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Pulmonary Langerhans Cell Histiocytosis Proceeding with Inguinal Lymph Node Infiltration: A Case Report

İnguinal Lenf Nodu Tutulumu ile Seyreden Pulmoner Langerhans Hücreli Histiyositoz: Olgu Sunumu

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Abstract

Langerhans cell histiocytosis (LCH) is a myeloproliferative disorder characterized by the clonal neoplastic proliferation of dentritic cells containing CD1a/S100/Langerin proteins. The BRAF V600E mutation causes hyperactivation in the MAPK pathway, and plays a role in misguided myeloid cell differentiation in LCH development. The incidence of the disease in the adult population is 2/1 million. Multi-organ involvement can be seen, although bone involvement is the most common site, and lung, skin and central nervous system involvement can also be seen. Isolated pulmonary involvement (pulmonary LCH) occurs between the ages of 20 and 40 years in adults, and more than 90% of cases are heavy smokers. We present here a case of pulmonary LCH identified with a bilateral micronodular infiltration on chest radiograph with details of clinical-radiological follow-ups.

Keywords: *Langerhans cell histiocytosis, MAPK, micronodular infiltration.*

Öz

Langerhans hücreli histiyositoz (LHH); CD1a/S100/Langerin proteinlerine sahip dendritik hücrelerin klonal neoplastik çoğalması ile karakterize miyeloproliferatif bir hastalıktır. LHH gelişiminde; bozulmuş miyeloid hücre diferansiasyonuna yol açan, hücre sinyalizasyonunda rol alan MAP kinaz yolağında uygunsuz aktivasyona neden olan BRAF V600E mutasyonu rol almaktadır. Hastalığın erişkin yaş grubundaki insidansı milyonda 2 olarak bildirilmiştir. LHH, çoğu organı etkilemekle birlikte kemik en sık tutulum yeridir. Akciğer, cilt, merkezi sinir sistemi tutulumları görülebilmektedir. İzole akciğer tutulumu (pulmoner LHH) çoğunlukla 20-40 yaş arası genç erişkenlerde görülmektedir ve %90'ından fazlasında sigara öyküsü bulunmaktadır. Bu olgu sunumunda radyolojik olarak her iki akciğerde mikronodüler infiltrasyonlar ile başvuran bir bir pulmoner LHH olgusu ve klinik-radyolojik takibindeki süreçten bahsedilmiştir.

Anahtar Kelimeler: *Langerhans hücreli histiyositoz, MAPK, mikronodüler infiltrasyon.*

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Histiocytic disorders originate from mononuclear phagocytic cells as macrophages and dendritic cells, and Langerhans cell histiocytosis (LCH) has been defined as a subgroup of these disorders. LCH is a myeloproliferative disorder that is characterized by the clonal neoplastic proliferation of dendritic cells containing CD1a/S100/Langerin proteins (1).

Different classifications of the disease have been put forward due to its clinical-histopathological heterogeneity. Unifocal, multifocal and multisystemic disease forms were first reported by the Histiocyte Society based on disease progression and organ involvement, and in this classification liver, spleen and hematopoietic system involvements were accepted as risk-organ involvements (2). The disease can occur at any age, although it is more common among pediatric patients aged 1–3. The incidence of the disease among children is 4/1 million, compared to 2/1 million in adults (3,4). It is thus considered uncommon in the adult population, and clinicians may not consider the disease as an entity.

LCH can affect various organs, although bone involvement is the most common form (5), while lung, skin and central nervous system involvements may also be seen (6). Isolated pulmonary involvement (pulmonary LCH) occurs between the ages of 20 and 40 years in adults, and more than 90% of cases are heavy smokers. The relationship between the disease and smoking is considered to be associated with bombesin-like peptide production and tobacco glycoproteins, which are thought to trigger an immune response resulting in chemotaxis and cytokine release (7), leading to infiltration of the lung parenchyma by Langerhans cells (8).

The pulmonary LCH case presented was identified with a bilateral micronodular infiltration on chest radiograph, and is reported with details of the clinical-radiological follow-ups.

CASE

A 43-year-old male patient with a 20/pack-year smoking history and a background in ship construction with work-related galvanization exposure was admitted to the outpatient clinic with symptoms of breathlessness and cough for 2 months. A chest radiograph revealed bilateral micronodular infiltrations and bilateral centrilobular micronodular infiltrations were detected on thorax computerized tomography (CT) (Figure 1). A fiberoptic-bronchoscopic (FOB) examination planned after an initial oral antibiotic regimen revealed no endobronchial lesions, while bronchial lavage contained no evidence of acid-resistant bacilli (ARB). Cytological findings of bronchial lavage were non-diagnostic. After being discharged, the patient was rehospitalized some weeks later for further investigation since the pulmonary symptoms had persisted, and miliary tuberculosis and occupational exposure were initially considered as a pre-diagnosis based on the imaging results and the patient's occupational history. A physical examination at admission revealed bilateral rales on auscultation, and a pulse oximeter recorded an oxygen saturation level of 95%. The significant laboratory results at the time of admission were Leukocyte: 13400 and C-reactive protein (CRP): 24 mg/L (normal range: 0–5), while all other results were insignificant. Intravenous ampicillin/sulbactam and oral clarithromycin were administered initially. Bacteriological and serological tests revealed no pathogenic bacteria in the sputum culture and no ARB was detected in the sputum sample. Serological tests for HBsAg, anti-HCV and anti-HIV produced negative results, and it was subsequently decided to take a surgical biopsy specimen given the lack of any significant pathological-microbiological results and no response to antibiotic treatment. The patient was transferred to the thoracic surgery clinic of our hospital and, after a pre-operative evaluation, underwent video-thoracoscopic surgery (VATS), during which a lung wedge biopsy specimen was taken. The macroscopic structure of the specimen in the operating theater was reported as "nodulary and palpated as hepatized" by the surgeon. The pathological result of the biopsy specimen supported an LCH diagnosis and immunohistochemistry staining for CD1a, S-100 provided a positive result.

After the cessation of smoking, a prominent regression of pulmonary infiltration was seen on a chest radiograph (Figure 2). During follow-up, the patient reported right inguinal pain and swelling that had not existed at the time of the initial admission. The patient was referred for an ultrasonographic examination for further assessment and bilateral inguinal lymphadenopathy (LAP) which right-sided LAP dominated was detected. An excisional biopsy was taken for the investigation of LAP in another surgery clinic, and the pathology of the excisional biopsy indicated a diagnosis of LCH. A follow-up thorax CT scan revealed bilateral multiple parenchymal lung nodules, the largest of which was 20 mm, and radiology specialist reported the imaging as lung metastases (Figure 3). Consequently, a whole-body positron emission tomography (PET) scan was planned, revealing increased Fluorodeoxyglucose (18F-FDG) uptake in the bilateral lung parenchymal nodules, iliac lymph nodes and inguinal regions.

The patient was referred to hematology clinic for the investigation of lymphoproliferative diseases, where bone marrow biopsy was administered with normocellular results. The hematology clinic decided to start administration of cytotoxic drug regimen and to monitor progress at follow-up.

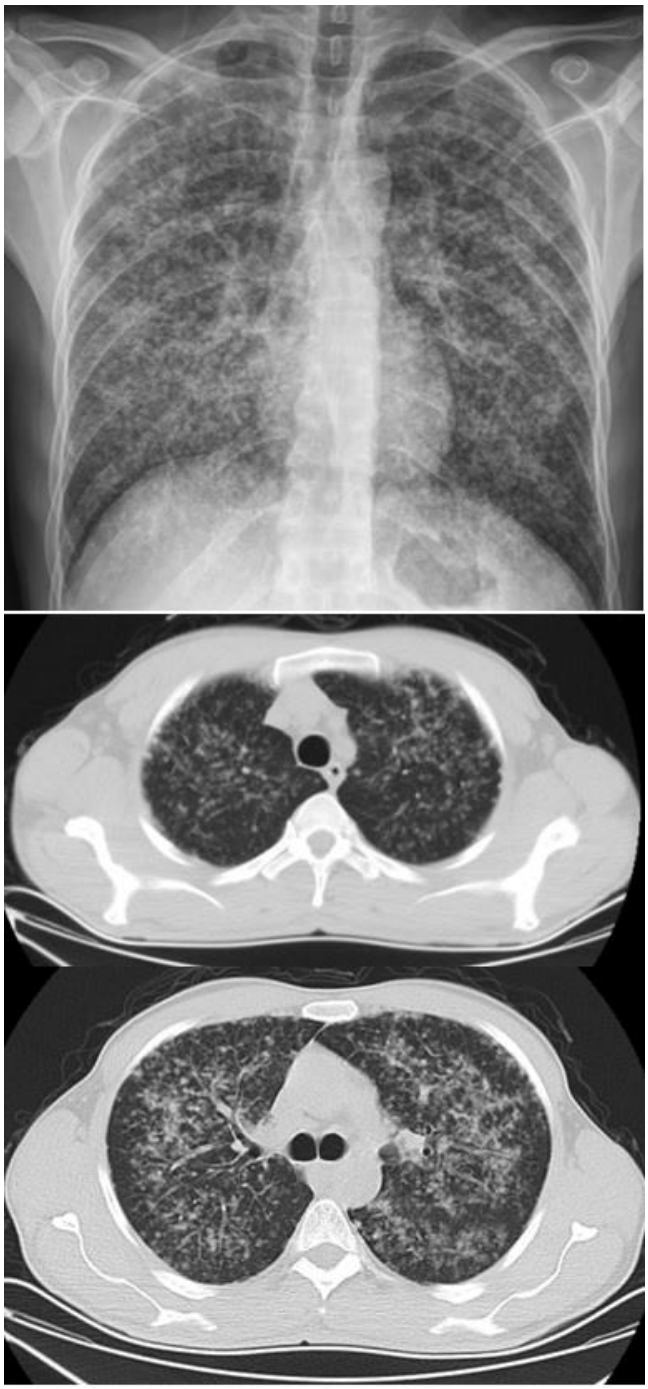

Figure 1: Chest X-ray and Thorax CT at Admission

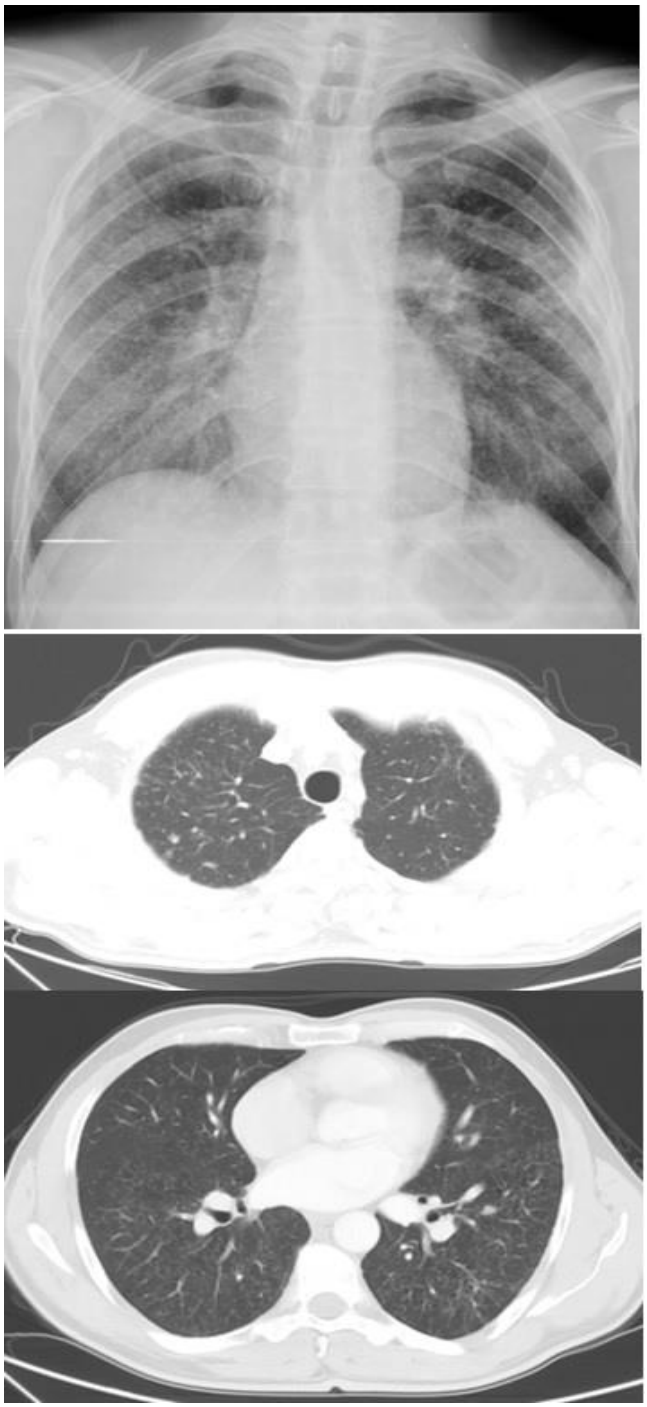

Figure 2: Chest X-ray and Thorax CT After Cessation of Smoking

DISCUSSION

LCH is a prominent disease in pulmonary medicine given its prevalence among young adults with a history of smoking and its presentation with isolated pulmonary involvement. The incidence of the disease is very rare, and its co-existence with various malignancies has been reported. Retrospective studies have suggested that the risk of acute myeloid leukemia is increased in cases with LCH (9). Thus, the risk of secondary malignancies should be considered during follow-up.

In a study reporting on a 42-year-old male patient with an asymptomatic skin lesion on the left arm, a biopsy specimen revealed a diagnosis of LCH. On follow-up, the patient was admitted to hospital with gastrointestinal symptoms such as vomiting and diarrhea. An esophagogastroduodenoscopic evaluation revealed LCH involvement of the duodenum and esophagus with features of Langerhans cell sarcoma, and a cytotoxic drug regimen of cytarabine was administered. During treatment, the patient was diagnosed with acute monoblastic leukemia that progressed aggressively and resulted in the death of the patient (10).

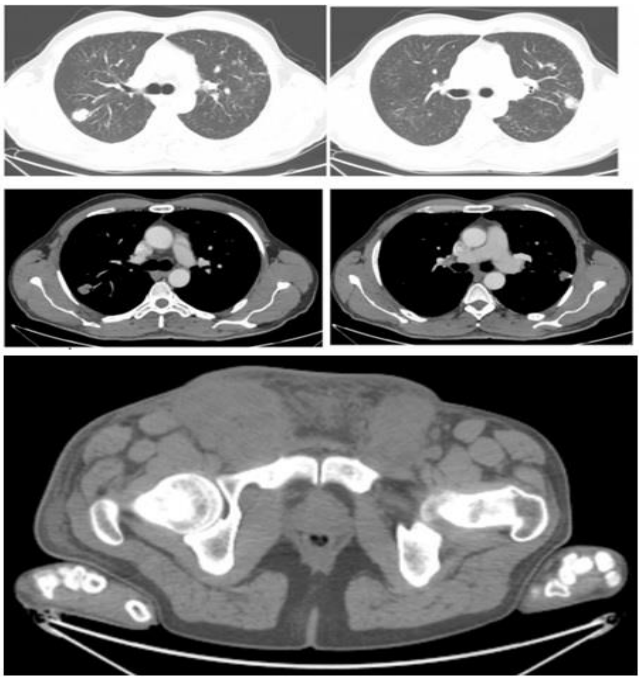

Figure 3: Parenchymal Lung Nodules and Inguinal Lymph Node on CT

The main symptoms of LCH are non-productive cough and shortness of breath (7); 25% of patients have no symptoms; 20% with chest pain are identified with spontaneous pneumothorax; and around 10% of the cases have extrapulmonary organ involvement (11).

Physical examinations and chest radiographs are primary approaches to the assessment of respiratory symptoms. Around 10% of patients have normal chest X-ray findings, while radiological findings may alter during different stages of the disease. Reticulomicronodular infiltration is the most common finding, and cystic lesions may be found in the upper and middle lung zones, whereas costophrenic sinuses are not involved (12).

High-resolution computed tomography (HRCT) imaging is the main approach to the detailed investigation of lung parenchyma, potentially revealing small nodules, cavitary nodules, and thick and thin-walled cystic changes. Nodules are generally found to have a centrilobular distribution, and as the disease progresses, cystic lesions tend to predominate. Nodules transform gradually into cavitary nodules, and then into thick-walled and thin-walled cysts (13). Pleural effusion and mediastinal LAP are not seen (11).

While transbronchial lung biopsy is diagnostic, with a success rate of 15–40%, thoracoscopic biopsy is usually recommended for diagnosis (14).

Studies of patients with PLCH published in Türkiye have reported on the clinical course of the disease. One case series followed six cases over the course of 6 years, five of whom were smokers, and the common finding from HRCT imaging was cystic lesions. The main approaches to the management of the disease were cessation of cigarette smoking and the administration of methylprednisolone 0.5 mg/kg daily. Diabetes insipidus developed in two of the cases, who were treated with desmopressin 0.1 mg/d leading to clinical improvement 1 month later (15).

Another case series from Türkiye followed four cases for 8 years, all of whom were smokers and two had a history of spontaneous pneumothorax. The cessation of cigarette smoking, and the administration of methylprednisolone 0.5 mg/kg daily were the main treatment approaches. One patient in his 20s declined the treatment and developed respiratory failure 3 years later. Echocardiographic evaluation revealed a pulmonary artery pressure of 80 mmHg. The patient was hypoxemic, and so long-term oxygen therapy was planned, and he was referred to a lung transplantation center (16).

Mutations in the MAP kinase pathway (RAS-RAF-MEK-ERK signaling) resulting in disruptions in myeloid cell differentiation have been suggested as contributing to disease development. The BRAF V600E mutation leads to the excessive activation of this pathway (Figure 4) (17), and so approaches involving such pathway proteins as MEK and BRAF are thought to have therapeutic potential.

Spontaneous remissions may occur in cases with pulmonary LCH, and the disease may not progress without treatment (7). There is a lack of consensus on the optimum treatment regimen due to the rarity of the disease and the shortage of randomized controlled trials. The currently applied treatment regimens are based generally on pediatric clinical trials and experience.

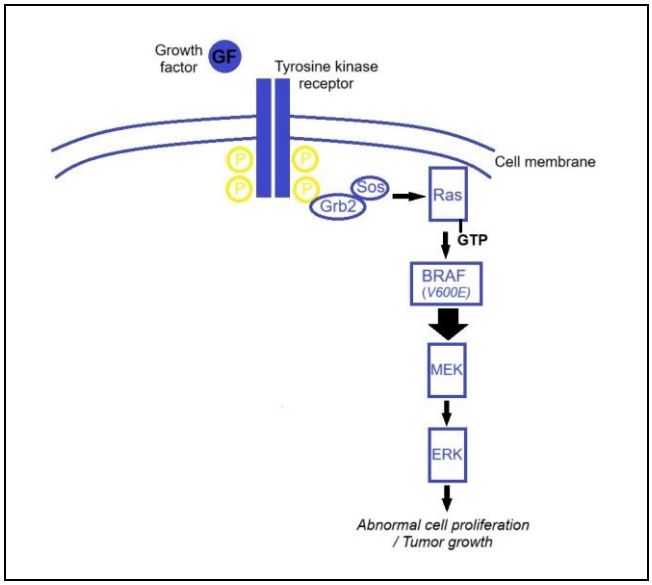

Figure 4: MAP Kinase Pathway

First-line systemic treatment regimens have been categorized by the European Consortium for Histiocytosis (ECHO), and these regimens are based primarily on case series reports and expert opinions. For cases with mild symptoms that do not have the involvement of risk organ, a regimen of methotrexate 20 mg per week po/IV or Azathioprine 2 mg/kg/d po is proposed, while for symptomatic cases, a regimen of cytarabine or etoposide 100 mg/m2 d1-5 q4w is suggested (18).

The cessation of cigarette smoking is a vital aspect of disease management. Glucocorticoid and cytotoxic treatment regimens are used empirically (11).

In another case report detailing a 31-year-old female patient with a suspected left femur lesion, an excisional biopsy revealed a diagnosis of LCH. Chemotherapy involving vinblastin and prednisolone was administered. Aside from her bone involvement, the case had multiple cystic lung infiltrations and involvement of the pituitary stalk. Recurrent pneumonia and pneumothorax developed during follow-up that led to septicemia and the death of the patient (19).

Some 25% of pulmonary LCH patients may progress aggressively and undergo diffuse cystic/destructive changes that result in end-stage fibrotic lung disease (7). The identification, investigation and reporting of new cases is vital due to the severity and lack of clinical data on adult patients, and would contribute significantly to medical literature.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

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

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