

Adenocarcinoma of the Lung Presenting with Idiopathic Interstitial Pneumonia and Various Paraneoplastic Syndromes: A Case Report

İDİYOPATİK İNTERSTİSYEL PNÖMONİ VE ÇEŞİTLİ PARANEOPLASTİK SENDROMLARLA BİRLİKTE OLAN AKCİĞER ADENOKARSİNOMU

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Abstract

We report a patient with adenocarcinoma of the lung presenting with idiopathic interstitial pneumonia (IIP) and various paraneoplastic syndromes (PS). A 65-year-old man presented to our clinic with a 1-year history of exertional dyspnea, fatigue, weight loss of 5 kilograms, 6 months history of lumbar, neck and joint pain, and 3 months history of dry eyes, dry mouth, dysphagia, hoarseness and headache. He had a history of tuberculous pleurisy 8 months before his admission. Based on clinical data, pulmonary function tests, radiographic and bronchoalveolar lavage findings, the patient was diagnosed as IIP. In order to evaluate the etiology of lumbar pain, the patient underwent thoracolumbal vertebral MRI and multiple metastatic lesions were seen. After re-evaluation of the thorax CT, a transthoracic biopsy was obtained from the subpleural nodular lesion on the right upper lobe anterior segment. The histological diagnosis was adenocarcinoma. Cranial nerve dysfunction, facial pain, hyponatremia and eosinophilia were the accompanying PS.

Key Words: Pneumonia, paraneoplastic syndromes, adenocarcinoma

Özet

İdiyopatik interstisyel pnömoni (İİP) ve çeşitli paraneoplastik sendromlarla (PS) birlikte olan akciğer adenokarsinomu olgusunu sunuyoruz. Altmış beş yaşındaki erkek hasta kliniğimize 1 yıldır olan efor dispnesi, halsizlik, 5 kilogram kilo kaybı, 6 aydır olan bel, boyun, eklem ağrısı, 3 aydır olan kuru göz, kuru ağız, yutma güçlüğü, ses kısıklığı ve baş ağrısı şikayetiyle başvurdu. Özgeçmişinde 8 ay önce tüberküloz plörezi tanısı almıştı. Klinik veriler, solunum fonksiyon testleri, radyolojik ve bronkoalveoler lavaj bulgularına dayanılarak hastaya İİP tanısı kondu. Bel ağrısı nedenini araştırmak için çekilen torakolumbal vertebral MRI'da çok sayıda metastatik lezyon görüldü. Toraks BT'si yeniden değerlendirilerek sağ akciğer üst lob anterior segmentte yerleşen subpleural nodüler lezyondan transtorasik biyopsi yapıldı. Histolojik tanı adenokarsinomdu. Kranial sinir disfonksiyonu, yüz ağrısı, hiponatremi ve eozinofili eşlik eden PS'lerdi.

Anahtar Kelimeler: Pnömoni, paraneoplastik sendrom, adenokarsinom

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More than 90% of patients with lung cancer are symptomatic at the time of clinical presentation.¹ The symptoms and signs of lung cancer may result from the central or peripheral growth of primary tumor, regional spread into the mediastinum, systemic spread, and paraneoplastic syndromes (PS). While the majority

of patients present with the commonest symptoms related to the primary tumor and its distant metastases, understanding of the rarer manifestations such as PS may help the clinician to diagnose the malignancy promptly.^{2,3}

Besides its natural history of being recognized late usually, associated diseases make it harder to diagnose lung cancer. Lung cancer is reported to be frequently associated with idiopathic interstitial pneumonia (IIP). In addition, the relative risk of lung cancer in patients with IIP is higher compared with the general population.⁴ Other rare lung cancer patients associated with

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other IIPs such as non-specific interstitial pneumonia (NIP) and lymphocytic interstitial pneumonia (LIP) are also present.^{5,6}

In this case, we report a patient with adenocarcinoma of the lung presenting with IIP and various PS such as cranial nerve dysfunction, facial pain, hyponatremia and eosinophilia.

Case Report

A 65-year-old man presented to our clinic with a 1-year history of exertional dyspnea, fatigue, 6 months history of lumbar, neck and joint pain, 3 months history of dry eyes, dry mouth, dysphagia, hoarseness and a cluster headache. He had lost 5 kilograms of body weight during the last year. He was a truck driver and did not have a history of occupational or environmental exposure to toxic materials. He had a smoking history of 25 pack-years and he gave up smoking 20 years ago. He congenitally had one kidney. He had received a diagnosis of tuberculous pleurisy 8 months before his admission and had used antituberculous agents for 6 months. The diagnosis had been based on the lymphocytic cytology of the pleural effusion. He had not used any medications other than the antituberculous drugs (isoniazid, rifampine, morphoiznamide, ethambutol).

On physical examination, the temperature was 36.7°C, pulse rate 80/min, respiratory rate 28/min, and arterial blood pressure 110/70 mmHg. Chest examination revealed a collapsed right hemithorax with diminished respiratory sounds and rare end-expiratory rhonchi in the left hemithorax. Other systems were normal.

On laboratory analysis, complete blood count was normal; erythrocyte sedimentation rate was 36 mm/hour. The differential revealed normal erythrocyte morphology, copious thrombocytes and eosinophilia (52% neutrophils, 30% lymphocytes, 16% eosinophiles, 2% basophiles). Urinary osmolarity and sodium excretion were increased. Biochemical tests were within normal limits other than hiponatremia (Na: 128 mmol/L). Anti-HIV and anti-HCV antibodies and HBsAg were negative.

Sputum smear was negative for acid-fast bacilli in specimens obtained on three consecutive mornings. Tuberculin skin test was 15 mm. Arterial blood gas analysis revealed a mild hypoxemia (PaO₂: 74 mmHg). Pulmonary function tests showed a restrictive ventilatory impairment with a low carbon monoxide diffusion capacity (DLCO: 52%). The ratio of DLCO to alveolar volume (VA) was 97%.

A chest radiography showed diffuse pleural thickening and volume loss of the right hemithorax and reticulo-nodular infiltrates in the middle and lower zones of the left hemithorax. On computed tomography (CT) of thorax, pleural thickening of the right hemithorax and a subpleural nodule (3 cm in diameter) adjacent to the pleura of the right upper lobe anterior segment were noted (Figure 1). High-resolution CT sections revealed bilateral interstitial pattern, honeycombing and ground glass opacities more prominent in the lung periphery (Figure 2).

The bronchial system was normal on fiberoptic bronchoscopy. Bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) specimens were obtained from the lingula. The cell differential of BAL was 38% lymphocytes, 21% neutrophils, and 41% macrophages. The ratio of T helper lymphocytes (CD4) to suppressors (CD8) was 1.48. TBLB was not adequate for proper investigation. Based on clinical and laboratory data we suspected Sjögren's syndrome. Biopsy specimens of

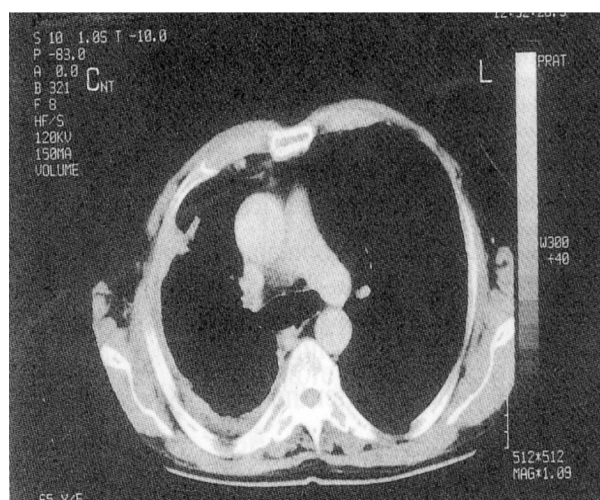


Figure 1. CT of thorax showing irregular pleural thickening of the right hemithorax and subpleural nodule of the right upper lobe anterior segment.

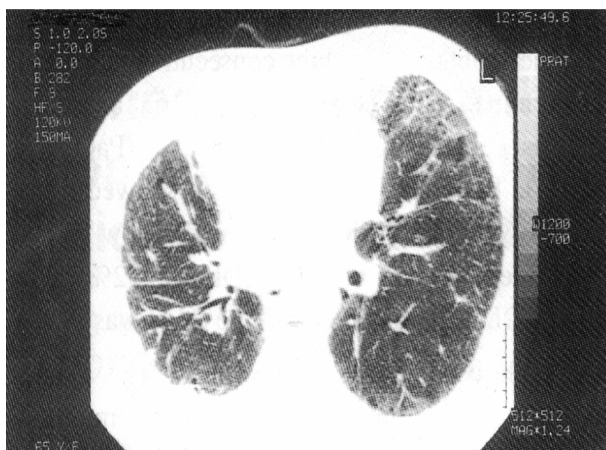


Figure 2. High resolution CT showing bilateral interstitial pattern, honeycombing and ground glass opacities more prominent in the lung periphery.

labial salivary glands were normal. Schirmer test revealed dry eyes (3 mm on the right, 2 mm on the left eye). Rheumatoid factor, antinuclear antibodies, anti-SS-A and anti-SS-B, Scl 70, and anti Jo-1 antibodies were negative. Immunoglobulin levels were within normal limits. Based on these results, we instituted methyl prednisolon therapy (40 mg/day) with the diagnosis of IIP.

The cluster headache localized on the temporal region was diagnosed as trigeminal neuralgia and was treated with carbamazepin. On ear, nose, and throat examination, the functions of the right soft palate and vocal cord were limited suggesting pathology of the 9th and 10th cranial nerve. Thin section cranial CT and magnetic resonance imaging (MRI) examinations were normal.

To evaluate the etiology of lumbar pain, the patient underwent thoracolumbal vertebral MRI and multiple metastatic lesions were identified. After re-evaluation of the thorax CT, a transthoracic biopsy was obtained from the nodular lesion adjacent to the pleura of the right upper lobe anterior segment. The diagnosis was adenocarcinoma. The patient was referred to an oncology clinic for chemoradiotherapy. He died 2 months after the diagnosis of cancer.

Discussion

We presented a patient with the diagnosis of IIP and pulmonary adenocarcinoma. The symptoms of dry eyes, dry mouth, and exertional dysp-

nea, and the presence of interstitial lung disease were initially attributed to Sjögren's syndrome. Lumbar, neck, and joint pain also suggested rheumatic disease. Besides, the Schirmer test was positive and the BAL cytology was mainly lymphocytic. However, normal salivary gland biopsy and negative anti-SS-A and anti-SS-B antibodies were not consistent with the diagnosis of Sjögren's syndrome. Other markers for collagen tissue disease were also negative and immunoglobulin levels were within normal limits. There was no history of using medications other than antituberculosis therapy and occupational or environmental exposure to toxic materials that can cause interstitial lung disease. Thus, the most likely diagnosis was IIP.

IIPs are characterized histologically by interstitial inflammatory infiltrates with variable fibrosis and collagen deposition. The joint committee of American Thoracic Society and European Respiratory Society classified IIPs in seven groups as: IIP, desquamative IP, NIP, LIP, acute IP, cryptogenic organizing pneumonia, and respiratory bronchiolitis associated interstitial lung disease.⁷ Although the gold standard method for the diagnosis of IP is thoracoscopic or open lung biopsy, clinical findings, BAL pattern and TBLB may be helpful from time to time. In our patient, BAL fluid cytology was mainly lymphocytic but TBLB was not adequate for the diagnosis and could not demonstrate lymphocytic infiltration. However, based on clinical data, radiologic features, and BAL cytology, LIP was the most likely diagnosis.

Since the patient gave a history of tuberculous pleurisy and a 6-month history of antituberculosis therapy administered in another medical center, the thickening and nodularity of the pleura of the right hemithorax were considered a sequel. However, the diagnosis of tuberculous pleurisy was doubtful since the patient was old and the diagnosis had been based solely on lymphocytic cytology. After the determination of metastatic lesions, the pleural thickening was the first place to be suspected to harbor the primary tumour. Transthoracic biopsy from the subpleural nodular lesion of right upper lobe anterior segment confirmed the diagnosis of

lung adenocarcinoma. After the diagnosis of malignancy, surgical lung biopsy for the diagnosis of IIP was not considered.

An association between pulmonary fibrosis and lung cancer was first reported in 1965.⁸ Since then, several publications have documented an excess risk of lung cancer among patients with pulmonary fibrosis.⁹ Lung cancer is frequently associated with IIP.⁴ Primary lung cancer associated with NIP was reported by Yamadori et al.⁵ Takabatake et al were the first who reported the association of lung adenocarcinoma and LIP due to primary Sjögren's syndrome.¹⁰ Bando et al described a patient with stage 1 lung adenocarcinoma complicated with focal LIP.⁶ The lung cancer was surrounded by LIP in the same lobe. Immunohistochemical study disclosed that CD8 positive T cell constituted the major element of the infiltrated lymphocytes in the tumor, and were also found in the enlarged alveolar septa suggesting an association between lung cancer and LIP.⁶ They suggested that focal LIP probably reflected local immune response to an antigenic stimulus caused by lung cancer and hypothesized that antitumor immunity might play an important role in the pathogenesis of LIP associated with lung cancer. Even though we did not prove the presence of LIP by lung biopsy, predominant lymphocytic cytology was remarkable. In our patient, the stage of lung cancer was 4 and IP was diffuse. As in all other patients associated with LIP, our patient also had adenocarcinoma.

A constellation of symptoms and signs at a site distant to the primary tumour, unrelated to local effects or metastases, is termed as PS.^{2,3} These syndromes may be due to the production of biologically active substances either by the tumor or in response to the tumor. However, the mechanism is often poorly recognized. Pulmonary carcinoma has frequently been associated with PS.¹¹ Cranial nerve dysfunction, facial pain, hyponatremia and eosinophilia were the PS in this patient. They all were present before the diagnosis of lung cancer.

A variety of poorly understood neurologic syndromes may occur in lung cancer patients. Al-

though the production of antibodies to neural antigens may explain some of these neurologic syndromes, nonimmunologic mechanisms are also present.¹¹ Hoarseness and dysphagia were thought to be due to the limited functions of the right soft palate and right vocal cord suggesting a pathology of the 9th and 10th cranial nerve. Thin section cranial CT and MRI were normal.

Referred pain, due to invasion or compression of the vagus nerve, as well as PS secondary to the production of circulating humoral factors by the malignant tumor cells, is implicated in the pathophysiology of facial pain associated with non-metastatic lung cancer. Sarlani et al reviewed 32 reported cases of lung-cancer related facial pain.¹² The facial pain was almost always unilateral, and was most commonly localized to the ear, the jaws, and the temporal region. The pain was frequently described as severe and aching, and could be continuous or intermittent.¹² The cluster headache that was diagnosed as trigeminal neuralgia did not resolve by carbamazepin therapy and it was thought to be cancer related paraneoplastic facial pain. Thus, lung cancer should be included in the differential diagnosis of facial pain that is refractory to treatment.

Hyponatremia, associated with increased urinary sodium excretion and osmolality was thought to be due to the PS of inappropriate secretion of antidiuretic hormone.

Eosinophilic leukomoid reactions may be related to metastases in the bone marrow, presence of extensive areas of necrosis inside the primary tumor, or production of colony stimulating factors by the tumor. Eosinophilia was also a paraneoplastic finding.

In conclusion, IIPs may accompany pulmonary malignancy and obscure the diagnosis of malignancy. PS may be the leading findings of a pulmonary malignancy before the diagnosis.

REFERENCES

1. Carbone PP, Frost JK, Feinstein AR, et al. Lung cancer: Perspectives and prospects. *Ann Intern Med* 1970;73:1003-24.
2. Scagliotti GV. Symptoms, signs and staging of lung cancer. *Lung cancer. Eur Respir Mon* 2001;17:86-119.

3. Beckles MA, Spiro SG, Colice GL, Rudd RM. Initial evaluation of the patient with lung cancer. Symptoms, signs, laboratory tests, and paraneoplastic syndromes. *Chest* 2003;123:97-104.
4. Turner-Warwick M, Lebowitz M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis and lung cancer. *Thorax* 1980;35:496-9.
5. Yamadori I, Sato T, Fujita J, et al. A case of non-specific interstitial pneumonia associated with primary lung cancer: Possible role of antibodies to lung cancer cells in the pathogenesis of non-specific interstitial pneumonia. *Respir Med* 1999;93:754-6.
6. Bandoh S, Fujita J, Haba R, et al. Lung cancer with focal lymphocytic pneumonia. *Intern Med* 2002;41:997-1001.
7. The joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS). Idiopathic pulmonary fibrosis: Diagnosis and treatment. *Am J Respir Crit Care Med* 2000;161:646-64.
8. Meyer EC, Liebow AA. Relationship of interstitial pneumonia honeycombing and atypical epithelial proliferation to cancer of the lung. *Cancer* 1965;18:322-51.
9. Turner-Warwick M, Lebowitz M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis and lung cancer. *Thorax* 1980;35:496-9.
10. Takabatake N, Sayama T, Shida K, et al. Lung adenocarcinoma in lymphocytic interstitial pneumonitis associated with primary Sjögren's syndrome. *Respirology* 1999;4:181-4.
11. Gerber RB, Mazzone P, Arroliga AC. Paraneoplastic syndromes associated with bronchogenic carcinoma. *Clin Chest Med* 2002;23:257-64.
12. Sarlani E, Schwartz AH, Greenspan JD, Grace EG. Facial pain as first manifestation of lung cancer: A case of lung cancer related cluster headache and a review of the literature. *J Orofac Pain* 2003;17:262-7.