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KLİNİK ÇALIŞMA
RESEARCH ARTICLE

General features of patients with Pulmonary Langerhans Cell Histiocytosis followed in our instution

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SUMMARY

General features of patients with Pulmonary Langerhans Cell Histiocytosis followed in our instution

Introduction: *Pulmonary Langerhans Cell Histiocytosis (PLCH) is a rare disease affecting young smokers. It is more common between the ages of 20-40 and equals the male/female ratio. Lung biopsy is the most useful methods for diagnosis. The first treatment is to quit smoking. Corticosteroids or chemotherapeutic agents can be used in severe progressive cases despite of quiting smoking. The patients with PLCH followed in our clinic were assessed with general clinical features in the light of the literature.*

Materials and Methods: *We retrospectively evaluated patients with PLCH in our clinic between January 1999 and June 2017.*

Results: *The female and male distribution of the 21 patients was 11/10. The average age was 35.04 ± 11.78 years. All patients were active smokers at the time of admission. The most common symptom was dyspnea. The most common finding in the pulmonary function tests was obstructive ventilatory defect. The DLCO value of the 70% patient in the carbonmonooxid diffusion test was below 80%. The most common pathologic findings detected in high-resolution chest tomography (HRCT) were cystic lesions involving bilateral upper and middle areas. There were 3 (14%) patients with pneumothorax at the time of admission and 6 (28.5%) patients with pneumothorax history before. The most common diagnostic method was open lung biopsy. All the patients quit cigarette after the diagnosis. There were 6 patients using steroid therapy, 1 patient receiving steroid and bosentan therapy, and 1 patient made pleurectomy due to recurrent pneumothorax. Lung transplantation was done to patient who received combined bosentan treatment with steroids.*

Conclusion: *PLCH is a rare disease and should be considered in young, smokers with spontaneous pneumothorax and cystic lung disease in the differential diagnosis. As more diffusions are affected in patients, respiratory functions for follow-up should be evaluated with diffusion tests. It is essential to quit smoking in therapy.*

Key words: *Pulmonary Langerhans Cell Histiocytosis; smoking; spontan pneumothorax*

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ÖZET

Kliniğimizde takip edilen Pulmoner Langerhans Hücreli Histiyositozis olgularının genel özellikleri

Giriş: *Pulmoner Langerhans hücreli histiositozis (PLHH) genellikle sigara içen genç erişkinleri etkileyen nadir görülen difüz parankimal akciğer hastalığıdır. Yirmi ila kırk yaşlar arasında daha sık olup kadın/erkek oranı eşittir. Kesin tanı bronkoskopik veya cerrahi akciğer biyopsisiyle konur. Tedavi rejiminin ilk basamağı sigarayı bırakmaktır. Sigarayı bırakmasına rağmen ciddi progresif hastalarda kortikosteroid veya kemoterapötik ajanlar kullanılabilir. Kliniğimizde takip edilen PLHH olgular literatür eşliğinde genel klinik özellikleriyle değerlendirilmiştir.*

Materyal ve Metod: *Kliniğimizde Ocak 1999- Haziran 2017 tarihleri arasında PLHH tanısıyla takip edilen hastalar retrospektif olarak değerlendirildi.*

Bulgular: *Yirmi bir hastanın kadın erkek dağılımı 11/10'du. Yaş ortalamaları 35.04 ± 11.78 yıldı. Tüm hastalar başvuru anında aktif sigara içiyorlardı ve sigara içme süreleri median 10 (min:1-max:80) paket/yıl'dı. En sık başvuru semptomu nefes darlığıydı. Solunum fonksiyon testlerinde en sık bulgu obstrüktif tip solunum defektiydi. Karbonmonoksit difüzyon testinde %70 hastanın DLCO değeri %80'in altındaydı. Yüksek çözünürlüklü akciğer tomografisinde (YÇBT) saptanan en sık patolojik bulgu bilateral üst ve orta alanları tutan kistik lezyonlardı. Başvurusunda YÇBT'sinde pnömotoraks olan 3 (%14) hasta varken daha önce pnömotoraks öyküsü olan hasta sayısı 6 (%28.5)'ydı. Tanı iki hastada klinik ve radyolojik olarak konulmuştu, diğer hastaların biyopsi tanısı mevcuttu. En sık kullanılan tanı yöntemi açık akciğer biyopsisiydi. Bronkoalveolar lavaj sıvısında CD1a pozitifliği görülse de sadece 2 hastada %5'in üzerindeydi. Tüm hastalar tanıdan sonra sigarayı bıraktı. Steoroid tedavisi kullanan 6 hasta, steroid ve bosentan tedavisi alan 1 hasta, tekrarlayan pnömotoraks nedeniyle plörektomi uygulanan 1 hasta mevcuttu. Steroidle kombine bosentan tedavisi alan hastamıza akciğer transplantasyonu uygulandı.*

Sonuç: *PLHH nadir görülen bir hastalık olup spontan pnömotoraks nedeniyle başvuran genç, sigara içen hastalarda kistik akciğer hastalığı ayrıcı tanısında düşünülmelidir. Hastalarda daha çok difüzyon etkilendiğinden takip için solunum fonksiyonları difüzyon testleriyle birlikte değerlendirilmelidir. Tedavide sigaranın bırakılması esastır. Progrese hastalarda steroid gibi immünsüpresif ilaçlar kullanılabilir. İleri evre hastalar transplantasyon için değerlendirilmelidir.*

Anahtar kelimeler: *Pulmoner Langerhans Hücreli Histiositoz; sigara; spontan pnömotoraks*

INTRODUCTION

Pulmonary Langerhans Cell Histiocytosis (PLCH) is an uncommon diffuse interstitial lung disease generally affecting young smokers. Although the prevalence is unknown, it is generally thought to comprise 3-5% of adults with diffuse interstitial lung disease (1). Approximately 10-20% of adult patients with PLCH show extrapulmonary involvement such as diabetes insipidus (DI), endocrine, skin and bone disease. The relative role of reactive or neoplastic pathogenic process in PLCH is still debated. Monoclonal neoplastic processes have been described as a group of PLCH patients, although it is often seen as a disease with polyclonal nonneoplastic process. These patients frequently carry oncogenic BRAF V600E mutations. BRAF proteins coordinate cellular signaling pathways related to cellular proliferation, differentiation, survival and apoptosis. Thus, mutations of the BRAF gene are thought to contribute to clonal cellular proliferations (2). Vemurafenib, BRAF inhbitor, has been reported to be beneficial in the treatment of advanced PLCH. A similar benefit has been observed in 1-3% of patients with non small cell lung cancer, mostly adenocarcinomas (3-5). Definitive diagnosis of the disease is possible by bronchoscopic or surgical lung biopsy. The mainstay of treatment is smoking cessation; corticosteroids or chemotherapeutic agents can also be used (6). In this study, we aimed to present the collected data of the patients with PLCH followed in our clinic.

MATERIALS and METHODS

Patients followed in our clinic with a diagnosis of PLCH from January 1999 to June 2017 were included in the study. Records of patients were retrieved from the archive and computerized archive of the clinic. Demographic characteristics of the patients, symptoms, physical findings, laboratory and radiological findings, follow-up duration, pulmonary functions tests and outcomes were recorded. The statistical package for social sciences (SPSS) version 22.0 for Windows software (IBM SPSS Statistics Data Editor) was used for statistical analysis of the data. The Shapiro-Wilk test was used to determine whether the continuous variables were normally distributed. Normally distributing variables were given as mean and standard deviation. Variables with no normal-distribution were given as median (minimum-maximum). The study was approved by the ethical committee of the Medical Faculty of the Karabuk University.

Table 1. Demographic, clinical and radiological features of the patients

	(n= 21)
Female/Male	**10/11**
Age (year) (mean ± SD)	**35.04 ± 11.78**
Duration of disease (months) (median, min-max)	**13 (2-119)**
Cigarette (pack-year) (median, min-max)	**10 (1-80)**
Clinical findings	
• Asymptomatic	• 1 (4.7%)
• Cough	• 5 (24%)
• Dyspnea	• 13 (62%)
• Fever	• 1 (4.7%)
• Chest pain	• 5 (24%)
• Hemoptysis	• 2 (9.5%)
• Pneumothorax history	• 6 (28.5%)
• Diyabetes insipidus	• 1 (4.7%)
• Diarrhea	• 1 (4.7%)
• Weight loss	• 1 (4.7%)
HRCT	
• Interseptal thickening	• 3 (14%)
• Nodules	• 7 (33%)
• Cysts	• 14 (66%)
• Pleural thickening	• 3 (14%)
• Unilateral pneumothorax	• 1 (4.7%)
• Bilateral pneumothorax	• 2 (9.5%)

RESULTS

There were 21 patients, 10 males and 11 females. The mean age was 35.04 ± 11.78. The mean age at presentation was 38.3 ± 9.1 for females and 32.09 ± 13.5 for males. All patients were active smokers and the median smoking duration was 10 pack years (min:1- max: 80). The most common symptom was dyspnea. The frequencies of the remaining symptoms are given in Table 1.

The results of pulmonary function tests (PFT) were available for seventeen patients. The PFT showed an obstructive ventilatory defect in 9 (53%), a restrictive ventilatory defect in 4 (23.5%) and was normal in 4 (23.5%). The carbonmonoxide diffusion test (DLCO) was below 80% in 12 patients (70%). The results of PFT and DLCO were presented in Table 2. The most common findings on the high resolution computerized tomography (HRCT) of the lungs were bilateral cystic lesions affecting the upper and middle zones. The HRCT findings were summarized in Table 1. One patient had central DI, suppurative hydradenitis and bone involvement (Hand-Schuller Christian Syndrome) while 1 patient had extrapulmonary involvement comprising gingival, external ear canal and axillary skin lesions. Six patients had a history of recurring pneumothorax, 3 had clubbing, 1 had hypoxemic respiratory failure without pneumothorax and 1 had pulmonary arterial hypertension (PAH) in addition to hypoxemic respiratory failure. Two patients had a

Table 2. Results of pulmonary function test

PFT	**n= 17**
FEV_1 (L) (mean ± SD)	2.33 ± 0.97
FEV_1 (%) (mean ± SD)	71.06 ± 21.64
FVC (L) (mean ± SD)	3.11 ± 1.13
FVC (%) (mean ± SD)	79.77 ± 19.31
FEV_1/FVC (mean ± SD)	74.39 ± 13.78
DLCO (mL/mmHg/dk) (mean ± SD)	13.89 ± 8.73
DLCO% (mean ± SD)	66.41 ± 31.05
Normal pulmonary function test n(%)	4 (23.5%)
Restrictive n(%)	4 (23.5%)
Obstructive n(%)	9 (53%)
DLCO < 80% n(%)	12 (70%)

Table 3. Diagnostic methods and success rates

Diagnostic method	Number of patients underwent diagnostic process	Number of patients whose process is diagnostic	Success rate (%)
Bronchoalveolar lavage	13	2	15
Open lung biopsy	15	15	100
Axillary lesion biopsy	2	2	100
Gingival biopsy	2	2	100

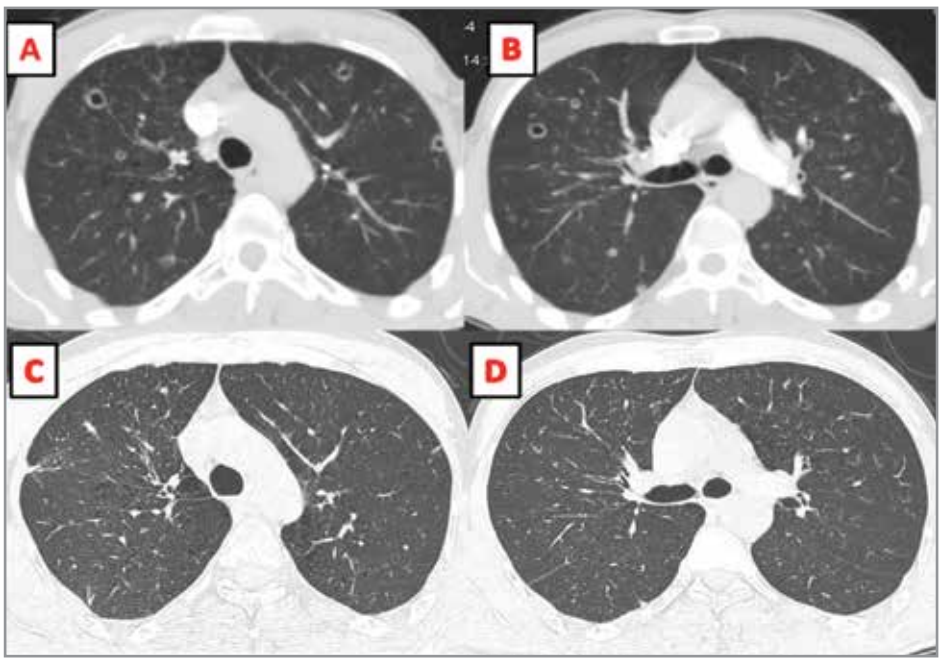

Figure 1. Thorax CT showing the regression **(C,D)** of the cavitary lesions **(A,B)** within 3 months following smoking cessation.

clinical and radiological diagnosis, the remaining were diagnosed by biopsy. Open lung biopsy was the most frequently used diagnostic method and used for 15 patients. Bronchoalveolar lavage demonstrated an increase in the number of CD1a positive cells of more than 5% in 2 patients. Diagnostic modalities and their success are shown in Table 3. The median follow-up time was 13 months (min 2, max 119). All patients quit smoking. One patient with cavitary nodular lesions had complete resolution within 3 months following cigarette cessation (Figure 1). While 13 patients had a non-progressive course and required no treatment, 6 patients with clinically and functionally progressive course were treated with steroids and 1 patient with PAH was treated with bosentan in addition to steroids. For one patient with systemic disease, therapy with cladribine was planned but the patient has not yet received treatment. One patients with recurrent pneumothorax underwent pleurectomy. The patient treated with steroid and bosentan had a lung transplantation but died following transplantation.

DISCUSSION

PLCH is a rare, diffuse interstitial lung disease that can affect single or multiple organs. True incidence and prevalence of disease are unknown given the rarity of the disease and possibly due to cases remaining undiagnosed. Although it affects men and women equally, male patients experience symptoms at an earlier age (7). In accord with previous reports, the gender ratio of the patients was 1:1 and average age of male patients was younger than females in our study. The most common symptoms of the disease are nonproductive cough, dyspnea and chest pain. Nonspesific symptoms such as malaise, weight loss, night sweats and fever can also be seen. Approximately

20% of patients are asymptomatic in the early stages of the disease while half present acutely with symptoms related to pneumothorax (8). Three patients (15%) presented with pneumothorax, while the most common presenting symptom was dyspnea followed by cough. The most common radiological findings of the disease in adults are localised nodules and cysts mostly seen in the upper lobes, sparing the costophrenic sinuses. The initial findings of the disease on HRCT are 1-10 mm sized peribronchial and centrilobular nodules with irregular borders that cavitate and assume a cystic appearance as the disease progresses. Nodules and cysts are frequently found concomitantly. Irregularly shaped cysts of different sizes with a tendency to coalesce predominate in later stages of the disease. The initially thick walls of the cysts become thinner as the disease progresses. There is a wide range of neoplastic inflammatory and infectious diseases featuring similar radiological findings; not to be overlooked are patients with solitary nodular lesions, which broadens the range of differential diagnosis to include sarcoidosis, hypersensitivity pneumonitis and infections (9-11). In our patients, the most common findings on HRCT were cystic lesions with tending to coalesce. In 6 patients the HRCT showed mixed cavitary and solitary nodules seen in the same or different computerized tomography (CT) slices in addition to the cystic lesions. One patient had bilateral multiple cavitary nodules located predominantly in the upper and middle zones. This patient's symptoms included fever, loss of appetite and weight loss and diseases with similar CT findings such as tuberculosis, vasculitis, metastatic colon carcinoma and sarcoidosis were considered in the differential diagnosis and diagnosis of PLCH was established by open lung biopsy.

Despite the fact that young adults with PLCH usually have isolated pulmonary disease, extrapulmonary involvement should be considered and investigated. The most common type consists of skin lesions, cystic bone lesions and DI. The skin lesions are described as red colored papular and subcutaneous nodular lesions affecting the axillary, inguinal, perianal, neck and retroauricular skin that can ulcerate and can be resistant to treatment. Less common is hepatic and lymph node involvement. Liver involvement should be considered if hepatomegaly is present. When coexistent liver enzyme abnormalities are present further evaluation should take place. Invasion of the biliary tract by Langerhans cells can result in cholestasis. Oral cavity involvement such as intraoral masses, gingivitis, mucosal ulcers and loss of teeth can be the first sign of the disease (12-14). Two patients in our study had extrapulmonary involvement; one patient had axillary lesions, cystic bone lesions and DI, another patient had ulcerated axillary, gingival and periauricular lesions. Both patients' HRCT showed bilateral cystic lesions sized over 10 mm with a strong tendency to coalesce, suggestive of PLCH which was confirmed in both by biopsy of the skin lesions.

Pulmonary function testing demonstrate an obstructive ventilatory disorder in more than 50% of PLCH patients while a smaller percentage have restrictive ventilatory disorder or normal pulmonary function. The severity of airflow restriction is related to the extent of parenchymal involvement (15). The diffusion capacity of most patients is disproportionally decreased relative to the spirometric results (16). Similarly, our patients most commonly had decreased DLCO; 53% of patients had an obstructive ventilatory disorder on pulmonary function testing while one half of the remaining patients had a restrictive ventilatory disorder and the other had normal results.

Demonstration of more than 5% of CD1a positive cells supports the diagnosis of PLCH. This result is neither sensitive nor specific because it can also be found in asymptomatic smokers. In a retrospective study by Harari et al., among 16 PLCH patients who had undergone BAL, 10 were found to have positive cells by immune-histochemical and cytoflowmetric methods and only 4 (25%) have more than 5% cells. They observed 100% diagnostic success in the 10 patients who underwent open lung biopsy (17). Thirteen of our patients had BAL, just 2 patients (15%) had more than 5% CD1a positive disease; similar to previous studies. In a study by Sezgi et al., among 6 patients with PLCH, 4 had BAL of which none was diagnostic. In 3 patients who had undergone VATS and 2 patients who had open lung biopsy, the diagnostic success was 100% (18). In our clinic, all 15 patients who underwent open lung biopsy received a diagnosis. One patient was diagnosed by gingival biopsy and another by biopsy of axillary lesions. Even though current data demonstrate that the best method for a definitive diagnosis of the disease is open lung biopsy, we found that similar results can be obtained by biopsies of easily accessible lesions of the tissues affected by the disease. For active smokers, smoking cessation is the cornerstone of treatment. Currently there are no studies comparing the effectiveness of the different treatment protocols. Systemic steroids are suggested as an alternative treatment especially in patients with respiratory

symptoms and a predominance of nodular lesions. In cases with multiorgan involvement and progressive disease not responsive to steroids, chemotherapeutic agents such as vinblastin, methotrexate, cyclophosphamid and etoposide have been used (7). There are limited data on the efficiency of vinblastin in patients with PLCH. A multicenter study showed that a combination of vinblastin and steroids had either no effect or that it did not prevent the progression of lung disease. Cladribin has been reported as a promising treatment for these patients (19). In a study of patients with worsening pulmonary functions despite smoking cessation and steroid treatment, Grobost, et al. have obtained favorable results in both pulmonary function tests and HRCT findings with single-drug Cladribin therapy. Four patients' FEV_1 was improved and 1 patient's FEV_1 decline was stopped. Patients responding best to treatment were those who had hypermetabolism on F-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET-CT) before treatment (20).

In our study one patient showed regression of the lesions within 3 months of smoking cessation. One patient with systemic disease is scheduled to receive cladribin treatment. In treatment resistant cases who have BRAF mutations, drugs acting on the MAP kinase pathway are recommended. Further studies are needed to evaluate their effectiveness (21). An important aspect of treatment is the management of complications. Precapillary PAH is an important complication because it is a bad prognosis indicator. In a study involving 39 PLCH patients that underwent lung transplantation, the prevalence of PAH was 92%, 72.5% of these had moderate to advanced PAH. This study showed that PAH is common among late stage PLCH patients (22). Patients receiving tadalafil demonstrated improvement in functional capacity and 6 minute walk tests (23,24). Le Pavec, et al. have evaluated the efficacy and safety of PAH therapies (endothelin receptor antagonists, phosphodiesterase 5 inhibitor and iloprost/single drug or triple combination) in patients with PLCH associated PAH. They have observed a mild increase in mean pulmonary arterial pressure and pulmonary vascular resistance without a worsening of oxygenation levels (25). Respiratory failure should be treated with long term oxygen. It is suggested that patients with isolated lung involvement and respiratory failure should be referred for lung transplantation (1,9). There were 6 patients who developed pneumothorax during follow-up and one of them underwent pleurectomy. There were 2 patients with hypoxemic respiratory failure and one of them additionally had PAH. It is suggested that PLCH should be followed periodically by physical examination, X-Rays and pulmonary function tests. Sometimes PLCH shows an early progressive course, for this reason during the first year following initial diagnosis, periodic controls should be done every 3 to 6 months. Although lung HRCT is essential for diagnosis, its role in follow-up is not well established. It is suggested in the evaluation of clinical deterioration, worsening pulmonary functions or radiographic progression. Patients with unexpected dyspnea or isolated/disproportionate decrease in DLCO should have echocardiography to evaluate pulmonary hypertension (26,27). The disease generally has a good prognosis. A review encomprising the clinical data of 102 PLCH patients showed a mean survival time of 12.5 years after diagnosis which was shorter that of an age matched control group. Mean 5 and 10 years survival rate were 74% and 64% respectively. Thirty three had died during follow-up and half of the deaths were secondary to respiratory failure. Epithelial or hematologic malignancies were other major causes of death (28). Another study evaluating 29 patients with concurrent PLCH and PAH reported mean 1,3 and 5 year survival of 96%, 92% and 73%, respectively (25). Our patients' median follow-up duration following diagnosis was 13 months (min 2-max 119). We could not access the follow-up data of one of the 2 patients with respiratory failure. Our patient with concurrent respiratory failure and PAH had been treated with steroids and endothelin receptor antagonist and had later received lung transplantation. The patient's survival time after diagnosis was 96 months.

In conclusion, PLCH is a rare disease that should be strongly considered in the differential diagnosis of young, smoking patients with cystic lung disease who present with spontaneous pneumothorax. Because the disease predominantly effect the diffusion capacity, patients should be followed with both pulmonary function tests and diffusion tests. Smoking cessation is essential in the treatment of the disease.

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