient, who was subjected to rigid bronchoscopy and bougie dilation procedures by the thoracic surgeon, and the extracted samples were sent for microbiological and pathological examination, revealing intense mixed cellular inflammation, neovascularization and focal vasculitis-like leukocytoclastic activity in the sub-epithelial connective tissue.

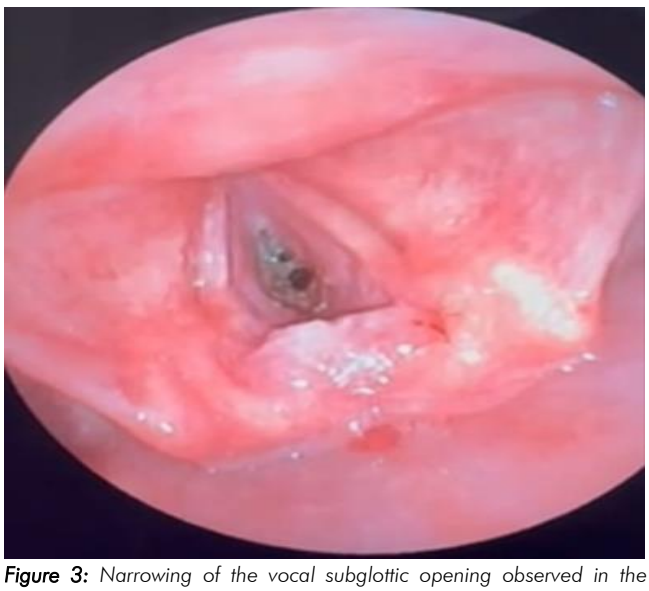

Figure 3: Narrowing of the vocal subglottic opening observed in the FOB

The patient's collagen tissue markers were studied revealing a positive ANA profile, and the SS-A/Ro 52 also came back positive, while the SS-B/La value and other markers came back negative. The patient had no family history of tuberculosis, and the ARB result from the sputum sample was negative with no bacterial growth identified in the sputum culture. Genetic testing for familial Mediterranean fever (FMF) and Behçet's disease were conducted with negative results, a Rose-Bengal test for brucellosis was also negative, and there was no recurrent polychondritis in the patient. When the patient's complaints were questioned in detail, she also reported a dry mouth, whereupon a salivary gland biopsy was performed by the ENT revealing chronic sialadenitis. The patient was diagnosed with Sjögren's disease based on her clinical, laboratory and pathological values by rheumatology, and was started on hydroxychloroquine and pilocarpine. A follow-up neck CT scan was performed at the end of the 4th month after the patient had started treatment, and the stenosis observed on the previous neck CT could not be detected (Figure 4). A control bronchoscopy performed on the patient 3 months later revealed the tracheal passage to be open with no evidence of stenosis (Figure 5). The patient's symptoms regressed with the disappearance of the tracheal stenosis.

DISCUSSION

Connective tissue diseases are known to affect the respiratory system at various levels to varying degrees. Airway involvement, especially in the trachea, is less common than lung parenchyma, and can be more difficult to diagnose. Sjögren's syndrome is a chronic autoimmune disease characterized by the lymphocytic infiltration of the exocrine glands, and especially the salivary and lacrimal glands (1). The effects on the mucus-secreting glands in the upper and lower respiratory tract lead to dryness in the trachea, nose and pharynx, and an increase in the frequency of pneumonia, bronchitis and bronchiectasis due to the disruption of the secretion-clearing mechanism and the drying of secretions (6,7).

In SLE, the most common lesions in the laryngeal region occur in the cricoarytenoid joint and glottis region, although other laryngeal regions may be affected. The symptoms of laryngeal involvement in SLE include hoarseness, dysphonia and sore throat (8). The diagnosis of SLE based on laryngeal findings can be quite difficult, and so micro-laryngoscopy and naso-endoscopy procedures may be required in SLE with upper respiratory tract symptoms (9).

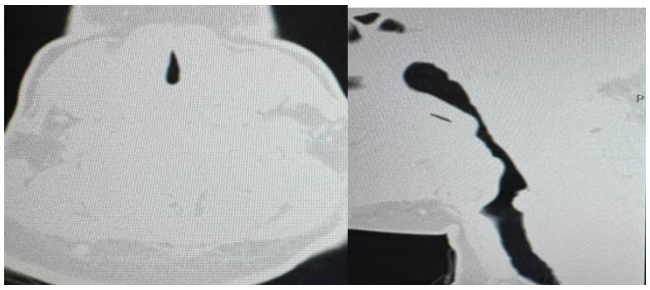

Figure 4: Post-treatment images of the patient's axial and sagittal CT sections

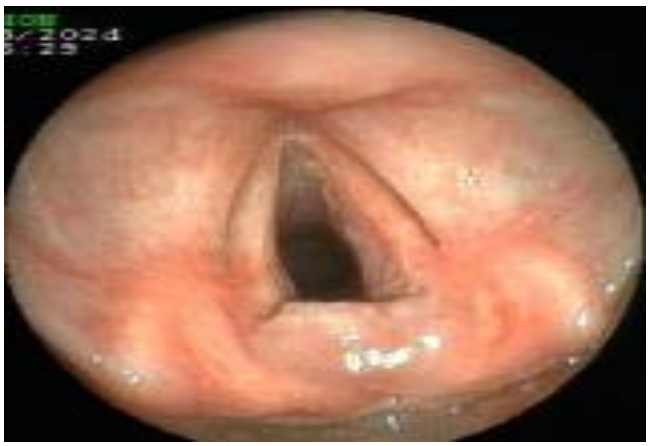

Figure 5: Subglottic opening achieved as observed in the control FOB

The subglottic region is the area extending from the vocal cords to the first tracheal ring. Subglottic stenosis that is unassociated with malignancy can be eliminated with simple surgical procedures (10). Subglottic stenosis is one of the main causes of chronic airway obstruction. Subglottic stenoses are congenital or acquired, intrinsic or extrinsic, and long segment or short segment (11).

The symptoms of subglottic stenosis vary depending on the size of the stenosis, with the most common symptom being aphonia. Stenosis may be confused with asthma and treated as such for years due to the presence of wheezing and cough, but can be correctly diagnosed when exertional dyspnea develops (12). The most common cause of subglottic space stenosis is abnormal wound healing resulting from damage caused by an endotracheal tube or tracheostomy. Other causes of subglottic stenosis include external factors such as malignancy, toxic inhalation, tuberculosis, vasculitis (especially granulomatous polyangiitis), diphtheria, polychondritis, sarcoidosis and goiters (13). Subglottic stenosis may occur alongside systemic inflammatory diseases, but may also be idiopathic. The condition occurs in 10–23% of patients with granulomatosis and polyangiitis (GPA) (14). While ear and nose involvement in GPA patients has a good prognosis, subglottic stenosis is a rare life-threatening finding (15). Subglottic stenosis can also occur alongside amyloidosis, sarcoidosis, cicatricial pemphigoid and inflammatory bowel disease (16), and the management of such forms of stenosis remains challenging, although systemic therapy and interventional endoscopy may be combined for a diagnostic biopsy along with specific procedures to improve morbidity and mortality (14). MALT lymphoma can be counted among the extranodal marginal zone B-cell lymphomas. Extragastric MALT lymphoma is thought to be predominant in such autoimmune diseases as rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome and Hashimoto's thyroiditis. Hematopoietic neoplasms are rarely found in the larynx, particularly in the subglottic region, and. can lead to subglottic stenosis (17). The primary imaging methods requested are lateral neck radiography and anteroposterior lung radiography. Chest X-ray can reveal any narrowing of the air passage in the laryngeal region. After tracheal stenosis has been detected, magnetic resonance and computed tomography imaging can be used to confirm the diagnosis (18).

Dryness and related infections have been found to develop due to the tracheobronchial involvements of Sjögren's syndrome, and may also lead to subglottic stenosis, as in the presented case. Similarly, our case leads us to believe that rheumatological diseases should also be kept in mind when investigating the etiological factors associated with tracheal stenosis. Another inference from this case is that making asthma in patients presenting with complaints such as shortness of breath, cough, wheezing can lead to delays in the correct diagnosis and treatment of the patient. As a final conclusion drawn from the presented case, while asthma may be the initial indication in patients presenting with such complaints as shortness of breath, cough and wheezing, tracheal stenosis should also be kept in mind in the differential diagnosis, and rheumatological diseases such as Sjögren's syndrome should be kept in mind in the differential diagnosis when investigating the etiology of subglottic stenosis.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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Fibrotic Hypersensitivity Pneumonia: Three Cases Diagnosed Histopathologically

Fibrotik Hipersensitivite Pnömonisi: Histopatolojik Tanılı Üç Olgu

Coşkun Doğan, Göksel Menek

Abstract

Hypersensitivity Pneumonia is a lung disease with two forms – fibrotic and non-fibrotic – which predominantly progress with lymphocytic infiltration and granulomatous inflammation as a result of both humoral and cellular response following the exposure of susceptible individuals to any antigen. In cases with the appropriate clinical features, high-resolution lung tomography can aid the diagnosis. Coarse reticulations with irregular linear opacities/lung distortions, traction bronchiectasis and honeycombing, centrilobular nodules, ground glass densities, mosaic perfusions and air imprisonment areas can be counted among the most significant radiological features. Treatment withdrawal is the basis for corticosteroids or immunosuppressive therapies, while antifibrotic agents hold promise as new treatment options in the future. In the present study, the diagnosis, imaging and treatment characteristics of three cases with Hypersensitivity Pneumonia diagnosed using different histopathological methods are reviewed in the light of current literature.

Keywords: *Fibrosis, Hypersensitivity Pneumonia, Interstitial lung diseases.*

Öz

Hipersensitivite Pnömonisi; Duyarlı bireylerde, herhangi bir antijene maruz kaldıktan sonra meydana gelen hem humoral hem hücresel yanıt sonucunda ağırlıklı olarak lenfositik infiltrasyon ve granülomatöz inflamasyon ile seyreden fibrotik ve non fibrotik iki formu olan bir akciğer hastalığıdır. Uygun klinik özellikleri taşıyan olgularda yüksek rezolüsyonlu akciğer tomografisi tanıda çok yardımcıdır. Düzensiz lineer opasiteler/akciğer distorsiyonu ile birlikte kaba retikülasyonlar, traksiyon bronşektazisi ve bal peteği, sentrilobüler nodüller, buzlu cam dansiteleri, mozaik perfüzyon ve hava hapsi alanları önemli radyolojik özellikleri arasındadır. Tedavisinde etkenden uzaklaşma, kortikosteroidler veya immünsüpresif tedaviler temeli oluşturur iken, antifibrotik ajanlar gelecekteki yeni tedavi seçenekleri açısından umut vadetmektedir. Bu yazıda, tanısı farklı histopatolojik yöntemler ile koyulan üç Hipersensitivite Pnömonisinin tanı, görüntüleme ve tedavi özellikleri güncel literatür eşliğinde gözden geçirilmiştir.

Anahtar Kelimeler: *Fibrozis, Hipersensitivite Pnömonisi, İntertisyel akciğer hastalıkları.*

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Hypersensitivity Pneumonia (HP) is an immune-mediated inflammatory and/or fibrotic disease that affects the lung parenchyma and small airways and is caused by an antigen in susceptible individuals. It was previously referred to as extrinsic allergic alveolitis and classified as acute, subacute or chronic, but is today referred to as HP and classified as fibrotic or non-fibrotic. HP may require differential diagnosis, primarily to distinguish it from fibrotic HP (FHP) and other interstitial lung diseases (ILD). HP should be considered in the differential diagnosis of newly identified ILD cases, given its unique diagnostic approaches and treatment options when compared to other ILDs (1). Today, hundreds of organic and inorganic causes have been linked to HP (Table 1) (2).

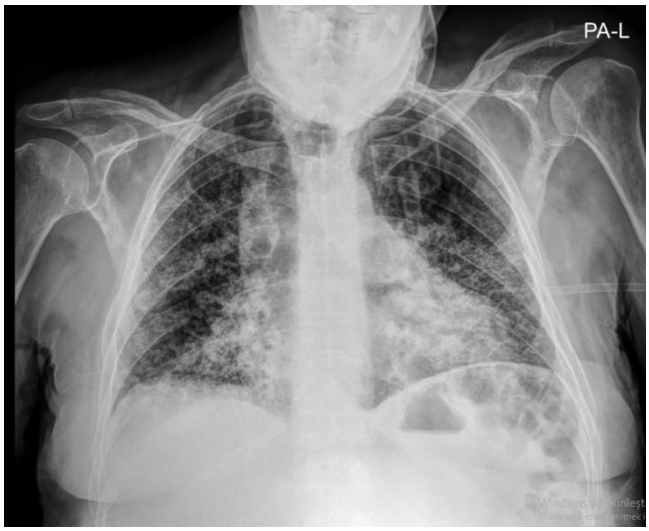

Figure 1a: Chest radiography revealing reticular-reticulonodular infiltration of the bilateral middle lower areas

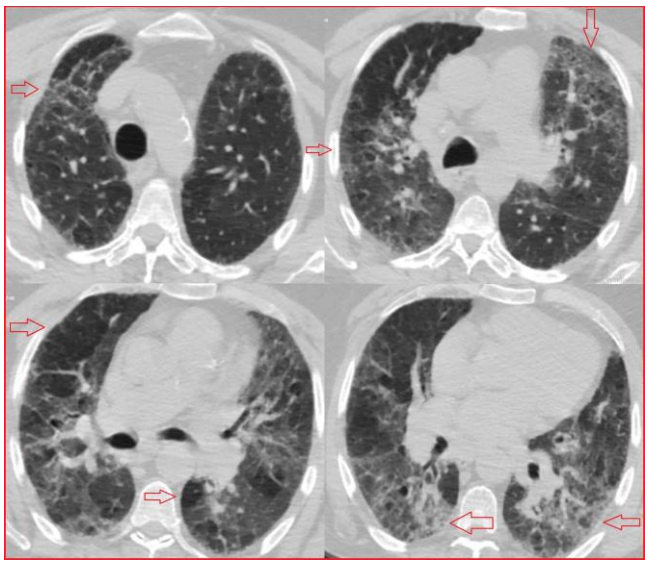

Figure 1b: HRCT revealing linear opacities in the central lung areas, increased reticular density, traction bronchiectasis, ground glass densities, mosaic perfusion and air trapping areas in places

Expected life spans have increased over time with developments in diagnostic procedures, imaging methods and treatment options, and so an increase should be expected in the number of cases with ILD and HP, which is a subheading. The diagnosis and treatment of ILD and HP usually involved multidisciplinary approach (Chest Diseases, Radiology, Pathology, Thoracic Surgery…) (3). In this article, three histopathologically diagnosed FHP cases are presented in the light of current literature to contribute to the body of literature on the diagnosis and treatment of FHP.

CASE

Case 1: A sixty-eight male farmer applied to our center complaining of dyspnea on exertion. The patient had a 20-pack-year smoking history but no significant medical or family history. Although there was no history of animal feeding in the house, he was involved in cattle care and feeding in his work. No drugs or other remarkable exposures within the home were identified. A physical examination (PE) revealed rales in the middle and lower zones of both lungs, beginning mid-inspiration and continuing through to the end. A posterior-anterior chest radiography (PACR) revealed a bilateral reticulonodular appearance (Figure 1a), and a Thorax computed tomography (CT) of the case was reported to be compatible with HP (Figure 1b). Pulmonary function and carbon monoxide diffusion tests (PFT-DLCO) produced the following results: FEV1/FVC: 69%; FEV1: 2.00 L, 72%; FVC: 2.75 L, 78%; DLCO: 3.71 L, 46%; and DLCO/VA: 0.96 L, 78%. No Broncho Alveolar Lavage (BAL) cell analysis was carried out due to the lack of facilities in our hospital, and no Fiberoptic Bronchoscopy (FOB)-BAL was performed as the patient could not have the procedure performed in a private institution. The results of an open lung biopsy of the case, decided upon by the multidisciplinary council, were found to be compatible with FHP. The patient was started on Methylprednisolone 40 mg and advised to steer clear of potentially contributing factors. The patient voluntarily discontinued the methylprenisolone treatment due to side effects in the first month of the treatment, and was followed up without medical treatment. Written informed consent from the patient for their inclusion in the study was obtained.

Case 2: A 67-year-old housewife applied to our center with complaints of dry cough and shortness of breath with effort that had increased gradually over the past year. She was a nonsmoker and had undergone an operation due to breast cancer 10 years earlier. Her father had been diagnosed with lung cancer and had worked in a medical laboratory for 10 years but had retired 22 years ago. The patient had never fed a pet, and denied any environmental or drug exposure. PE revealed clubbing of the toes

and crackles in the bilateral middle lower zones that started at the middle of inspiration and continued until the end. PACR revealed a bilateral reticulonodular appearance (Figure 2a). A Thorax CT of the case was reported as compatible with HP (Figure 2b). PFT-DLCO produced the following results: FEV1/FVC: 75%; FEV1: 1.78 L, 71%; FVC: 2.13 L, 71%; DLCO: 2.69 L, 38%; and DLCO/VA: 0.92 L, 71%. An open lung biopsy of the patient requested by the multidisciplinary council of an external center was reported to be compatible with HP, and the patient was started on Methylprednisolone 40 mg. Written informed consent from the patient for their inclusion in the study was obtained.

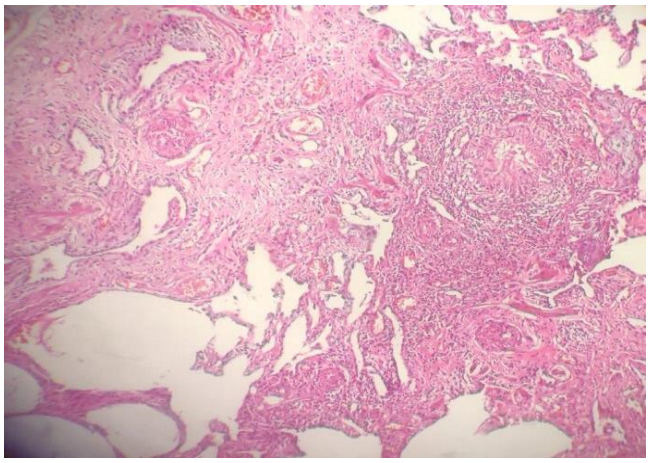

Figure 1c: *Granuloma formation and interstitial lymphocyte infiltration in a case of fibrotic hypersensitivity pneumonitis*

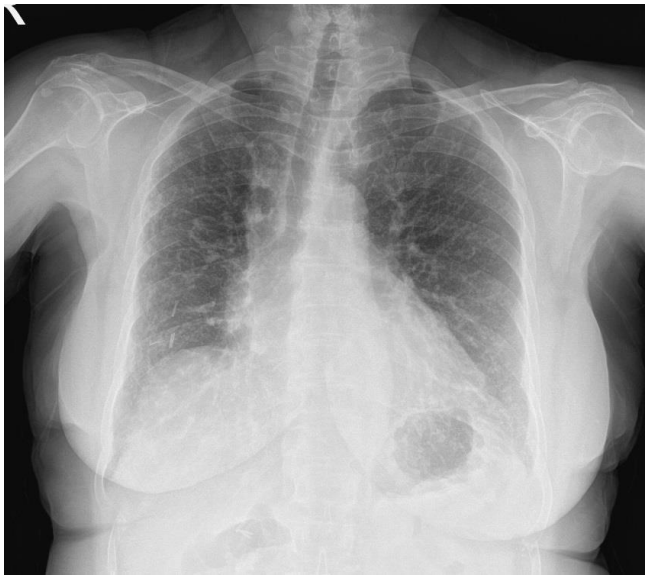

Figure 2a: *Chest radiography revealing bilateral volume loss, more prominent on the right, and reticular infiltration of the peripheral and lower areas*

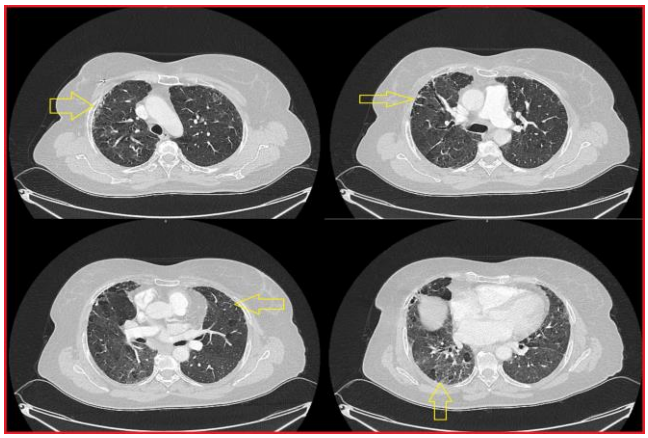

Figure 2b: *HRCT revealing peripherally located fibrotic density increases, traction bronchiectasis, ground glass densities, mosaic perfusion and air trapping areas, mostly in the central lung fields*

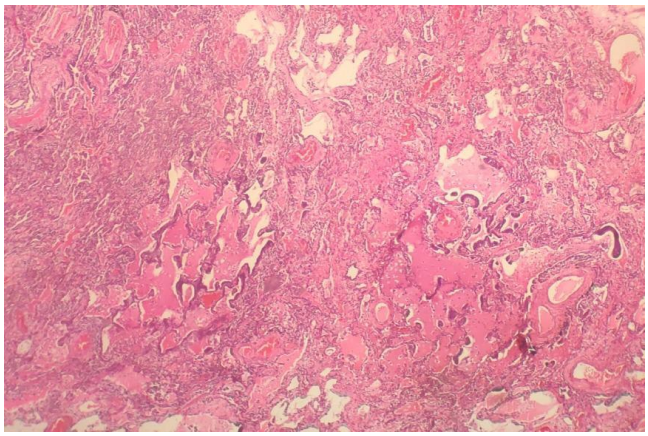

Figure 2c: *Honeycomb areas in a case with FHP*

Case 3: A 68-year-old housewife presented with exertional dyspnea and dry cough that had persisted for 3 years. She was a non-smoker, and her personal and family history were insignificant. There was no history of pet keeping, drug exposure or other notable exposure in the household. A physical examination revealed rales in the middle and lower zones of both lungs, starting mid-inspiration and continuing until the end; PACR revealed a bilateral reticulonodular appearance (Figure 3a); and a Thorax computed tomography was reported to be compatible with HP (Figure 3b). The PFT-DLCO results were as follows: FEV1/FVC: 76%; FEV1: 1.57 L, 108%; FVC: 1.93 L, 123%; DLCO: 16.4 L, 90%; and DLCO/VA: 4.47 L, 99%. A cryo-biopsy was carried out upon the request of the multidisciplinary council, and the results were reported to be compatible with HP. The patient was duly started on Methylprednisolone 40 mg. Written informed consent from the patient for their inclusion in the study was obtained.

*Table 1: Hypersensitivity Pneumonia causes**

Type of antigens	Specific antigens	
Animal protein	Bird protein, chinchilla, flour mite	
Fungi	• Trichosporon spp. • Eurotium amstelodami • Cryptococcus spp. • Absidia corymbifera • Alternaria spp. • Exophiala spp. • Bjerkandera adusta • Sphaerotheca fuliginea • Aspergillus spp. • Fusarium spp. • Candida spp. • Mucor spp. • Aureobasidium pullulans • Phoma spp. • Curvularia lunata	• Ulocladium botrytis • Penicillium spp. • Lichtheimia corymbifera • Rhizopus spp. • Scopulariopsis spp. • Cephalosporium acremonium • Rhodotorula spp. • Humicola fuscoatra • Wallemia sebi • Cladosporium spp. • Chrysonilia sitophila • Paecilomyces spp. • Neurospora crassa • Trichoderma spp. • Peziza domiciliana
Bacteria	• Thermoactinomyces spp. • Streptomyces spp. • Ochrobactrum spp. • Brevibacterium spp. • Pantoea agglomerans • Saccharopolyspora rectivirgula • Acinitobacter spp. • Staphylococcus spp. • Sphingobacterium spiritivorum	• Saccharomonospora viridis • Pseudomonas spp. • Arthrobacter spp. • Enterobacter spp. • Bacillus spp. • Stenotrophomonas spp. • Paenibacillus spp. • Rhanella spp.
Mycobacteria	• Mycobacterium avium complex • M. İmmunogenum • M. gordonae	• M. mucogenicum • M. chelonae • M. Fortuitum
Other antigens	• Mushroom spores • Cork • Sausage dust • Catechin • Hay/damp straw/silage • Metalwork fluid • Wood products • Phytase	• Isocyanates • Corn • Bacilli Calmette–Guérin • Proteolytic enzyme • Water from humidifiers • Wheat/flour • Argan • Tiger nut
Inorganic material exposure	• Wood dust • Flour mite • Proteolytic enzyme • Tiger nut • Konjak flour • Phytase • Chinchilla • Shrimp shell powder	• Sausage dust • Isocyanates • Diisocyanate • Acid anhydrides • Chloroethylenes • Acrylate compounds • Cosmetic products • Catechin phenol compounds

** Adapted from source number*

DISCUSSION

Hypersensitivity Pneumonia, especially FHP, is clinically and radiologically similar to other ILDs, although both the diagnostic and treatment characteristics are different. We report here on three histopathologically diagnosed cases who were followed for 6 years to clarify the current diagnosis, treatment and follow-up approaches to HP in the light of current literature, and to draw attention to FHP.

Table 2: *Chest HRCT Scan Features of the typical nonfibrotic/fibrotic Hypersensitivity Pneumonia**

	Scan Features of the typical nonfibrotic HP Pattern
Description	**The "typical HP" pattern is suggestive of a diagnosis of HP.** It requires *a*) at least one HRCT abnormality indicative of parenchymal infiltration and *b*) at least one HRCT abnormality indicative of small airway disease, both in a diffuse distribution
Relevant radiological findings	**HRCT abnormalities indicative of parenchymal infiltration:** • GGOs • Mosaic attenuation (Mosaic attenuation corresponding to parenchymal infiltration is created by GGOs adjacent to normal-appearing lung) **HRCT abnormalities indicative of small airway disease:** • Centrilobular nodules • Air trapping Distribution of parenchymal abnormalities: Craniocaudal: diffuse (with or without some basal sparing), Axial: diffuse
	Scan Features of the typical fibrotic HP Pattern
Description	**The "typical HP" pattern is suggestive of a diagnosis of HP.** It requires *a*) an HRCT pattern of lung fibrosis (as listed below) in one of the distributions and *b*) at least one abnormality that is indicative of small airway disease
Relevant radiological findings	HRCT abnormalities indicative of lung fibrosis are most commonly composed of irregular linear opacities/coarse reticulation with lung distortion; traction bronchiectasis and honeycombing may be present but do not predominate The distribution of fibrosis may be: • Random both axially and craniocaudally or • Mid lung zone–predominant or • Relatively spared in the lower lung zones HRCT abnormalities indicative of small airway disease: • Centrilobular nodules and/or GGOs Mosaic attenuation, three-density pattern,** and/or air trapping (often in a lobular distribution)

** Adapted from source number 1*
*** The three-density pattern was formerly called the "headcheese sign."*
Indicative of a mixed obstructive and infiltrative process:
a. The obstructive abnormality (seen in small airway disease) is manifested by areas of decreased attenuation and decreased vascularity
b. The infiltrative disorder results in GGO surrounding preserved normal lobules
Highly specific for fibrotic HP; has not been shown to be specific for nonfibrotic HP
GGO: *ground glass opacity,* **HP:** *Hypersensitivity Pneumonia,* **HRCT:** *high resolution computed tomography*

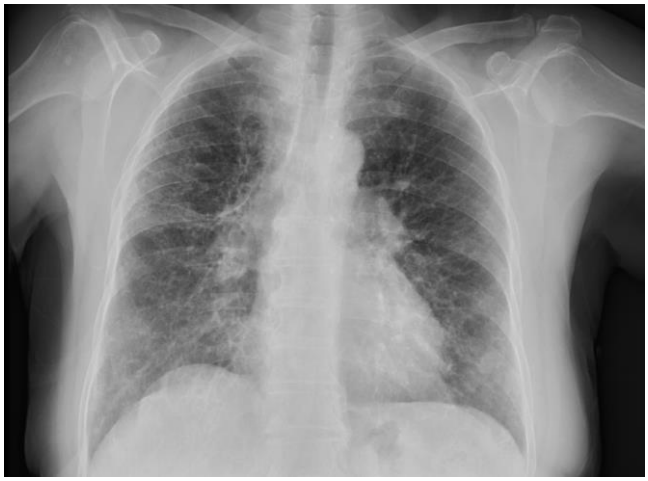

Figure 3a: *Chest radiography revealing reticular-reticulonodular infiltration in all zones, more dominant in the peripheral and middle-lower areas*

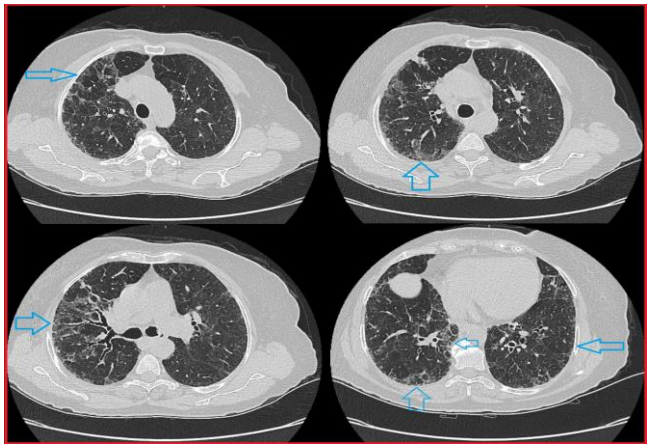

Figure 3b: *HRCT revealing ground-glass densities, traction bronchiectasis, ground-glass densities, mosaic perfusion and air trapping areas mostly in the middle lung fields*

*Table 3: Histopathological Criteria for the Diagnosis of Fibrotic Hypersensitivity Pneumonia**

Typical histopathological features of fibrotic HP; 1 or 2 and 3 in at least one biopsy site:	Both of the following features (1 or 2 from first column) in at least one biopsy site:	Either one of the following features in at least one biopsy site:
1. Chronic fibrosing interstitial pneumonia -Architectural distortion, fibroblast foci ± subpleural honeycombing -Fibrotic NSIP-like pattern 2. Airway-centered fibrosis ±Peribronchiolar metaplasia ±Bridging fibrosi 3. Poorly formed nonnecrotizing granulomas ±Cellular interstitial pneumonia ±Cellular bronchiolitis ±Organizing pneumonia pattern and Absence of features in any biopsy site to suggest an alternative diagnosis • Plasma cells > lymphs • Extensive lymphoid hyperplasia • Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas • Aspirated particulates	1. Chronic fibrosing interstitial pneumonia -Architectural distortion, fibroblast foci ± subpleural honeycombing -Fibrotic NSIP-like pattern 2. Airway-centered fibrosis ±Peribronchiolar metaplasia ±Bridging fibrosi ±Cellular bronchiolitis ±Organizing pneumonia pattern an Absence of features in any biopsy site to suggest an alternative diagnosis • Plasma cells > lymphs • Extensive lymphoid hyperplasia • Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas • Aspirated particulates	1. Chronic fibrosing interstitial pneumonia -Architectural distortion, fibroblast foci ± honeycombing -Fibrotic NSIP-like pattern ±Cellular interstitial pneumonia ±Cellular bronchiolitis ±Organizing pneumonia pattern and Absence of features in any biopsy site to suggest an alternative diagnosis • Plasma cells > lymphs • Extensive lymphoid hyperplasia • Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas • Aspirated particulates

** Adapted from source number 1*

The American Thoracic Society, the Japanese Respiratory Society and the Asociación Latinoamericana del Tórax (ATS/JRS/ALAT), being the most up-to-date practical guidelines, recommend using the term "sensitized individuals" when referring to those with HP. In its pathogenesis, predominantly lymphocytic inflammatory patterns and granulomatous structures are observed as both humoral and cellular (antigen-specific IgG antibodies + T-helper cell type 1 (Th1) cellular immune responses) responses after exposure to any antigen in those who are susceptible (4). As a clinical feature, HP can be defined as a condition that is more common in sensitized older adults (generally in the fifth or sixth decade), in which dyspnea and cough together with mid-inspiratory squeak ral form a triad (1). Other potential symptoms include tightness in the chest, wheezing, weight loss and weakness. There is no specific laboratory value available for a firm diagnosis, although low vital capacity and diffusion capacity identified in PFT-DLCO tests, and lymphocyte dominance in bronchoalveolar lavage fluid obtained bronchoscopically are two important laboratory findings (1,5). Since surgical biopsy and Cryobiopsy were preferred for diagnostic procedures in our cases, any cellular changes in bronchoalveolar lavage fluid are unknown. That said, the clinical and laboratory changes identified supported FHP, in accordance with previous studies in literature.

While no well-defined laboratory test or auxiliary methods exist for the radiological diagnosis of HP, such methods are very useful in diagnostic studies. The currently preferred imaging approach to the diagnosis of HP is non-contrast HRCT. Although inspiratory HRCT reveals all the radiological characteristics of the disease in both FHP and nonfibrotic HP, expiratory HRCT is also recommended, due especially to its ability to reveal air trapping areas in FHP. Radiological features are classified as typical, compatible with HP and uncertain for HP, while typical HRCT findings for non-fibrotic HP (in the presence of at least one parenchyma and one airway change) are parenchyma change, ground glass opacity (GGO) and mosaic perfusion, centrilobular nodules not well defined as airway change and air trapping areas. Typical HRCT findings for FHP include (in the presence of at least one abnormal finding in both lung parenchyma and airways) parenchymal abnormalities such as fibrosis that are axially and craniocaudally randomly distributed; sparing lower lung areas are relatively; coarse reticulations with irregular linear opacities/lung distortion may be present in the middle lung areas, traction bronchiectasis and honeycombing may be present but not dominant and airway pathologies such as centrilobular nodules or GGO or mosaic perfusion, three-density pattern (Formerly head-cheese sign) or air trapping areas are not well defined airway changes. The conditions of all three patients in the present study were classified as standard inspiratory HRCTs prior to histopathological diagnosis, and all had typical HRCT findings for FHP (6,7). The chest HRCT scan results of typical nonfibrotic/fibrotic HP are presented in Table 2.

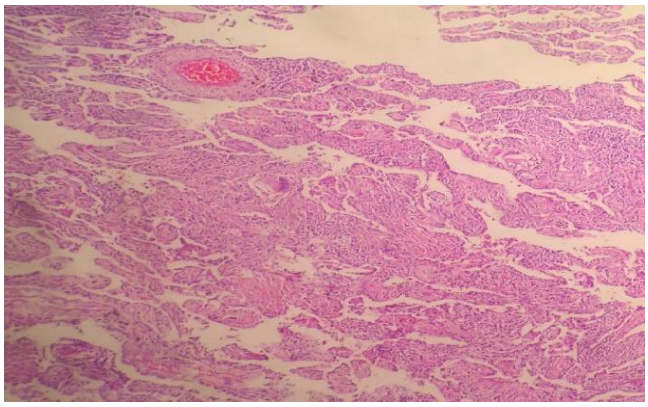

Figure 3c: Multinuclear giant cells, cholesterol clefts, alveolar septum thickening and lymphocyte infiltration in a case with FHP

In all three cases, the diagnosis was made histopathologically (2 cases surgical, 1 case cryobiopsy). Transbronchial biopsy (TBB), cryobiopsy (CB) and open lung biopsy (AAB) are the three options today for the histopathological diagnosis of HP, which can be difficult to diagnose using clinical radiological methods. Studies have reported the diagnostic efficiency of TBB to be in the range of 41–50%, CB to 82–91% and AAB to be 96–98%. As the degree of invasiveness of the method increases, so does the diagnostic efficiency rate, as expected. Today, a careful and comprehensive history is most commonly recommended, alongside radiological (HRCT) investigations and possible environmental factors/exposures. In cases identified with HP, a serum IgG antibody test is recommended against potential antigens associated with HP, along with BAL with a lymphocyte cell analysis. If a definitive diagnosis still cannot be made, TBB, CB or AAB should be taken into account (1,8,9). Fibrotic HP disease can be differentiated from all diseases with radiological interstitial involvement, especially idiopathic pulmonary fibrosis (IPF). In the differential diagnosis of HP from other ILDs, it differs from other ILDs especially with the ability to identify any exposure (exposure identification), specific HRCT findings, and histopathological/BAL cellular findings. Current guidelines related to this issue claim that in the differential diagnosis of HP, a diagnosis of HP will be definite in the presence of typical HRCT findings for HP and a typical HP histopathology in the presence of defined exposure, probable HP histopathology, lymphocytosis in BAL and indeterminate histopathology, Lymphocytosis in BAL without histopathological specimen suggests high confidence HP, indeterminate histopathology without BAL or lymphocytosis in BAL, or moderate confidence HP in the presence of only typical HRCT findings and defined exposure without histopathology (1).

The primary step in the treatment of HP should be the removal of the causative agent/cessation of exposure if the precipitating factor can be identified. Aside from this, while corticosteroids-immunosuppressive drugs can play an important role, studies of antifibrotic drugs are continuing. In non-fibrotic HP, corticosteroids are often the drug of choice, with a treatment regimen of 0.5–1 mg/kg/day prednisone for 1–2 weeks, followed by a gradual reduction to a maintenance dose of 10 mg/day. The fibrotic HP empirical starting dose is maintained for 4–8 weeks, after which it is gradually reduced to the lowest effective dose, usually 10 mg/day. The duration of treatment can be extended (months, years) based on clinical, radiological and functional data, unlike with non-fibrotic HP. There continues to be a lack of consensus on treatment durations. Mycophenolate or azathioprine can be prescribed as alternative immunosuppressive treatment options in cases that respond poorly to corticosteroids or that encounter frequent relapses. Previous studies have reported that antifibrotic treatments may be beneficial in HP cases with advanced fibrosis (10,11). The treatment of choice in all cases in the present study was methylprednisolone.

The diagnosis, imaging and treatments of three cases diagnosed with HP by histopathologic methods are presented here in the light of current literature. HP maintains its importance in routine practice related to chest diseases, due primarily to the difficulties associated with multidisciplinary diagnosis, its frequent confusion with other ILDs and the long-term treatment process.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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Scimitar Syndrome Diagnosed in Adulthood

Erişkin Dönemde Tanı Konulan Scimitar Sendromu

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Abstract

Scimitar syndrome is a congenital heart anomaly characterized by the drainage of one or more accessory veins, usually from the right pulmonary veins, into the right atrium. We present here the case of a 44-year-old patient who was followed up with a diagnosis of asthma but whose dyspnea continued despite treatment and who was subsequently diagnosed by thoracic tomography. It is important to perform additional investigations during the differential diagnosis of patients with respiratory symptoms.

Keywords: *Scimitar syndrome, partial pulmonary venous return anomaly, differential diagnosis of asthma.*

Öz

Scimitar sendromu, doğumsal bir kalp anomalisi olup, genellikle sağ pulmoner venlerden bir veya daha fazla aksesuar venin sağ atriyuma drenajı ile karakterizedir. Bu yazıda, 44 yaşında astım tanısı ile takip edilen ancak tedaviye rağmen nefes darlığı devam eden ve toraks tomografisi ile tanı konulan hasta sunulmuştur. Solunum semptomları nedeniyle takip edilen hastalarda ayırıcı tanıda ek incelemelerin yapılması önem arz etmektedir.

Anahtar Kelimeler: *Scimitar sendromu, parsiyel pulmoner venöz dönüş anomalisi, astım ayırıcı tanısı.*

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Scimitar syndrome is a congenital cardiac anomaly characterized by drainage of one or more accessory veins from the right pulmonary veins into the right atrium (1). In such cases, venous drainage of the right lung is abnormally sent to the right system, leading potentially to such symptoms as pulmonary hypertension, heart failure and severe respiratory distress (2).

Scimitar syndrome is usually diagnosed in childhood, with such symptoms as respiratory and cardiac problems such as respiratory distress, recurrent infections and impaired growth (3). Although the number of cases diagnosed in adults is low, it should be noted that the condition can also occur in adulthood (4).

CASE

A 44-year-old female patient who had been followed up with asthma for 1.5 years presented to our pulmonology outpatient clinic with exertional dyspnea, despite treatment. Head and neck, cardiac and respiratory examinations were normal. One-way posteroanterior chest radiography and pulmonary function test with reversibility were ordered for the patient, who had been followed up in an external center with a diagnosis of asthma, with the following results: FEV1: 65%, FVC: 82%, FEV1/FVC 68% and negative reversibility. The patient had no history of smoking, although chest radiography showed volume loss in the right lung (Figure 1). Thorax CT was ordered for further examination, the results of which pointed to Scimitar syndrome, with decreased right hemithorax volume (Figure 2), and the drainage of some pulmonary veins in the right hemithorax into the hepatic vein (Figure 3). The patient was referred to the cardiology outpatient clinic for further investigation and treatment, where a patent foramen ovale and thrombus in the interatrial septum were identified on echocardiography. A decision was made to continue with an anticoagulant, and for intermittent follow-up with echocardiography.

DISCUSSION

Scimitar syndrome, referred to also as pulmonary venous drainage anomaly, is a rare congenital cardiovascular malformation characterized by the partial or complete drainage of the right-sided pulmonary veins into an anomalous venous channel, typically the inferior vena cava (5). In our case, in the right lung, vena cava drainage was observed. Scimitar syndrome occurs in 3/100,000 cases, however, the number of cases detected does not reflect the real numbers due to its asymptomatic course (6,7). Scimitar syndrome is characterized by the following unique features: partial or total abnormal curved venous drainage of the right lung into the inferior vena cava; correlation with hypoplasia of the pulmonary arteries and varied right lung; dexterity of the heart; and unusual blood supply to the ipsilateral lung throughout the body (8). In our case, hepatic vein drainage was noted in the right lung and pulmonary artery hypoplasia, although the heart was normally located on the left.

The clinical presentations of Scimitar syndrome can be widely varied, ranging from asymptomatic incidental findings to severe respiratory distress and pulmonary hypertension. Heart abnormalities can lead to various symptoms, and diagnosis is typically made in childhood (infantile form). In those who exhibit the infantile form, the condition is typically associated with pulmonary hypertension and has a worse prognosis due to the greater severity of the illness. Adult diagnoses (adult version) are less common, and patients typically present with less severe symptoms or not at all (9). Our case was admitted with the complaint of shortness of breath.

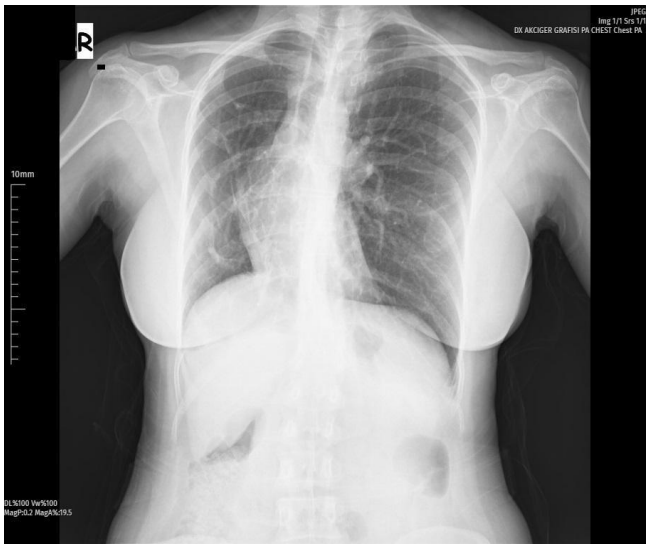

Figure 1: Chest X-ray image taken at the time of application revealing decreased right hemithorax volume and the deviation of the mediastinum to the right

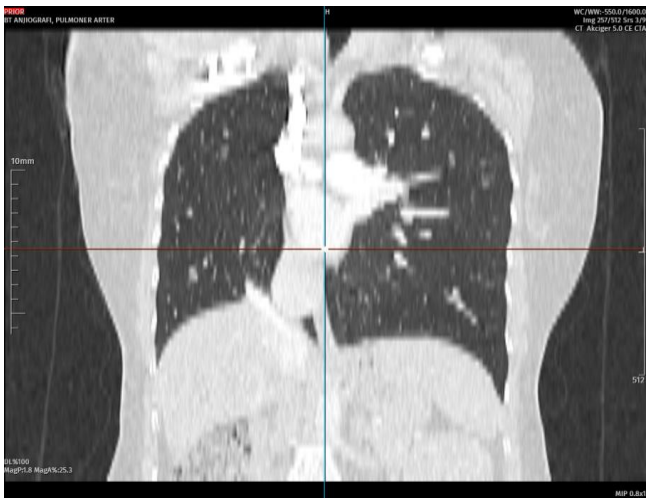

Figure 2: Patient's thorax CT parenchyma images showing the mediastinal structures displaced to the right. Evaluation of the sections in the lung parenchyma window revealing reduced right hemithorax volume

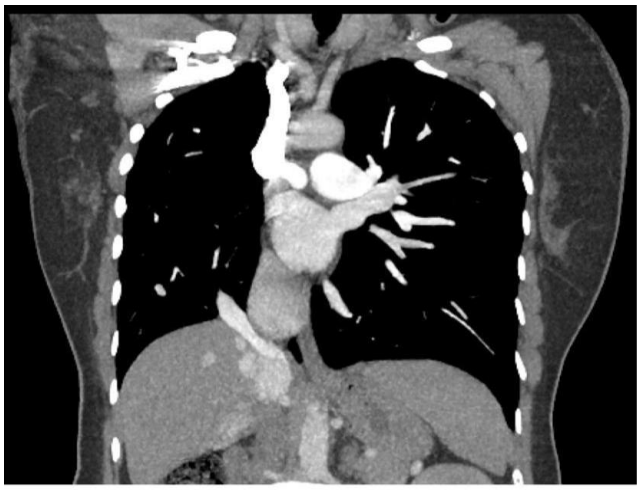

Figure 3: Mediastinal structures displaced to the right. The sectional evaluations in the lung parenchyma window reveal the right hemithorax volume to be reduced. In the right hemithorax, the pulmonary veins drain into the hepatic vein. This appearance is typical of Scimitar syndrome

Echocardiography is the primary diagnostic modality and is often supported by advanced imaging techniques such as computed tomography or magnetic resonance imaging for the delineation of anatomical details. In some cases, anomalous pulmonary venous drainage may not be visually apparent, necessitating the use of contrast echocardiography to confirm the diagnosis (10). The diagnosis of our case was made without the need for contrast-enhanced echocardiography.

The accurate diagnosis and prompt management of Scimitar syndrome are crucial, as significant morbidity and mortality can develop if left untreated (9). The management of Scimitar syndrome is complex and may require a multidisciplinary approach. Surgical correction may be necessary in patients with significant hemodynamic compromise or pulmonary hypertension, typically involving the redirection of the anomalous pulmonary venous drainage to the left atrium. Surgical interventions can be a safe and effective approach to some conditions, and are most commonly performed in children. Adult-age therapies may also be needed, especially in symptomatic patients (5). Our case was also decided to be followed up due to a mild clinical course.

CONCLUSION

Scimitar syndrome is a rare cardiac anomaly that may also be detected in patients presenting with respiratory symptoms. For this reason, angiographic and cardiologic investigation of patients with suspected Scimitar syndrome is vital. Respiratory diseases such as asthma and chronic obstructive pulmonary disease in patients with respiratory symptoms tend to be prioritized due to their frequency, although additional investigations such as pulmonary function tests and chest radiographs are important in a differential diagnosis. As Scimitar syndrome can lead to serious complications if left untreated, accurate and early diagnosis are important for treatment and follow-up. Patients diagnosed with Scimitar syndrome should be treated with a multidisciplinary approach and subjected to long-term follow-up.

In our study, the appropriate evaluations and examinations were performed in all branches, without limitations, although echocardiography images of the patient could not be obtained due to technical problems.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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RESPIRATORY CASE REPORTS

Patient-based Assessment of Treatment Options for Pulmonary Sequestration: Two Case Reports

Pulmoner Sekestrasyon için Tedavi Seçeneklerinin Hasta Bazlı Değerlendirilmesi: İki Olgu Sunumu

Shukur Musayev[1], Halil Bozkaya[2], Kutsal Turhan[3], Özgür Samancılar[1]

Abstract

Pulmoner sekestrasyon (PS), nadir görülen bir konjenital pulmoner displazidir. PS, en önemli özelliği vaskülarizasyonu olan konjenital pulmoner displazinin nadir bir formudur. Genellikle torasik ve abdominal aortadan kaynaklanan atipik arterlerle vaskülarizasyon görülür. PS'nin interlobar (ILS) ve ekstralobar (ELS) olmak üzere iki formu vardır ve bunlar visseral plevra ile ilişkilerine göre ayırt edilebilir. Besleyici damarların cerrahi rezeksiyonu ve ligasyonu bu durum için standart tedavilerdir. Bu çalışmada, farklı sekestrasyon tiplerine sahip iki olgu, tedavi seçeneklerinin gözden geçirilmesiyle birlikte sunulmaktadır.

Keywords: *Pulmoner sekestrasyon, embolizasyon, video yardımlı torakoskopik cerrahi.*

Öz

Pulmonary sequestration (PS) is a rare congenital pulmonary dysplasia. The most important feature is vascularisation with Pulmonary sequestration (PS) is a rare form of congenital pulmonary dysplasia, with the most significant feature being vascularization with atypical arteries, generally originating in the thoracic and abdominal aorta. There are two forms of PS, interlobar (ILS) and extralobar (ELS), which are distinguishable based on their relationship with the visceral pleura. Surgical resection and ligation of the feeding vessels are the standard treatments for the condition. In the present study, two cases with different sequestration types are presented along with a review of the treatment options.

Anahtar Kelimeler: *Pulmonary sequestration, embolization, video-assisted thoracoscopic surgery.*

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Pulmonary sequestration (PS) is characterized by a bronchial anomaly, parenchymal dysgenesis and vascularization of abnormal systemic artery. It accounts for less than 6.4% of all pulmonary congenital malformations (1). Such cystic structures are localized in the posterior basal segment of the right and left lung lower lobe in 80–90% of cases (2). The ILS form is more common (75–84% of the total), with 74% of feeding arteries identified as arising from branches of the thoracic aorta (3). The most common symptoms of PS include cough or expectoration, fever, hemoptysis and chest pain. Herein, we present a case of ILS with a systemic artery originating directly from the thoracic aorta, and an ELS sequestration with multiple branches of systemic arteries supplied from the abdominal aorta, both of which were safely resected in our clinic.

CASE

Case 1: A 49-year-old non-smoking male was admitted with cough and hemoptysis. Laboratory results were normal, while a thorax computed tomography (CT) scan revealed limited lung parenchyma in the right lower lobe that was typical for ELS (Figure 1a, b and c). The dominant artery supplying the sequestrated lung tissue was found to arise from the abdominal aorta. It was decided to perform an endovascular embolization as the first step and VATS resection on the following day.

Celiac trunk and phrenic angiographies were obtained selectively using a hydrophilic guide wire and an angiography catheter. A peripheral microcatheter (with microwire) was sent through the diagnostic catheter using the coaxial technique and a super selective catheterization was performed. A control angiogram revealed that the aberrant systemic artery was divided into three branches and supplied sequestration (Figure 2a). Each involved artery was super selectively embolized with mechanical peripheral fibrillar coils, and a post-embolization angiogram revealed the sequestered pulmonary tissue to be completely embolized (Figure 2b).

One day after the embolization, a sublobar resection was carried out with minimally invasive surgery. After double lumen intubation, the patient was placed in the left-lateral decubitus position. An extralobar sequestration connected to the lower right lobe was detected during the operation (Figure 3a). The adhesions of the lobe to the diaphragm were dissected and the branches coming from the abdominal aorta were exposed through three-port video-assisted thoracoscopic surgery (VATS) (Figure 3b). The atypical arteries were divided with a stapler and the sequestrated segment was resected. The patient was discharged on the third postoperative day. A pathological examination revealed an extralobar sequestration. No hemoptysis recurred within the one-year follow-up period.

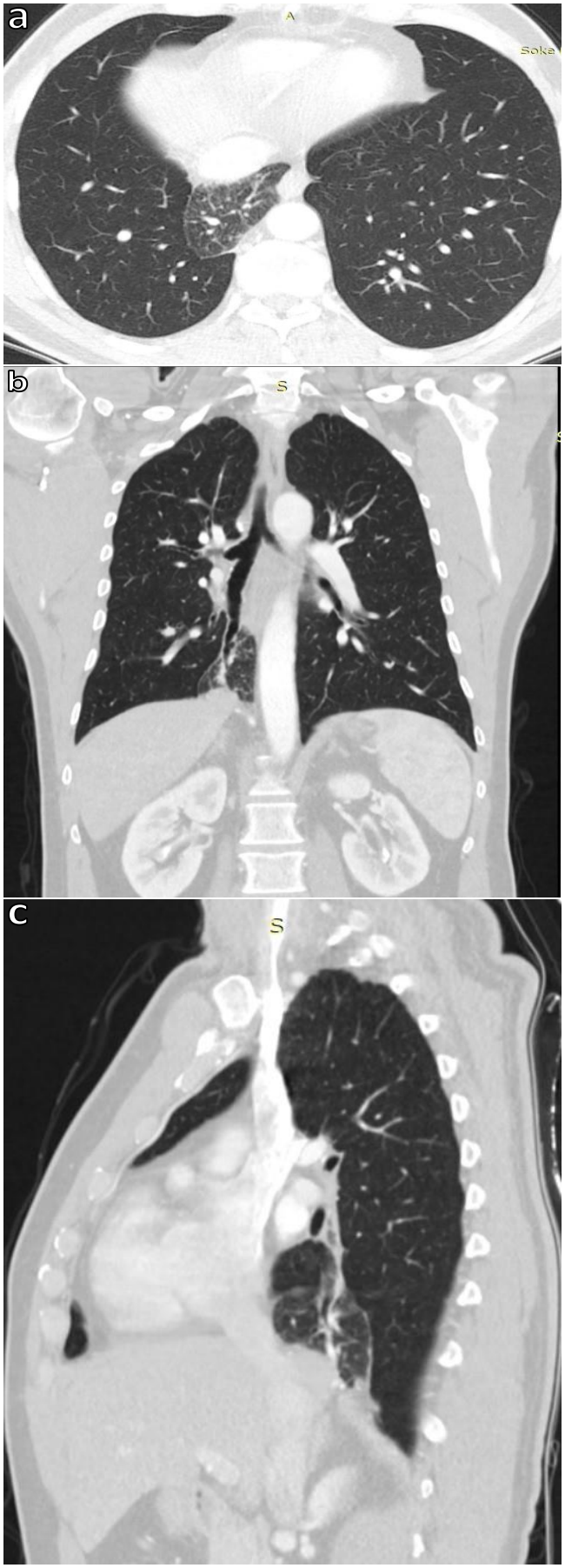

Figure 1a: *Views of right lower lobe ELS on thoracic CT image; axial* ***(a)****,* ***(b)*** *and sagittal* ***(c)***

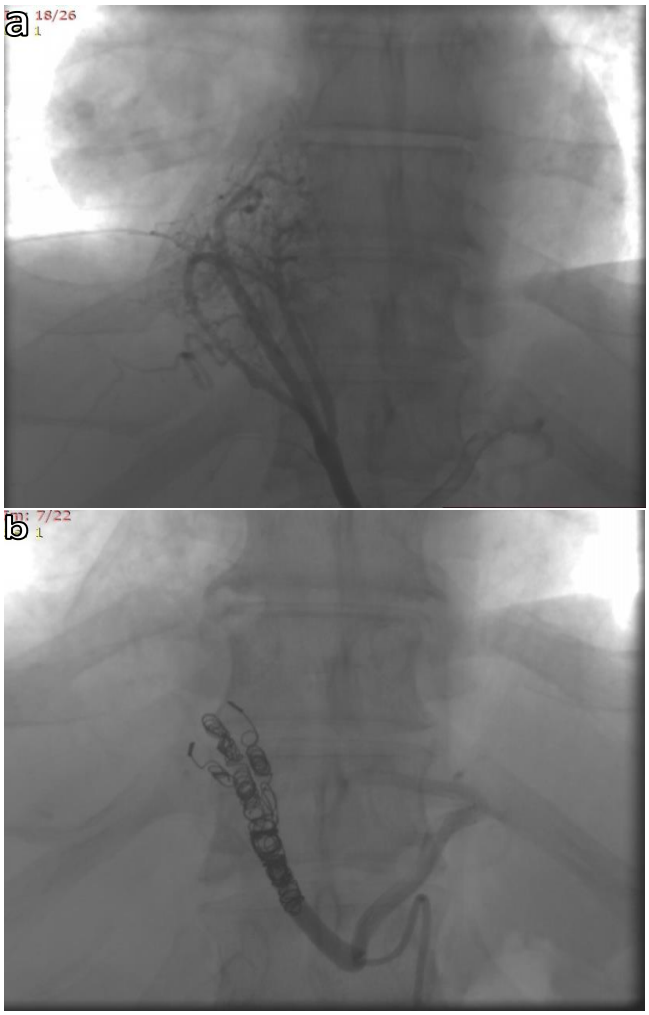

Figure 2: Angiography of the aberrant artery during embolization; Feeding artery on control angiogram (a), Artery after embolization with a coil (b)

Case 2: A 35-year-old non-smoking female patient was admitted to our clinic with a history of repeated left-sided pneumonia. The cause of the pneumonia was investigated with a CT scan that revealed diffuse and prominent segmental cystic bronchiectasis in the lower lobe superior and anteromediobasal segments of the left lung, and partially in the posterior basal segment in the paravertebral areas and perihilar regions. The lesion was seen to be supplied by a 5.9 mm diameter systemic artery arising directly from the thoracic aorta, and was identified as ILS (Figure 4a, b and c). The patient was planned to undergo left lower lobectomy by VATS.

After double-lumen intubation, one utility and two port incisions were made on the left side. Upon exploration, the left lower lobe was identified as destroyed and ineffective, and an abnormal aberrant branch directly originating from the thoracic aorta was noted to be supplying the lobe. The feeder arterial branch was first dissected and devised with a vascular stapler (Figure 5a and b), after which, the left lower lobe was resected with a left lower lobectomy. The patient was discharged on the fifth postoperative day. A pathological examination revealed an intralobar sequestration in the left lower lobe. The patient was noted to be in good health throughout the 6-month follow-up.

DISCUSSION

PSs are rarely encountered malformations that are supplied by atypical arteries originating from the thoracic aorta, and more rarely from the abdominal aorta. The location of arterial supply and venous drainage should be determined preoperatively, and so preoperative imaging studies are of vital importance. In our first case, three arteries originating from the abdominal aorta were found to supply the ELS, while in the other case, a 5.9 mm diameter artery originating from the thoracic aorta was found to supply the ILS.

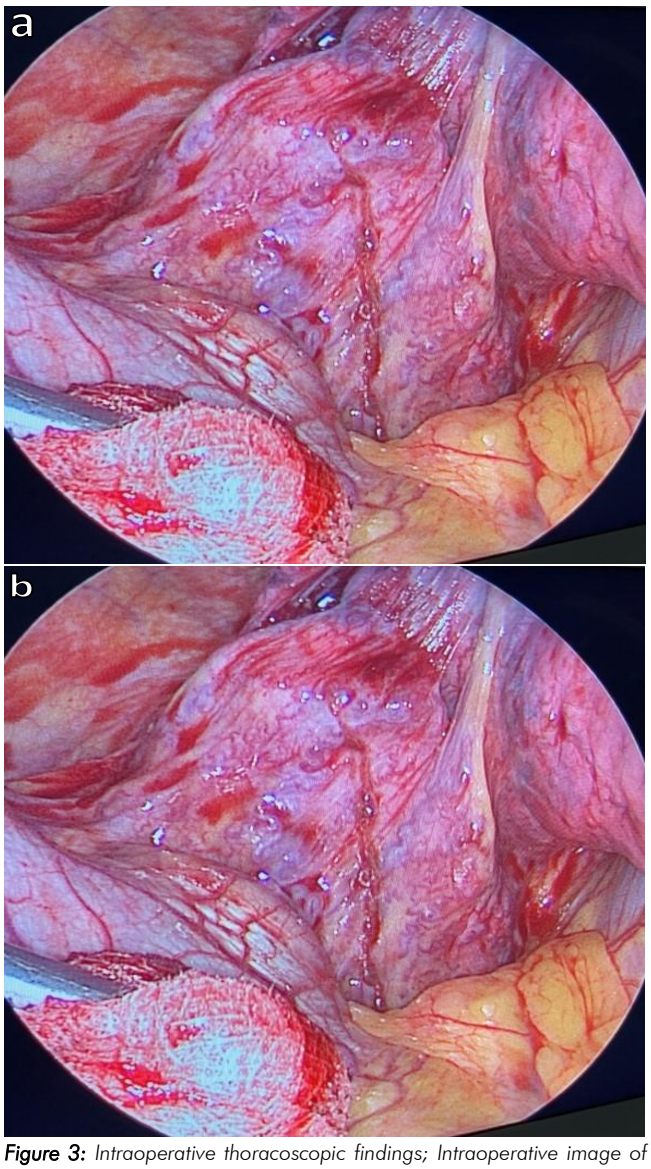

Figure 3: Intraoperative thoracoscopic findings; Intraoperative image of ELS (a), feeding artery arising from the abdominal aorta (b)

Currently, the most widely accepted treatment for PS is surgical resection, which can prevent possible infection. In the treatment of PS, both conventional thoracotomy and VATS can be used for the sublobar resection or lobectomy. In a study by Zhang et al. (4), 15 patients underwent thoracotomy and six underwent minimally invasive surgery within 2 years. The authors reported VATS to be a better approach than thoracotomy for PS resection with the continuous development of thoracoscopic techniques. The outcomes of the minimally invasive surgery detailed in the present study support the findings reported Zhang et al., related to the easy pain palliation, shorter hospitalizations and aesthetic advantages.

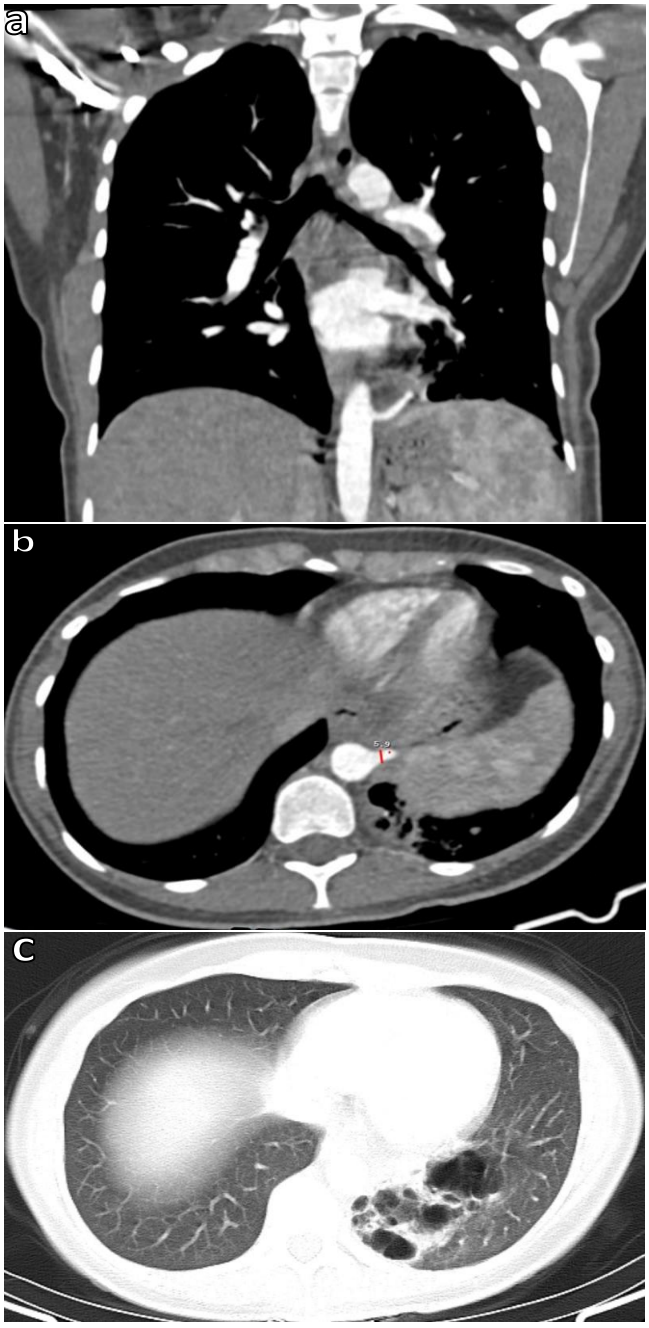

Figure 4: *Coronal and axial view of the feeding artery on a thoracic CT image* ***(a, b and c)*** *diffuse and prominent segmental cystic bronchiectasis on a thoracic CT image*

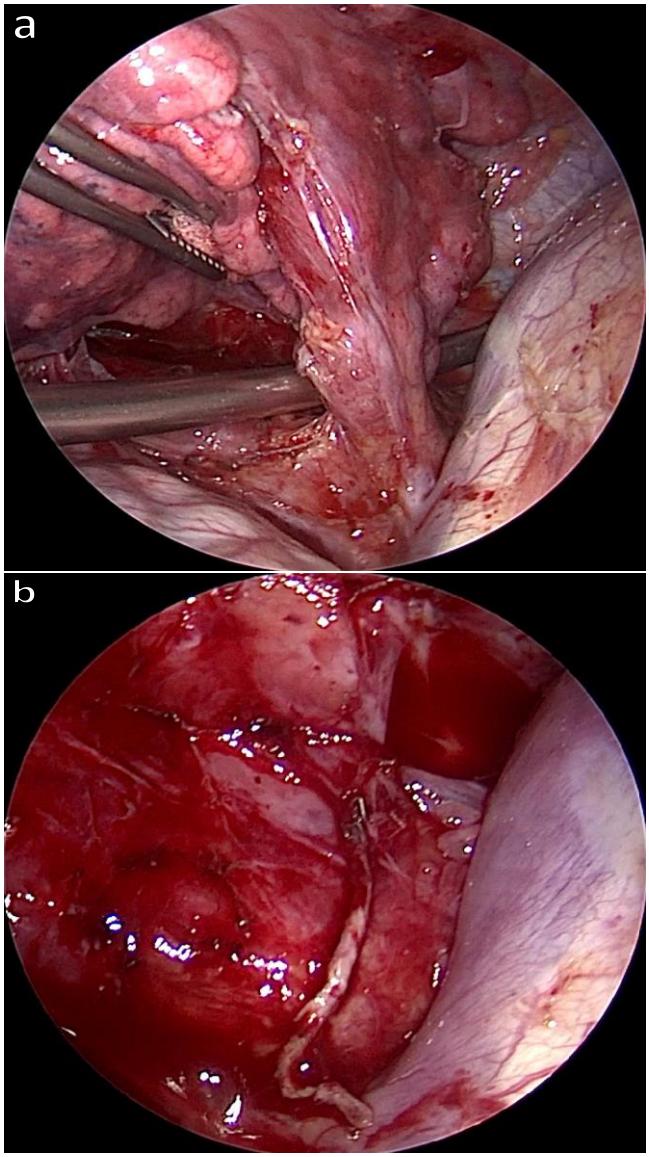

Figure 5: *Intraoperative thoracoscopic findings; Feeder artery arising from the aorta after dissection* ***(a)****, Image after the division of the feeder artery arising from the aorta* ***(b)***

Recurrent infection rates increase due to the cystic structure of PS, as a result, the vessels may be more fragile and thinner walled with inflammation. All of the above reasons can contribute to serious intraoperative bleeding, especially in patients with multiple arteries arising from the abdominal aorta, as in our first case, due primarily to the deep foci of bleeding in the diaphragmatic hiatus, making hemostasis difficult. Preoperative embolization has been reported to be especially effective in the prevention of intraoperative bleeding (5). In our second case, the surgical intervention was performed without embolization due to the large diameter of the single artery supplying the sequestration, arising directly from the thoracic aorta. The treatment of cases with such sequestrations should be decided upon on a patient-based basis.

Previous studies in literature recommend the treatment of small (<3 cm) interlobar sequestrations with endovascu-

lar embolization alone. Zhang et al. (4) achieved complete response in two patients and partial (<60%) response in five patients after the embolization of sequestrations of <3 cm. Recanalization after embolization is not uncommon, and is related to the time interval following the procedure (6). Based on this, we opted to operate on the patient the day after the embolization to avoid recanalization. In contrast, Cho et al. (7) recommended surgical resection in all patients, including asymptomatic patients, to exclude the risk of infection, post-embolization complications and other pathologies. In our first case, the patient was presented with hemoptysis. Since PS is directly related to the tracheobronchial system, we opted for curative treatment surgery after embolization. Anatomical resections are the most preferred procedure, and have produced excellent long-term results, especially in symptomatic patients who present with hemoptysis.

There is a lack of consensus on the optimum time interval between embolization and surgery in hybrid surgical treatments of pulmonary sequestration. VATS resections have been performed immediately, 4 days or 4 weeks after the embolization procedure in different studies (8,9). We opted to carry out a surgical resection 24 hours after the endovascular embolization in the absence of any problematic intraoperative events (9).

CONCLUSION

We believe that the treatment options in PS should be evaluated on a patient-by-patient basis. We recommend preoperative endovascular embolization as the safer surgery option, especially for sequestrations with feeder artery(ies) originating from the abdominal aorta. In cases of sequestration supplied by a single large-diameter artery arising directly from the thoracic aorta, surgical treatment may be considered without preoperative embolization. In symptomatic PS cases in which there is a direct relationship with the tracheobronchial system, embolization alone is not sufficient, and surgical resection may be appropriate as a curative treatment.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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RESPIRATORY CASE REPORTS

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