ORIGINAL ARTICLE

Clues for the differential diagnosis of hypersensitivity pneumonitis as an expectant variant of diffuse parenchymal lung disease

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Hypersensitivity pneumonitis, also called extrinsic allergic alveolitis, a type of diffuse parenchymal lung disease (DPLD), is an immunologically mediated pulmonary disease induced by inhalation of various antigens. As data on the frequency of hypersensitivity pneumonitis are lacking in Turkey, a retrospective analyses was performed in 43 patients with DPLD, followed up over seven years. The objective was to discover cases fulfilling the diagnostic criteria for hypersensitivity pneumonitis, to determine the frequency and/or the new characteristics of the disease, and to pick up clues for differentiating it from other DPLDs. The four subjects with hypersensitivity pneumonitis (9%) who lived in an urban area were studied in detail. The most common symptoms were dry cough and dyspnoea. According to the symptom duration, clinical features, radiological and pathological findings, three were diagnosed with chronic and one with subacute hypersensitivity pneumonitis. Patients with hypersensitivity pneumonitis and those with DPLD were compared by means of age, sex, smoking status, symptom duration, haematology, erythrocyte sedimentation rate, peripheral cell count, spirometric parameters, blood gases, and diffusion capacity. No statistically significant difference was detected in these parameters except for forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). In conclusion, patients with a history of antigen exposure, with mild symptoms such as dry cough and dyspnoea, and who have diffuse interstitial lung involvement on radiology should be carefully evaluated for hypersensitivity pneumonitis. Moreover, among other DPLDs, stable FEV_1 or FVC values may be the clues for establishing the diagnosis of hypersensitivity pneumonitis. However, further studies are needed in larger series of patients.

Hypersensitivity pneumonitis, an immunologically mediated diffuse parenchymal lung disease (DPLD), is induced by inhalation of a wide variety of organic antigens. According to the American Thoracic Society/European Thoracic Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias, hypersensitivity pneumonitis is accepted as a rare cause of DPLD. Studies on the immune pathogenesis of the disease suggest an initial immune complex mediated lung injury followed by cell mediated pulmonary damage.[1–5]

Hypersensitivity pneumonitis is characterised by diffuse inflammation of lung parenchyma and airways in previously sensitised patients. Based on length and intensity of exposure and subsequent duration of illness, clinical presentations of hypersensitivity pneumonitis are categorised as acute, subacute (intermittent), and chronic (progressive) (table 1). The acute form of the disease manifests as recurrent episodes of dyspnoea and coughs with fever, chills, and malaise occurring about 4–8 hours after exposure to the antigen and usually resolves within about 24–48 hours. In subacute hypersensitivity pneumonitis, an insidious onset of dyspnoea and cough can occur several days to weeks after exposure. Patients exposed over a long period of time (four months or more) to small amounts of antigen are more likely to present with chronic hypersensitivity pneumonitis. Prolonged exposure to low levels of pigeon antigens associated with cohabitation with a small number of birds may cause chronic hypersensitivity pneumonitis.[4 6–8]

Clinical, radiological, and bronchoalveolar lavage findings establish the diagnosis. The diagnosis is confirmed in patients fulfilling four of the major criteria and at least two of the minor criteria (box 1).[4 6 8]

In the United States, studies document 8–540 cases per 100 000 persons per year for farmers and 6000–21 000 cases per 100 000 persons per year for pigeon breeders. Prevalence varies by region, climate, and farming practices. Hypersensitivity pneumonitis affects 0.4%–7% of the farming population. Reported prevalence among bird fanciers is estimated to be 20–20 000 cases per 100 000 persons at risk. However, the overall incidence and prevalence of hypersensitivity pneumonitis is unknown worldwide.[1 2 9]

Similarly, we are unfortunately unaware of the incidence or prevalence of hypersensitivity pneumonitis in our country. Turkey is an agricultural country and many people have been subjected to organic dusts, which are causative agents for hypersensitivity pneumonitis. However, very few patients have been reported. The underestimation of mild symptoms by patients or poor diagnostic facilities in rural areas may account for this situation.

Hence, a retrospective analysis was performed in patients with DPLD to find out the cases fulfilling the diagnostic criteria for hypersensitivity pneumonitis with the aim of determining the frequency, to find out new characteristics of the disease, and to pick up clues for differentiating it from other DPLDs.

PATIENTS AND METHODS

We reviewed the medical records of 43 patients with DPLD from 1995 to 2002. The files of patients registered in the DPLD unit were retrospectively evaluated. The patients' age,

Abbreviations: DLCO, diffusion capacity of the lung for carbon monoxide; DPLD, diffuse parenchymal lung disease; FEV_1, forced expiratory volume in one second, FVC, forced vital capacity

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Table 1 Key features of clinical forms of hypersensitivity pneumonitis[7]

Clinical form	Time frame	Clinical features	Pathology	Findings on computed tomography	Prognosis
Acute	4–48 hours	Fever, chills, cough	Alveolitis	Ground glass infiltrate	Good
Subacute	Weeks–4 months	Dyspnoea, cough	Granulomas, bronchiolitis	Micronodules, air trapping	Good
Chronic	4 months–years	Dyspnoea, cough, fatigue	Lymphocytic infiltration and fibrosis	Fibrosis, honeycombing	Poor

gender, clinical features, smoking status, symptom duration, radiological and spirometric test findings, diffusion capacity of the lung for carbon monoxide (DLCO), arterial blood gas analyses, and peripheral blood smears and immunoglobulin levels, skin tests, initial diagnosis, and the end diagnosis were noted for all patients. Additionally, fibreoptic bronchoscopy findings, bronchoalveolar lavage results, and findings on histopathological examination were reviewed.

The diagnoses of DPLD and hypersensitivity pneumonitis were made according to the criteria of the American Thoracic Society/European Thoracic Society consensus classification for idiopathic interstitial pneumonias.

The measurable data were expressed as mean (SD). The statistical analyses were performed by using SPSS biostatistics program. Hypersensitivity pneumonitis and DPLD groups were compared by Mann-Whitney U test and a p value <0.05 was considered significant.

RESULTS

Forty three patients (M/F = 22/21) having the initial diagnosis of DPLD were enrolled in the study. The mean age was 48.76 (14.3) (range 23–77) years. Four patients fulfilled the diagnostic criteria of hypersensitivity pneumonitis; the remaining 39 subjects with the end diagnosis of DPLD (M/F = 20/19) were evaluated. The mean age of these DPLD patients was 49.20 (14.7) (range 23–77) years.

Box 1: Diagnostic criteria for hypersensitivity pneumonitis[11]

Major criteria

- History of symptoms compatible with hypersensitivity pneumonitis that appear or worsen within hours after antigen exposure.
- Confirmation of exposure to the offending agent by history, investigation of the environment, serum precipitin test, and/or bronchoalveolar lavage fluid antibody.
- Compatible changes on chest radiography or computed tomography of the chest.
- Bronchoalveolar lavage fluid lymphocytosis, if bronchoalveolar lavage performed.
- Compatible histological changes, if lung biopsy performed.
- Positive natural challenge or by controlled inhalational challenge.

Minor criteria

- Basilar crackles.
- Decreased diffusion capacity.
- Arterial hypoxaemia, either at rest or with exercise.

The final diagnosis of patients with DPLD is shown in table 2. The most common symptoms were dyspnoea and dry cough among DPLD patients. The mean duration of symptoms was 25.50 (30.7) (range 1–132) months (two patients had no symptoms). Seventeen patients smoked 13.84 (23.5) (range 7–120) pack-years of cigarettes. The occupations were 18 housewives, 17 civil servants, two farmers, one cook, and one student without any history of organic or inorganic dust exposure. The physical examination revealed Velcro-type end inspiratory crackles in most patients (n = 24, 61.5%) and ronchi in only three patients (7.6%).

The eosinophil counts were in the normal range (0.24 (0.2) $\times$ 10^9/l, range 0–0.5) in peripheral blood smears of DPLD patients. Iron deficiency anaemia was encountered in two patients (5.1%). IgE levels were determined in three patients and were in the normal range. Skin test was not performed in patients with DPLD.

Spirometric tests were done in all subjects but four patients did not cooperate. The spirometric test was normal in 18 (46.1%) patients. In 13 (37.1%) patients a restrictive pattern and in four (10.2%) patients an obstructive pattern was seen. The mean (SD) forced expiratory volume in one second (FEV_1) (% of predicted), forced vital capacity (FVC) (% of predicted), and the ratio of FEV_1 to FVC (FEV_1/FVC) of DPLD patients were 71.7 (20), 74.8 (22.1), and 81.3 (11.9) respectively. DLCO (% of predicted) was decreased in 20 DPLD patients (mean (SD) 56.4 (23), range 32–111), but 14 patients were not cooperative for diffusion testing and the remaining five were normal. DLCO adjusted for alveolar volume (% of predicted) was increased in 18 patients (mean (SD) 94 (29.9), range 39–200) supporting restrictive abnormality.

Chest radiography revealed diffuse reticulonodular involvement in nearly all patients (n = 32, 82%) with DPLD. High resolution computed tomography showed thickening of interlobular septa and ground glass opacities in most patients (n = 23, 58.9%). Hilar lymphadenopathy was detected in nine

Table 2 Diagnoses of the patients with DPLD

Diagnosis	No (%)
Idiopathic interstitial pneumonia (IPF: 14, AIP: 1, NSIP: 1, COP: 5, LIP: 1, DIP: 1, RB-ILD: 1)	24 (55)
Sarcoidosis	9 (21)
Hypersensitivity pneumonitis	**4 (9)**
Histiocytosis X	2 (4.6)
Ankylosing spondylitis + pulmonary involvement	1 (2.3)
Antracosis	1 (2.3)
Pneumoconiosis	1 (2.3)
Idiopathic pulmonary haemosiderosis	1 (2.3)
Total	43 (100)

IPF, idiopathic pulmonary fibrosis; AIP, acute interstitial pneumonia; NSIP, non-specific interstitial pneumonia; COP, cryptogenic organising pneumonia; LIP, lymphocytic interstitial pneumonia; DIP, desquamative interstitial pneumonia; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease.

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patients (23%) and alveolar consolidations in five patients (12.8%) with DPLD.

Fibreoptic bronchoscopy revealed no abnormality in any of the patients with DPLD. Bronchoalveolar lavage revealed various results. Lymphocytic alveolitis or neutrophilic alveolitis was found in patients with idiopathic interstitial pneumonia. Lymphocytic alveolitis and increased CD4/CD8 ratio were found in sarcoidosis patients. Eosinophil-like cells (n = 2) and Birbeck granules on electron microscopic evaluation (n = 1) were seen in patients with histiocytosis X. Charcoal pigment-laden macrophages and haemosiderin-laden macrophages were found on light microscopy in a patient with pneumoconiosis and another with pulmonary haemosiderosis respectively.

The type of DPLD was determined by transbronchial lung biopsy and/or open lung biopsies in all patients. Transbronchial lung biopsy was performed in 29 patients (74.3%) and revealed diagnostic findings in eight patients (27.5%). Open lung biopsies were performed in eight patients (20.5%) and revealed diagnostic findings in seven patients (87.5%).

Two patients diagnosed with idiopathic interstitial pneumonia and idiopathic pulmonary haemosiderosis died within a year of the establishment of the diagnosis. Twenty three patients were followed up for a total of 88.1 (253.0) months; the other 14 patients were lost to follow up.

Only four patients (9%) fulfilled the criteria for the diagnosis of hypersensitivity pneumonitis. Their mean age was 44.25 (10.6) (range 36–59) years with a M/F ratio of 2/2; they all lived in an urban area. The occupation of the subjects were archive clerk (n = 2) and bird fancier (n = 2) and they were never exposed to any kind of humidifier or air conditioning. They denied a history of asthma. All patients were admitted to hospital with dry cough and dyspnoea that they had for five months (n = 1), three months (n = 1), and three years (n = 2). All, but one were non-smokers. The physical examination of two patients was normal and the other two had basal crackling sounds and ronchi (table 3). None of the patients had abnormal IgE levels. They had normal eosinophil counts (0.12 (0.05) $\times 10^9$/l, range 0.1–0.2). Their non-specific bronchial provocation tests were negative. In cases 1 and 4 skin tests against common allergens and serum precipitins against thermophilic actinomycetes and *Micropolyspora faeni* were negative.

Findings on spirometric testing were in the normal range in all patients with hypersensitivity pneumonitis. DLCO was decreased in cases 2, 3, and 4. We observed hypoxaemia with exercise in case 1 and at rest in case 2 (table 3).

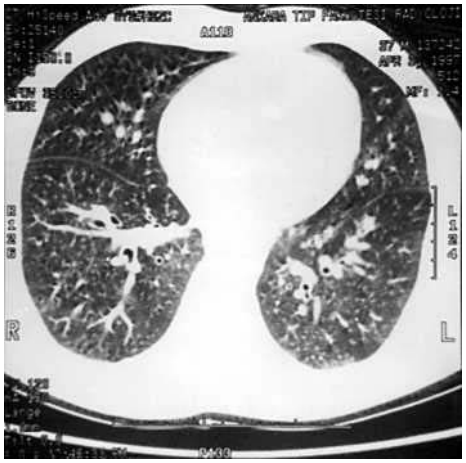


Figure 1 High resolution computed tomogram of case 1 showing micronodular infiltration in both medial and lower zones, ground glass opacifications in lower lobes with interlobular septal thickening representing chronic type hypersensitivity pneumonitis.

Chest radiography and high resolution computed tomography findings of the subjects are summarised in table 4 and shown in figs 1, 2A, 3A-B, and 4 A-B.

Fibreoptic bronchoscopy was performed in all cases except case 2, as she refused the procedure. The predominancy of lymphocytes was found in bronchoalveolar lavage fluid examinations; the CD4/CD8 ratio of the lavage fluid was decreased in cases 1 and 3 and increased in case 4 (table 4).

In case 1 transbronchial lung biopsy revealed lymphocytic infiltration, however in cases 3 and 4 the biopsy was non-diagnostic. The diagnosis of hypersensitivity pneumonitis was established via the history and from radiological and findings on bronchoalveolar lavage.

As findings on high resolution lung biopsy persisted after five months of inhaled steroid therapy, case 1 underwent open lung biopsy. Histopathological examination of the biopsy specimen showed a non-specific type of chronic inflammation and mild fibrosis (table 4; fig 5).

All subjects had been living in an urban area and were advised to avoid the possible antigen. Case 1 was treated with inhaled fluticasone propionate (2000 µg/day) for 16 months and at follow up he has been well for five years with normal findings on radiology, spirometric testing, and arterial blood gas analyses. Case 2 was treated with oral prednisolone

Table 3 Characteristics, spirometric findings, diffusion capacities, and arterial blood gas values of the four patients with hypersensitivity pneumonitis (HP)

Case	Age (years)	Gender	Tobacco (pack-years)	Exposure	Time frame	Clinical features	Physical examination	Stage of HP	Spirometric tests	Diffusion capacity (DLCO % of predicted, DLCO/VA)	Arterial blood gases
1	38	M	30	Archive clerk, dust	5 months	Dyspnoea, dry cough,	Crackles, ronchi	Chronic	Normal	Normal (101, 96.3)	Normal P_{O_2}; hypoxaemia after exercise (P_{O_2} 8.9 kPa)
2	45	F	0	Lovebird	3 months	Dyspnoea, dry cough	Crackles, ronchi	Subacute	Normal	Decreased (55, 70)	Hypoxaemia at rest (P_{O_2} 9.3 kPa)
3	36	M	0	Archive clerk, dust	3 years	Dry cough	Normal	Chronic	Normal	Decreased (44, 57)	Normal
4	59	F	0	Lovebird	3 years	Dry cough	Normal	Chronic	Normal	Decreased (64, 70)	Normal

DLCO, diffusion capacity of the lung for carbon monoxide; DLCO/VA, DLCO adjusted for alveolar volume; P_{O_2}, partial oxygen pressure.

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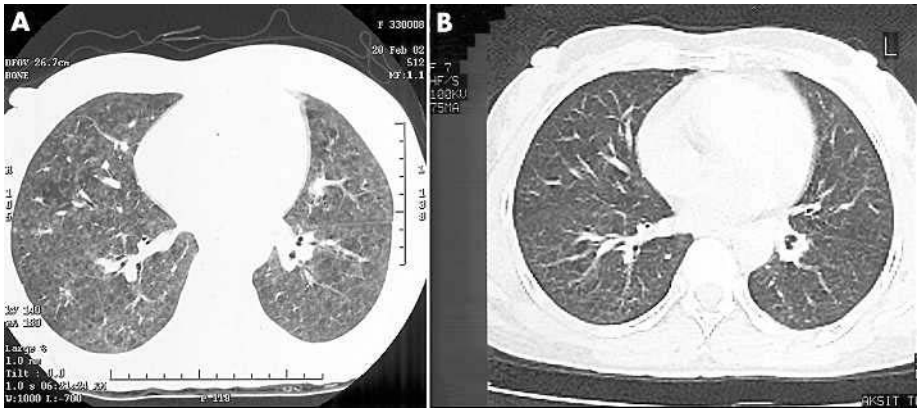


Figure 2 High resolution chest computed tomograms of the chest in case 2 with subacute hypersensitivity pneumonitis: (A) ground glass opacifications and centriacinar micronodules (before treatment) and (B) resolution of the findings (after treatment).

(40 mg/day; tapered gradually) for six months and after three months of steroid therapy a prominent regression was seen on chest radiography and high resolution computed tomography (fig 2B). The other two cases were not given any drugs: the symptoms and findings resolved with avoidance of the antigen exposure (table 4).

Patients with hypersensitivity pneumonitis and those with other DPLDs were compared by means of age, gender, smoking status, symptom duration, haematology, erythrocyte sedimentation rate, and peripheral cell count, spirometric parameters, arterial blood gas analyses, DLCO, and DLCO adjusted for alveolar volume. No statistically significant difference was detected in these parameters ($p>0.05$) excluding FEV_1 and FVC. These two parameters were found to be significantly high in patients with hypersensitivity pneumonitis ($p<0.05$) (table 5; fig 6A and B).

DISCUSSION

According to the American Thoracic Society/European Thoracic Society consensus classification for idiopathic interstitial pneumonias, hypersensitivity pneumonitis is a rare cause of DPLD.[5] Hypersensitivity pneumonitis, that is, extrinsic allergic alveolitis, is a disease which develops by inhalation of antigens, like micro-organisms, animal proteins, and haptens formed on endogenous proteins by inhalation of volatile chemicals.[6–8 10–12] It was first described by Finsen in 1874 in Iceland.[1] The prevalence of idiopathic interstitial pneumonias varies by population, probably due to differing intensity, frequency, and duration of inhalation exposure. Very few cohort studies of incidence rates of idiopathic interstitial pneumonias have been published.[8] Among pigeon breeders, 8%–30% were shown to have hypersensitivity pneumonitis. Also farmers have been shown to suffer this disease with an incidence of 0.5%–5%.[13]

Hypersensitivity pneumonitis is the result of a cell mediated immune response of the lung to a wide variety of inhaled antigens. The outcome is variable depending upon several factors, such as duration of the antigen exposure, the concentration and chemical composition of the inhaled antigens, and the age and genetic background of the subject.[1–3 7 8] Significant exposures occur at home; they are especially associated with pet birds and heavy concentrations of indoor moulds.[7 8] Two of the subjects reported here were bird fanciers and two others were working in archives full of dusty files where hermophilic agents can exist. Although we could not document the antigen objectively, the regression of the symptoms with avoidance of the antigenic media strongly suggested hypersensitivity pneumonitis.

Physical examination is unlikely to be helpful in establishing the diagnosis of hypersensitivity pneumonitis, but the presence of bibasilar crackles and wheezing is expected on auscultation of the lung.[1–3 7 11] Two of our four patients (cases 1 and 2) had bibasilar crackles; this is a minor criterion used to substantiate the diagnosis of hypersensitivity pneumonitis.

Although, hypersensitivity pneumonitis is also called extrinsic allergic alveolitis, it does not show evidence of allergy such as skin test positivity, high IgE levels, and eosinophilia.[7 8 11] Additionally, routine laboratory tests and specific serum precipitating antibodies were unhelpful to establish the diagnosis in present subjects. So, it was not possible to distinguish hypersensitivity pneumonitis from DPLD by these tests.

Spirometric testing usually demonstrates restrictive changes with impaired DLCO being neither specific nor

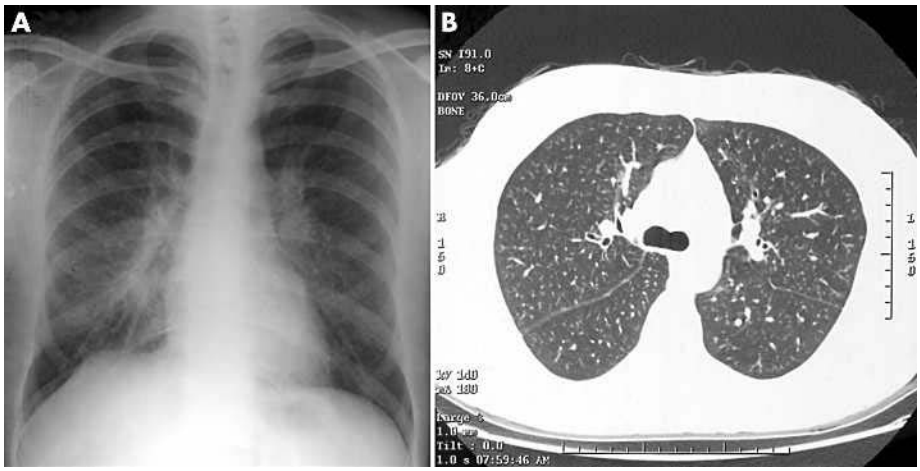


Figure 3 (A) Chest radiograph in case 3 with chronic hypersensitivity pneumonitis showing bilateral hilar enlargement and micronodular pattern in paracardiac region. (B) High resolution chest computed tomogram in case 3 showing bilateral micronodular interstitial infiltrations and nodules seen on both thick major fissures.

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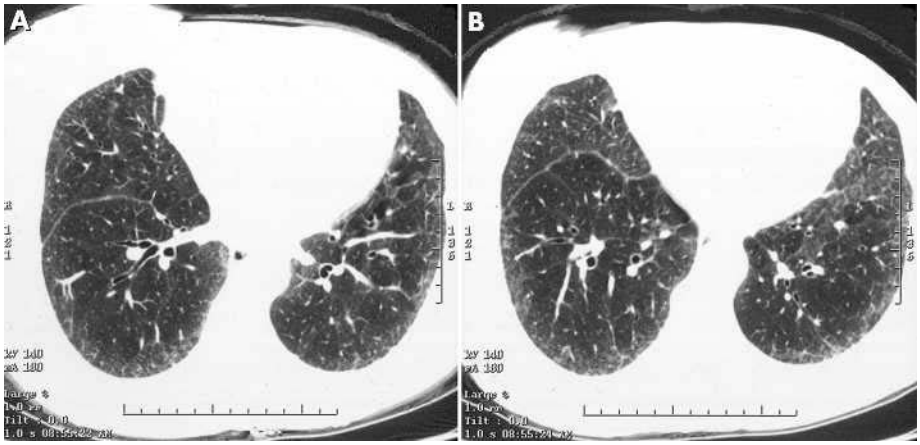


Figure 4 (A) and (B) High resolution chest computed tomogram in case 4 with chronic hypersensitivity pneumonitis showing bilateral interlobular septal thickening, subpleural linear opacities, and scattered ground glass opacifications.

diagnostic for hypersensitivity pneumonitis.[4 7 8 10 14] In the present cases no abnormality was detected on spirometric tests. Moreover, FEV_1 and FVC were found to be significantly higher than in the other DPLD group. Arterial blood gases and diffusion values can also be impaired in the early period of the disease like other DPLDs. Although spirometric measurements were preserved in the present cases, DLCO was decreased in two patients and hypoxaemia was detected at rest in one patient and after exercise in one. The point of interest is that, despite the normal spirometric findings, DLCO and partial oxygen pressure were decreased, indicating that gas exchange in the lungs was disturbed. These were other important clues in differential diagnosis hypersensitivity pneumonitis from other DPLDs.

A particularly characteristic pattern of the high resolution computed tomography is the presence of ground glass shadowing, bilateral micronodular infiltrates, and honeycomb lung depending on the stage of the disease.[4 5 7 8 10 15] Chest radiography and high resolution computed tomography of the chest supported the diagnosis of hypersensitivity pneumonitis in the present subjects, showing ground glass attenuation with a micronodular pattern. The radiological findings of cases 1 and 2 resolved on treatment (inhaled and oral steroids respectively) and in cases 3 and 4 they resolved with avoidance of antigen exposure. As all DPLDs represent with similar radiological findings, chest radiography and high resolution computed tomography of the chest are hardly helpful in distinguishing hypersensitivity pneumonitis from DPLD. However, they may be useful in the follow up of the patients.

The next step in the diagnosis of hypersensitivity pneumonitis is bronchoscopy to obtain lung tissue and bronchoalveolar fluid. The most characteristic cell profile in bronchoalveolar fluid is of a lymphocytic alveolitis with a predominance of CD8(+) T cells. However, findings may vary depending on the timing of the last antigen exposure and the stage of the disease. After acute exposure neutrophils predominate; later, as the disease progresses, the CD4/CD8 ratio increases. But in the subacute form of hypersensitivity pneumonitis, lymphoid follicles containing plasma cells also develop in the lesions and the proliferation of CD4(+) T lymphocytes can be seen in bronchoalveolar fluid.[1–3 5 7 8] In case 4, bronchoalveolar fluid showed CD4(+) T lymphocyte predominance. This fact was probably due to the persistent antigen exposure. The other patients had a predominance of CD8(+) T lymphocytes. These findings were compatible with hypersensitivity pneumonitis, supporting the diagnosis.

In patients with hypersensitivity pneumonitis, a transbronchial lung biopsy was obtained in cases undergoing fibreoptic bronchoscopy. It was non-diagnostic in cases 3 and 4; in case 1 it showed lymphocytic infiltration but did not provide enough proof for the diagnosis.

Although the diagnosis of hypersensitivity pneumonitis can be established by clinical, radiological and bronchoalveolar lavage fluid findings, open lung biopsy may still be required in patients with symptoms of insidious onset and that cannot be clearly related to any particular exposure.[4 7 8] In cases not fulfilling the criteria and not responding to antigen avoidance and therapy, open lung biopsy should be kept in mind as an option. Although case 1 fulfilled the criteria for hypersensitivity pneumonitis, he did not respond to treatment and underwent open lung biopsy.

Antigen avoidance and early diagnosis are the key elements in the treatment of hypersensitivity pneumonitis;

Table 4 Radiological findings, cytohistopathological findings, treatment, and prognosis of patients with hypersensitivity pneumonitis (HP)

Case	Chest radiography	Computed tomography	Bronchoalveolar lavage	CD4+/CD8+(%)	Transbronchial lung biopsy	Open lung biopsy	Treatment	Prognosis
1	Diffuse reticulonodular pattern	Ground glass pattern	Lymphocytic	27/64	Lymphocytic infiltration	HP	Inhaled fluticasone propionate (2000 μg/day)	Good
2	Diffuse reticular pattern	Ground glass pattern, centriacinar micronodules	Not done	Not done	Not done	Not done	Prednisolone 40 mg/day, by mouth	Good
3	Micronodular pattern	Micronodular pattern	Lymphocytic	3/52	Non-diagnostic	Not done	Avoidance of antigen exposure	Good
4	Diffuse reticulonodular pattern	Reticulonodular pattern	Lymphocytic, neutrophilic	52.7/1.3	Non-diagnostic	Not done	Avoidance of antigen exposure	Good

CD4+, T lymphocyte subset presenting CD4 antigen; CD8+, T lymphocyte subset presenting CD8 antigen.

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Table 5 Descriptive features of patients with hypersensitivity pneumonitis (HP) and DPLD and comparative statistics; values are mean (SD)

	HP (n = 4)	DPLD (n = 39)	p Value
Age (years)	44.25 (10.6)	49.20 (14.7)	NS
Gender (M/F)	20/19	2/2	NS
Symptom duration (months)	3.25 (1.5)	22.19 (29.8)	NS
Smoking status (pack-year)	7.50 (15.0)	13.84 (23.5)	NS
Haemoglobin (g/l)	140.5 (10.0)	142.2 (17.0)	NS
Leucocytes ($\times 10^9$/l)	7.02 (1.6)	8.28 (3.6)	NS
Eosinophils ($\times 10^9$/l)	0.12 (0.05)	0.24 (0.2)	NS
Erythrocyte sedimentation rate (hours)	16.5 (7.2	35.15 (25.8)	NS
FEV_1 (%)	103.50 (11.7)	71.79 (20.0)	<0.05
FVC (%)	100.75 (15.5)	75.14 (22.7)	<0.05
FEV_1/FVC	86.25 (3.4)	81.38 (11.9)	NS
DLCO (%)	67.75 (24.1)	56.61 (23.3)	NS
DLCO/VA (%)	73.50 (16.2)	94.03 (29.9)	NS
Po_2 (kPa)	10.9 (1.7)	8.4 (2.1)	NS

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1 to FVC; DLCO, diffusion capacity of the lung for carbon monoxide; DLCO/VA, DLCO adjusted for alveolar volume; Po_2, partial oxygen pressure; NS, not significant.

complete cessation of exposure to the provoking antigen is the safest advice for such patients.[4 7 8 14] Supportive management and a short trial of corticosteroids are appropriate strategies in acute hypersensitivity pneumonitis. Subacute stages might require higher doses of corticosteroids for several months. As it was impossible to avoid the antigen exposure immediately, case 1 failed to respond to high dose inhaled steroids. He underwent an open lung biopsy and this excluded other forms of interstitial pathologies. He was treated with high dose inhaled steroid; the subject with the subacute form (case 2) received systemic steroids for six months. After treatment cases 1 and 2 completely improved clinically and radiologically. The remaining two subjects with chronic hypersensitivity pneumonitis showed spontaneous regression of the disease and remarkable radiological resolution, simply by avoidance of the antigen exposure.

The prognosis of hypersensitivity pneumonitis is quite variable. Many patients recover without any pulmonary physiological or radiological abnormality as seen in the present cases. Others progress to pulmonary fibrosis, often resulting in respiratory failure and death, but it is not predictable at the beginning of the disease.[4 6 7]

Hypersensitivity pneumonitis is not a rare disease in Turkey. We followed up four cases of the disease among 43 patients with DPLD (9%), and they showed a remarkable response to treatment and a good prognosis. Hypersensitivity pneumonitis should be kept in mind when making a differential diagnosis of DPLD. Findings on bronchoalveolar lavage, maintenance of normal FEV_1 and FVC values in the presence of a disturbed DLCO, and partial pressure of oxygen can provide clues leading to the diagnosis of hypersensitivity pneumonitis. Further studies in larger series are required to establish the value of spirometric tests, DLCO, and arterial blood gas analyses in the diagnosis of hypersensitivity

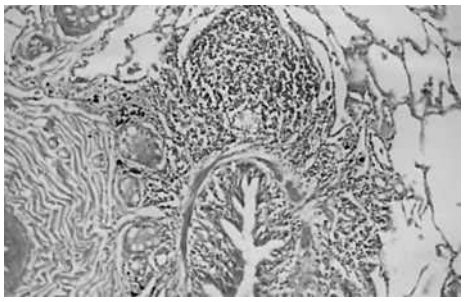


Figure 5 Pathological findings in case 1 with chronic hypersensitivity pneumonitis showing a non-specific type of chronic inflammation distributed around bronchioles leaving the intervening areas of parenchyma uninvolved. Lymphocytes comprised the majority of the infiltrating cells with some plasma cells. Eosinophils and neutrophils were not prominent and fibrosis is minimal, compatible with chronic type hypersensitivity pneumonitis.

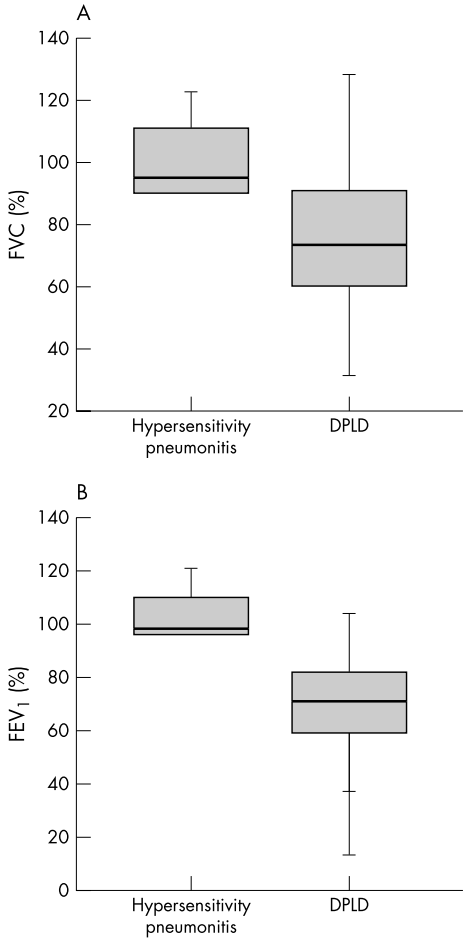


Figure 6 Mean values of (A) FVC and (B) FEV_1 showing significant increase in patients with hypersensitivity pneumonitis when compared with those with DPLD.

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pneumonitis. Open lung biopsy should also be kept in mind as a diagnostic option in selected cases. Avoidance of the antigen exposure is the key element in the treatment of the disease and steroids may be instituted.

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ECHO

Predicting functional outcome in acute stroke: comparison of a simple six variable model with other predictive systems and informal clinical prediction

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Background: Statistical models that predict functional outcome after stroke using six simple variables (SSV) have recently been developed and validated.
Objective: To compare the accuracy of these models with other simple ways of predicting outcome soon after stroke.
Methods: The SSV model for being alive and independent (modified Rankin score $\leqslant 2$) six months or one year after stroke was compared with predictions based on a model that included only age and Oxford community stroke project classification, with predictions based on conscious level and urinary continence, and with informal clinical predictions made by clinicians interested in stroke. Predictions were compared in an independent hospital based cohort of stroke patients using receiver operator characteristic (ROC) curves.
Results: The SSV model at six months had a significantly greater area under the curve (0.84) than the model with only age and stroke classification (0.75). Predictions based on conscious level and urinary continence were no better than those of the SSV model and were unable to predict subjects with a high probability of good outcome. The sensitivity and specificity for informal clinical predictions at one year lay on or below the SSV model curve, implying that the SSV model was at least as good as clinical predictions.
Conclusions: The SSV models performed as well as or better than other simple predictive systems. These models will be useful in epidemiological studies but should not be used to guide clinical management until their impact on patient care and outcome has been evaluated.

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