Respir Case Rep 2025;14(2):47-50 DOI: 10.5505/respircase.2025.48751

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

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

Kübra Taşkaraca Karabacak[1], Nevin Taci Hoca[1], Nilgün Yılmaz Demirci[1], Gunel Jeyranova[1], Ayşe Nur Demirci[2], Ali Celik[3], Ahmet Selim Yurdakul[1]

Abstract

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

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

Öz

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

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

[1]Department of Pulmonary Diseases, Gazi University Faculty of Medicine, Ankara, Türkiye
[2]Department of Pathology, Gazi University Faculty of Medicine, Ankara, Türkiye
[3]Department of Thoracic Surgery, Gazi University Faculty of Medicine, Ankara, Türkiye

[1]Gazi Üniversitesi Tıp Fakültesi Göğüs Hastalıkları Anabilim Dalı, Ankara
[2]Gazi Üniversitesi Tıp Fakültesi Patoloji Anabilim Dalı, Ankara
[3]Gazi Üniversitesi Tıp Fakültesi Göğüs Cerrahisi Anabilim Dalı, Ankara

Submitted (Başvuru tarihi): 18.12.2024 ***Accepted (Kabul tarihi):*** 01.03.2025

Correspondence (İletişim): Kübra Taşkaraca Karabacak, Department of Pulmonary Diseases, Gazi University Faculty of Medicine, Ankara, Türkiye
e-mail: kubrataskaraca@gmail.com

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

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

CASE

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

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

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

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

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

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

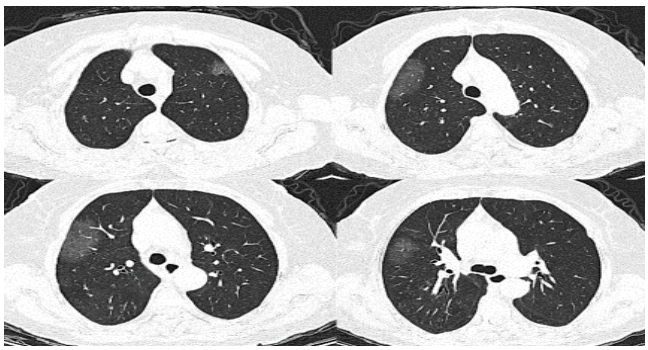

Figure 1: Peripheral ground-glass opacities (GGO) predominantly in the upper and middle lobes of both lungs

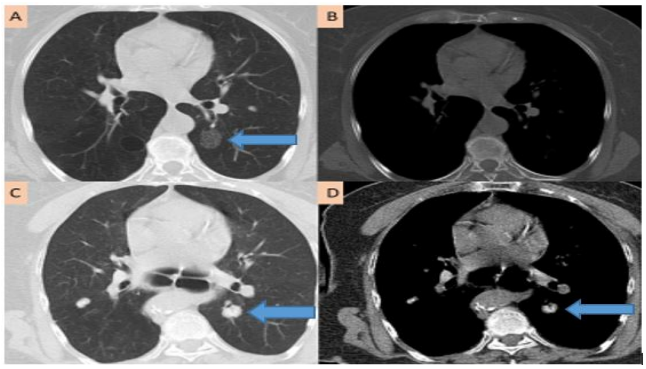

Figure 2: A nodule with an increasing solid component within the ground-glass opacity (blue arrow). Imaging from three years earlier, showing a well-defined ground-glass opacity (GGO) nodule (~1 cm in diameter) in the superior segment of the left lower lobe, and a regular lung cyst in the right lower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

DISCUSSION

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

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

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

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

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

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

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

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

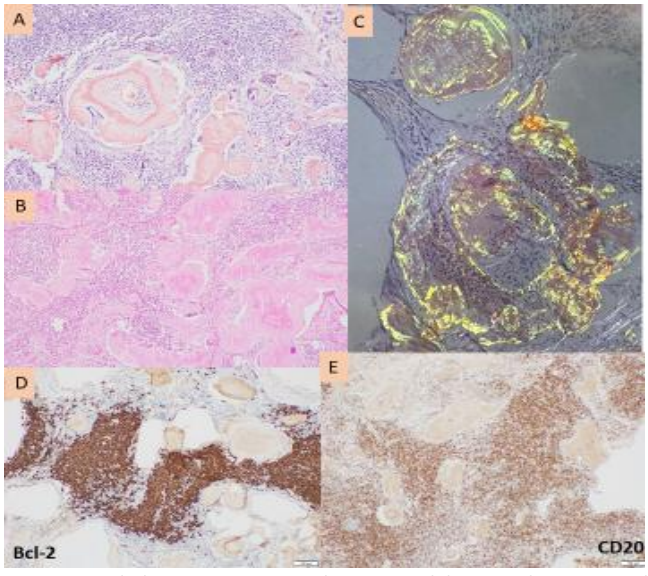

Figure 3: *Pathology specimen samples: Eosinophilic amorphous material identified as amyloid, showing salmon-colored staining with Congo red (100x)* ***(A)****; eosinophilic amorphous material deposition within the lymphoid cell infiltration (Hematoxylin and Eosin, 100x)* ***(B)****; under polarized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

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

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

REFERENCES

1. Chung A, Wilgus ML, Fishbein G, Lynch JP 3rd. Pulmonary and Bronchiolar Involvement in Sjögren's Syndrome. Semin Respir Crit Care Med 2019; 40:235-54. [CrossRef]
2. Seror R, Ravaud P, Bowman SJ, Baron G, Tzioufas A, Theander E, et al. EULAR Sjögren's Syndrome Disease Activity Index: Development of a Consensus Systemic Disease Activity Index for Primary Sjögren's Syndrome. Ann Rheum Dis 2010; 69:1103-9. [CrossRef]
3. Berk JL, O'Regan A, Skinner M. Pulmonary and Tracheobronchial Amyloidosis. Semin Respir Crit Care Med 2002; 23:155-65. [CrossRef]
4. Dacic S, Colby TV, Yousem SA. Nodular Amyloidoma and Primary Pulmonary Lymphoma with Amyloid Production: A Differential Diagnostic Problem. Mod Pathol 2000; 13:934-40. [CrossRef]
5. Flament T, Bigot A, Chaigne B, Henique H, Diot E, Marchand-Adam S. Pulmonary Manifestations of Sjögren's Syndrome. Eur Respir Rev 2016; 25:110-23. [CrossRef]
6. Casal Moura M, Navin PJ, Johnson GB, Hartman TE, Baqir M, Yi ES, et al. Pulmonary Nodules in Patients with Primary Sjögren's Syndrome: Causes, Clinico-radiologic Features, and Outcomes. Respir Med 2020; 174:106200. [CrossRef]
7. Voulgarelis M, Ziakas PD, Papageorgiou A, Baimpa E, Tzioufas AG, Moutsopoulos HM. Prognosis and Outcome of Non-Hodgkin Lymphoma in Primary Sjögren Syndrome. Medicine (Baltimore) 2012; 91:1-9. [CrossRef]
8. Nocturne G, Mariette X. Sjögren Syndrome-associated Lymphomas: An Update on Pathogenesis and Management. Br J Haematol 2015; 168:317-27. [CrossRef]
9. Koyama M, Johkoh T, Honda O, Mihara N, Kozuka T, Tomiyama N, et al. Pulmonary Involvement in Primary Sjögren's Syndrome: Spectrum of Pulmonary Abnormalities and Computed Tomography Findings in 60 Patients. J Thorac Imaging 2001; 16:290-6. [CrossRef]
10. Retamozo S, Brito-Zerón P, Ramos-Casals M. Prognostic Markers of Lymphoma Development in Primary Sjögren Syndrome. Lupus 2019; 28:923-36. [CrossRef]
11. Baqir M, Lowe V, Yi ES, Ryu JH. 18F-FDG PET Scanning in Pulmonary Amyloidosis. J Nucl Med 2014; 55:565-8. [CrossRef]
12. Zucca E, Arcaini L, Buske C, Johnson PW, Ponzoni M, Raderer M, et al; ESMO Guidelines Committee. Marginal Zone Lymphomas: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. Ann Oncol 2020; 31:17-29. [CrossRef]