Hypersensitivity Pneumonitis and Inhaled Steroid (A Case Report)

Demet KARNAK*, Oya KAYACAN*, Sumru BEDER*, Serpil DİZBAY SAK**

* Department of Chest Diseases and Tuberculosis Medical Faculty of Ankara University,
** Department of Pathology Medical Faculty of Ankara University, ANKARA

SUMMARY

It is known that inhaled steroids can be used for the treatment of interstitial lung diseases such as sarcoidosis to avoid systemic side effects of oral or intravenous forms. However there is no information about the role of inhaled steroids in the treatment of hypersensitivity pneumonitis (HP). Here in, a 38 year-old male patient with chronic HP treated by 16 months of high dose inhaled steroid is presented. Inspite of avoiding antigen exposure as much as possible, persisting radiological abnormalities necessitated histopathological confirmation of the diagnosis even if early-good clinical response. All findings were resolved after therapy and no pathology has been detected in a 1.5 year of follow-up. The authors recommend that high dose inhaled steroids should be considered in the treatment of HP. This observation needs to be supported by studies in large series.

Key Words: Hypersensitivity pneumonitis, interstitial lung disease, inhaled steroid.

ÖZET

Hipersensitivite Pnömonisi ve İnhaler Steroid (Olgu Sunumu)

İnterstisyel akciğer hastalıklarında, örneğin sarkoidozda, özellikle sistemik steroidlerin yan etkilerinden kaçınmak için inhaler steroidlerin kullanılıldığı bilinmektedir. Ancak hypersensitivite pnömonisi (HP) tedavisinde inhaler steroidlerin rolü konusunda kesin bir bilgi yoktur. Burada, 16 ay boyunca yüksek doz inhaler steroid tedavi verilen, kronik HP tanılı 38 yaşındaki bir erkek olgu sunulmaktadır. Antijen ekspozisyonundan olabildiğince kaçınmasına rağmen, radyolojik bozulukların kalıcı olması, erken ve iyi klinik yanıt gözleme bile, tanının histopatolojik açıdan doğrulanması gerekliğini ortamba çıkarmıştır. Olgunun tedavi sonrası tüm bulgular tamamen gerilemiş ve 1.5 yıllık izlemde olguda bir patoloji tespit edilememiştir. Yazarlar, yüksek doz inhaler steroidlerin HP tedavisinde akılda tutulması gerektiğini ve bu gözlem genis serilerde yapılan çalışmalarla kanıtlanması gerektiğini ileri sürmektedirler.

Anahtar Kelimeler: Hypersensitivity pneumonitis, interstitial lung disease, inhaled steroid.
In recent years, inhaled steroid therapy for interstitial lung disease has been used especially in pulmonary sarcoidosis without extrapulmonary involvement, bronchiolitis obliterans and organizing pneumonia (1-5). Hypersensitivity pneumonitis (HP) is an immunologically mediated pulmonary disease induced by the inhalation of any of a wide variety of antigens. Studies suggest that an initial immune-complex mediated lung injury is followed by cell-mediated pulmonary damage (6-8). Although systemic steroids are known to be used in the treatment of chronic HP, there is no previous report concerning on the role of inhaled steroids in the treatment of this disease. Therefore we present a case of chronic HP treated successfully with long term high dose inhaled steroid administration.

CASE REPORT

A 38 year-old male was admitted to the clinic with the complaints of dyspnea, wheezing, cough, night sweats and chest-pain of three months duration. These complaints had begun since he had started to work. We learn that he had close contact with file archives which was a dusty medium at work. He had smoked 30 pack-years of cigarette which he had omitted for four months. There was no history of respiratory illness and not any relevant family history.

On admission, his body temperature was 36.7°C. Auscultation of his chest revealed basal crackling sounds and sibilant rhonchi in both lung fields. There was no other pathology in his physical examination. Plain chest roentgenogram (CX-R) demonstrated diffuse fine reticulonodular pattern (Figure 1A). Computed tomogram (CT) of the chest showed a ground-glass like appearance and interstitial shadows throughout both lungs (Figure 1B). 67Galium pulmonary perfusion scintigraphy (67Ga scan) has also demonstrated diffuse increased uptake.

Pulmonary function tests (PFT) showed the forced vital capacity (FVC) to be 3.46 L (87% of predicted), forced expiratory volume in 1s (FEV₁) of 3.11 L (88% of predicted), forced mid-expiratory airflow (FEF25-75) of 4.32 L (100% of predicted), diffusion capacity (DLCO) of 29.6 mL min⁻¹ mmHg⁻¹ (101% of predicted) and transfer factor (DLCO/VA) of 4.64 mL min⁻¹ mmHg⁻¹ (96.3% of predicted). Arterial blood gas measurements were as follows, pH 7.42, PaO₂ 81 mmHg, PaCO₂ 37 mmHg and HCO₃⁻ 24 mEq/L. However, after a 6 minutes of treadmill exercise these measurements were pH 7.37, PaO₂ 67.2, PaCO₂ 39 mmHg, HCO₃⁻ 22.5 mEq/L. The erythrocyte sedimentation rate was 18 mmh⁻¹, leukocyte count was 8900 µL⁻¹. Biochemical parameters were in normal limits.

Skin tests against common allergens and serum precipitins against Thermophilic actinomyces and Micropolyspora faeni were negative. Bronchial provocation test was positive; a 20% of decrease in FEV₁ at concentration of 12.2 mg/mL was established. FEV₁ value was increased by 27% after an inhalation of salbutamol (100 µg) this was commented as positive for reversibility.
He had mild eosinophilia of 300 mm$^{-3}$ and total IgE level of 10.20 kU/mL (laboratory normal range: 1-100 kU/mL). On protein electrophoresis a polyclonal gammopathy was detected.

Fiberoptic bronchoscopy was normal. No asido-resistant basil was found in bronchial lavage or sputum. Bronchoalveolar lavage (BAL) demonstrated the total cell count to be 21 x 10$^6$ with a 43.4% lymphocyte predominance (CD4 27%, CD8 64%, CD4/CD8< 1). Macrophages were found in normal range (53.2%) and most of them had foamy degeneration and 3.4% of cells were granulocytes. Histopathological examination of the transbronchial lung biopsy (TBLB) revealed lymphocytic infiltration and fibrosis of the interstitial spaces.

A diagnosis of chronic type of HP was established through clinical, radiological, BAL and TBLB findings which met the major and minor criteria of the diagnosis (Table 1). The patient notified that it could not be possible to change his job but he would try to avoid of antigen exposure and he was on clinic follow-up. Theophylline derivatives and antibiotics were administered for fifteen days and he was started on high-dose inhaled dry powder steroid therapy (fluticasone propionate-2000 µg/day-fixotide diskus®), in the hospital. This therapy was initiated knowing that functional capacities and blood gases were not so much impared and expecting complete removal from exposure in hospitalization period (four week). The clinical symptoms and $^{67}$Ga scan findings improved in three months time after commencing the therapy in spite of starting to work at previous job. Because of persisting CT findings, the patient underwent an open lung biopsy after five months of therapy. Histopathological examination of biopsy specimen showed a nonspecific type of chronic inflammation distributed around bronchioles leaving the intervening areas of parenchyma uninvolved. Lymphocytes comprised the majority of infiltrating cells with some plasma cells. Eosinophils and neutrophils were not prominent and fibrosis was minimal (Figure 2).

On follow-up, the patient continued the same therapy for 16 months. Now, he has no respiratory complaint, and his PFT and DLCO are still normal and his exertional hypoxemia has disappeared (pH 7.41, PaO$_2$ 88.3 mmHg, PaCO$_2$ 34 mmHg and HCO$_3^-$ 21.6 mEq/L) although has been working at the same job. CX-R and CT findings are nearly normal with resolution of ground-glass like appearance (Figure 3). Galium scan changed to normal.

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
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<tr>
<td>Evidence of exposure to appropriate antigen from history or detection of serum antibody</td>
<td>Bibasilar rales</td>
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<tr>
<td>Symptoms compatible with HP</td>
<td>Decreased diffusing capacity</td>
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<tr>
<td>Findings compatible with HP on chest radiographs or high-resolution CT scan</td>
<td>Arterial hypoxemia, either at rest or during exercise</td>
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<tr>
<td>Pulmonary histologic changes compatible with HP</td>
<td>BAL fluid lymphocytosis</td>
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<td>BAL fluid lymphocytosis</td>
<td>Positive “natural challenge”</td>
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Figure 2. (HE x 50) open lung biopsy specimen; chronic inflammation around bronchioles.
DISCUSSION

The outcome of the HP is variable depending upon several factors, such as the duration of antigen exposure, the concentration and chemical composition of the inhaled antigens, and the age and genetic background of the patient. It is claimed that lung immunoregulatory T cells may play a major role in the development of pulmonary fibrosis in HP (6-8).

There is two different clinical presentation of HP; acute and chronic. Chronic HP presents with progressive and more severe dyspnea, nonproductive cough, weight loss, and often anorexia in a patient exposed to recognized cause of the disease. Symptoms are usually present for months to years. Tachypnea and bibasilar dry rales are usually present. Plain chest radiograms are notable for diffuse linear and nodular opacities, with upper lobe predominance. The diagnosis of HP is confirmed in a patient who fulfills all of the major or at least four of the minor criteria, after ruling out all other diseases with similar symptoms (Table 1) (6).

In the present case, clinical and radiological findings were compatible with all major criteria and some of the minor criteria of the disease and he was diagnosed to have chronic type of HP. A careful differential diagnosis was made among the other causes of pulmonary fibrosis. The patient denied exposure to any chemotherapeutic agent, radiation or toxins, which could cause a lung injury. Because of the lack of suggestive radiological and laboratory findings, sarcoidosis was also excluded. Pneumoconiosis was not a possible diagnosis either, because of the absence of history suggesting inorganic dust exposure (6,9-11).

Chronic HP may be indistinguishable from idiopathic pulmonary fibrosis (IPF). For IPF, a predominance of lymphocytes and neutrophils is found in BAL, and a rapid progression and poor prognosis even accompanied by cor pulmonale can be seen. The present case showed a good response to therapy, which diverted us from the diagnosis of IPF (6,12).

In the treatment of HP, the patient was recommended to change his environment in order to avoid possible antigen exposure. We know that avoidance of exposure usually is followed by resolution of signs and symptoms, but it could not be possible for the patient except hospitalization period. We also know that complete removal from antigen exposure may not always lead clinical and radiological improvement, and patients with chronic form of HP may manifest progressive pulmonary impairment even after avoidance (13).

Systemic steroids have been suggested to be effective in the medical treatment of HP (6-8). To our best knowledge of literature, inhaled steroids were not used in the treatment of HP. Standard or high doses of inhaled steroids (budesonide, fluticasone, triamcinolone) can be used in patients with bronchiolitis obliterans (BO) which develops after lung transplantation, BO with organizing pneumonia (BOOP) and pulmonary sarcoidosis without extrapulmonary involvement (1,3-5,14).

We preferred to initiate inhaled steroid knowing that steroid-sparing capacity was also documented if it would be needed (15-17). This drug (i.e. inhaled budesonide) has also been found to reduce the number and proportion of T-lymphocytes in BAL and to normalize the increased CD4/CD8 ratio and may reduce the concentration of hyaluronan in the BAL fluid, which can be a marker of early fibroblast activation. Finally, a normalization of BAL macrophage subpopulations with a decrease in antigen-presenting macrophages has been reported (15-19). As our patient had normal values of pulmonary function...
tests and DLCO, and a stable clinic condition with mild symptoms, he was followed-up on inhaled steroid therapy. We surprisingly observed gradually a successful recovery. Sixteen months later, this is documented by the disappearance of the ground glass like appearance on CT and exertional hypoxemia. We think that systemic effects of 2000 µg/day fluticasone may cause this result. As fluticasone at dose of 2000 µg/day has systemic effects, which has been recently demonstrated in the treatment of chronic asthma when compared with prednisolone 30 mg daily, this may not be topical effect alone (20). We believe that, this is the first documented case of clinical and histopathologically confirmed HP treated with inhaled steroids. A satisfactory response gained after long-term high dose inhaled steroid therapy suggested that inhaled steroid therapy could be a safe, effective and satisfactory alternative to systemic steroid administration even if it may have systemic effects at high therapeutic doses in the treatment of HP. We recommend high dose inhaled steroids should be considered in the treatment of HP and the efficacy of this modality of treatment needs to be determined in large series.

REFERENCES


Address for Correspondence:
Demet KARNAK, MD
Department of Chest Diseases and Tuberculosis
Ankara University Medical Faculty
06100, Cebeci, ANKARA

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