

# Paraneoplastic syndrome associated with desquamative interstitial pneumonia mimicking lung cancer: A case report

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## ABSTRACT

Paraneoplastic syndromes are generally caused by ectopic hormone production or immune-mediated tissue destruction caused by neural antigen expression of cancer cells. Here, we present a rare case of paraneoplastic syndrome associated with interstitial pneumonia mimicking lung cancer. Laboratory findings of the concerning patient revealed liver enzyme abnormalities, and elevated level of cancer antigen neuron specific enolase. Electrostimulation demonstrated changes typical of the Lambert-Eaton Myasthenic syndrome (LEMS). Additionally, histopathological findings of the liver confirmed intrahepatic cholestasis. The contrast-enhanced spiral computed tomography on admission showed a soft tissue mass near the main pulmonary artery on the right hilus and bilateral pulmonary infiltrates, which are prominent in the right lower lung field. On the basis of the tomography findings, which suggested the risk of lung cancer, we performed an open lung biopsy. However, biopsy showed the lung pathology to be desquamative interstitial pneumonitis. Fortunately enough, one month later, as a result of delivering the appropriate treatment, the symptoms subsided; and the lung function and the chest radiograph findings improved significantly. In addition, the abnormal values for tumor antigens and liver

enzymes returned to normal ranges. After 3 years, he was in remission. These findings suggest that paraneoplastic syndromes can also be associated with benign conditions, which require a careful clinical evaluation for the prevention of misdiagnosis. [Turk J Cancer 2008;38(2):78-82]

## KEY WORDS:

Lung cancer, desquamative interstitial pneumonia, intrahepatic cholestasis, interstitial lung diseases, Lambert-Eaton syndrome

## INTRODUCTION

Paraneoplastic syndromes are rare, immune-mediated syndromes occurring in patients with cancer, especially lung cancer. Their clinical features are heterogeneous and the pathogenesis is unclear. The antibodies, formed in response to the presence of a tumor, mostly cross-react with the cells of the nervous system. The diagnosis of these syndromes can sometimes be difficult because it is based mainly on the clinical evaluation. Therefore, these syndromes usually require invasive diagnostic procedures for differential diagnosis (1). Desquamative interstitial

pneumonia (DIP) is an interstitial lung disease with diffuse and uniform accumulation of alveolar macrophages (2,3). A course of DIP with immunological activation and extrapulmonary manifestations is rare (3,4). By now, the association of paraneoplastic syndromes with DIP has not been defined.

Here, we present a case of DIP mimicking lung cancer associated with severe intrahepatic cholestasis and LEMS. To reach a definite diagnosis, an extensive work up was carried out.

**CASE REPORT**

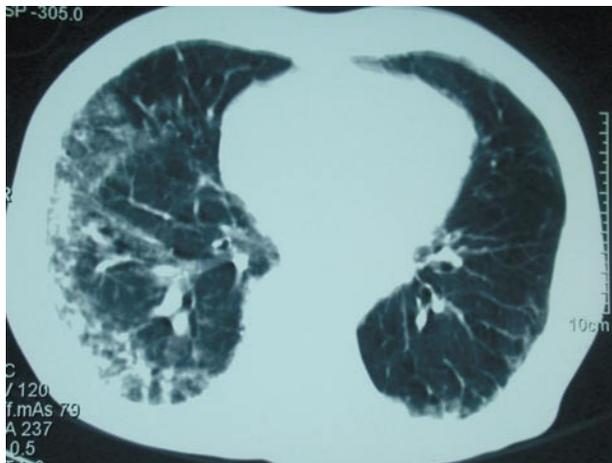
A 67-year old man was admitted to the hospital with a chronic cough, weight loss, muscle weakness, and cholestasis. The patient had been well until 1 year prior to when he began to manifest weakness and weight loss. He developed a mild exertional dyspnea 10 days before admission. The patient’s history was significant for 10 pack-years of cigarette smoking, but he had recently quit. However, it was known that the patient was a professional furniture maker who had a history of exposure to chemicals, which was used in the wood industry. On admission, his heart and respiratory rates and body temperature were 82/minute, 20/minute, and 37.8°C, respectively. Patient’s skin was pale and weakness in the proximal muscles of the extremities, particularly lower, suggested the occurrence of slight myalgia. Dry inspiratory crackles were heard bilaterally in the bases of the lungs, without signs of consolidation, and with occasional bilateral wheezes. On laboratory examination the following results were found; hemoglobin: 9.2 g/dL (14.00-18.00), Serum gamma glutamyl transpeptidase: 196 IU/L (7.00-60.00), alkaline phosphatase: 281 IU/L (25.00-100.00), unconjugated bilirubin: 1.2 mg/dL (0.10-0.50), conjugated bilirubin: 3.5 mg/dL (0.2-0.8), serum aspartate transaminase: 102 IU/L (12.00-50.00), alanine transaminase: 58 IU/L (10.00-70.00), alpha 2 globulin: 5.2% (8.0-12.0), C-reactive protein: 96 mg/dL (0.00-6.00), erythrocyte sedimentation rate: 110 mm/h (0.00-20.00), ferritin: 1244 ng/mL (18.00-250.00), creatinine kinase: 504 mg/dL (22.00-200.00), lactic dehydrogenase: 414 mg/dL (100.00-240.00), serum albumin: 3.2 g/dL (3.40-5.00), and globulin: 3.6 g/dL (1.50-3.50). Direct tests with standard and Ziehl-Neelsen

stains; cultures of blood, sputum, and urine; and antibodies against various infectious agents including viruses (hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus, cytomegalovirus, and Epstein-Barr virus), and chlamydia were negative, as were specific tests for autoimmune disorders (Table 1). Cancer antigens CA 15-3 and neuron specific enolase were found to be elevated in the patient’s serum (Table 1). Chest radiograph revealed occasional coarse reticular opacities in the lower lobes of both lungs. Serially obtained noncontrast- and contrast-enhanced spiral computed tomographic examination of the chest revealed a soft tissue mass (1x1.5 cm) near the main pulmonary artery on the right hilus and bilateral mild fibrotic changes with ground-glass appearance in the bases (Figure 1). Single-breath carbon monoxide diffusing capacity (mL/min/mm Hg) was 8.7 (59% of predicted value), and the carbon monoxide diffusing constant was 1.3 (61% of predicted value). In electrophysiological ex-

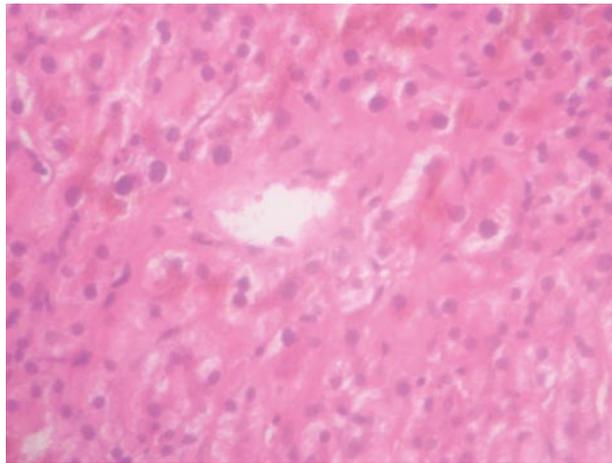
**Table 1**  
**Patient characteristics of the study group**

| VARIABLE                       | VALUE    | NORMAL RANGE |
|--------------------------------|----------|--------------|
| AFP (ng/mL)                    | 1.9      | 0-14         |
| CEA (ng/mL)                    | 4.0      | 0-4          |
| Ca 15-3 (U/mL)                 | 148.40   | 4.50-29      |
| Ca 19-9 (U/mL)                 | 2.9      | 0-37         |
| Neuron specific enolase (mg/L) | 36.2     | 15.7-17.0    |
| Anti-M (IU/mL)                 | 88.0     | 0-12         |
| Antithyroglobulin (IU/mL)      | 10.1     | 0-34         |
| PSA (ng/mL)                    | 0.27     | 0-4          |
| Direct Coombs                  | negative | negative     |
| ANA                            | negative | negative     |
| Anti La                        | negative | negative     |
| Anti Ro                        | negative | negative     |
| SMA                            | negative | negative     |
| AMA                            | negative | negative     |
| LKM-1                          | negative | negative     |

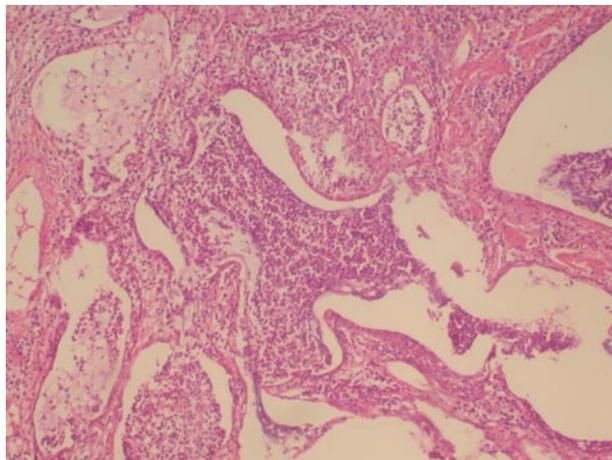
AFP: Alfa feto protein; CEA: Carcinoembryonic antigen; Anti-M: Anti-Microsomal antibody; PSA: Prostate specific antigen; ANA: Anti-nuclear antibody; SMA: Anti-smooth muscle; AMA: Anti-mitochondrial antibodies; LKM: Anti-liver-kidney microsomal antibodies



*Fig 1. Contrast-enhanced spiral computed tomography of the thorax: The high-resolution image of the lung bases reveals peripheral reticular opacities and peripheral ground-glass opacities in the lower lobes. Small round lucencies in the lower lobes suggest early honeycomb changes*



*Fig 2. Desquamative interstitial pneumonia (DIP): Interstitial lymphocyte and plasma cell infiltration and accumulation in the intraalveolar spaces, together with fewer numbers of polymorphonuclear leukocytes and eosinophils with mild interstitial fibrosis. The alveolar space is filled with alveolar macrophages, and type 2 pneumocyte hyperplasia, suggesting desquamative interstitial pneumonitis in the subacute phase (H&E, x200)*



*Fig 3. A biopsy specimen of the liver: Mononuclear infiltration in the portal area, centrilobular severe cholestasis with spotty necrosis, and mild fatty degeneration (H&E, x200)*

amination, small compound action potentials which underwent a significant increase to normal limit after brief exercise were found. Repetitive stimulation revealed a decrement of compound action potentials at low rates of stimulation and an increment (over 100%) at high rates of stimulation. On the other hand, motor and sensory nerve conduction velocities were within normal limits, F-waves had borderline latencies. Needle electromyographic examination demonstrated myogenic involvement in the proximal muscle, suggesting a Myasthenic syndrome (Lambert-Eaton type). An anthracotic lymph node was found in a percutaneous transthoracic tru-cut biopsy of soft tissue mass. Open lung biopsy revealed interstitial lymphocyte, and plasma cell infiltration and accumulation in the intraalveolar spaces, together with relatively few numbers of polymorphonuclear leukocytes and eosinophils with mild interstitial fibrosis. The alveolar space was observed to be filled with alveolar macrophages, and type 2 pneumocyte hyperplasia, suggesting the occurrence of desquamative interstitial pneumonitis in the subacute phase (Figure 2). A biopsy specimen of the liver revealed mononuclear cell infiltration in the portal area, severe centrilobular cholestasis with spotty necrosis, and mild fatty degeneration (Figure 3). A biopsy specimen of the muscle demonstrated immunoglobulin G, A, and M deposition in the immunohistochemical examination of the arterial walls.

The patient was given empirical antibiotic treatment initially (ceftriaxone 1 g/12 hours for 7 days). Shortly after, he was administered oral levofloxacin 500 mg/24 hours, and sulbactam-ampicillin 3 g i.v., b.i.d., for 7 days but to no effect. High-dose methyl prednisolone (initial dose 30 mg/kg/day) and cyclophosphamide (1000 mg once a month) therapy were started six weeks after admission, and symptomatic and clinical improvement were subsequently seen.

## DISCUSSION

To our knowledge, this is the first case in the literature describing muscle involvement, suggesting LEMS, severe cholestasis, elevation of cancer antigens and DIP.

The phenotypic heterogeneity of paraneoplastic syndrome often leads to misdiagnosis (1). Our case had an

initial pulmonary infiltrate mimicking neoplastic diseases. Subacute and chronic forms of hypersensitivity pneumonitis were unlikely diagnoses in this case owing to the absence of the nodular opacities in the lung (5). There is evidence suggesting that the patient's interstitial lung disease was associated with the connective tissue disease and/or vasculitis (6). Both polymyositis and sarcoid myositis are possible diagnoses because they are associated with pathological changes in the lungs (7,8). In the current case, the strong inflammatory response did not resolve with the therapeutic dose of methylprednisolone, as would be expected in sarcoidosis. Sarcoidosis predominantly affects the upper lung zones and dermatomyositis in the basal zones (8). However, histopathological findings of the lung and muscle in our case ruled out the diseases mentioned above. The open lung biopsy demonstrated DIP in our patient.

Desquamative interstitial pneumonitis is generally associated with smoking. However, in some rare cases, it has been associated with inhalation of inorganic particulates (9,10). Patients with desquamative interstitial pneumonia tend to present with a history of symptoms for three months to five years. Chest radiographs may reveal hazy, roundglass opacities or reticulonodular infiltrates in both lung bases (11). The predominant finding on CT scans is ground-glass opacities that may be patchy or diffuse and that mainly affect the middle and lower lobes. Our patient had a 35 year long history of occupational exposure to chlorinated hydrocarbons that are manufactured for the use of wood preservatives and glues. These might be a predisposing factor for DIP in this patient.

Extrapulmonary manifestation of DIP is rare (3,4). However, association of DIP with immune disorders has been reported such as rheumatic disorders and systemic lupus erythematosus (12,13). Abnormal liver function tests may be directly attributed to systemic lupus erythe-

matusus in some 3%-23% of patients, averaging some 9% in the cumulative analysis of relatively large series (14). The course of the disease and the absence of clinical and laboratory characteristics specific to systemic lupus erythematosus also allowed us to exclude this disease. Therefore, in our patient, the intrahepatic cholestasis was attributed to an immune reaction coexisting with the DIP.

LEMS is an autoimmune disorder of neuromuscular transmission, in which autoantibodies cause a decrease in the presynaptic release of acetylcholine. Approximately 60% of patients have associated small cell lung cancer. The neurological syndrome in LEMS is characterized by proximal muscle weakness, absent tendon reflexes and autonomic dysfunction. The association of immunological diseases such as systemic lupus erythematosus has also been reported (15). Autoantibodies against calcium channels may cross-react with voltage-gated calcium channels at presynaptic nerve terminals and induce a neurological syndrome (16,17). However, the association between DIP and LEMS has not been described in the literature. In our case, the diagnosis of LEMS was based on the patient's distinctive clinical and electrophysiological findings (17,18).

Paraneoplastic syndromes may antedate the diagnosis of cancer or occur at any time after the diagnosis of cancer. However, three years after immunosuppressive therapy, the patient was asymptomatic and the results of his physical, neurologic and electrophysiological examination were normal.

In conclusion, immune manifestations related to interstitial lung diseases including DIP can mimic lung cancer. The knowledge of the relationship between the development of characteristic features of paraneoplastic syndromes and the presence of a specific benign disease may prevent misdiagnosis.

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