A chronic eosinophilic pneumonia case with long exposure to isocyanates
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Abstract
Chronic eosinophilic pneumonia (CEP) is a disease with unknown etiology, characterized by peripheral blood eosinophilia and abnormal eosinophil accumulation in the lungs. A 43-year-old male with 30 years history of exposure to isocyanates was admitted with the complaint of sputum, cough, progressive dyspnoea, and weight loss. Physical examination revealed bilaterally decreased breath sounds and extensive rales. On laboratory analysis; leukocytosis (12.3 10^3/µL), hypereosinophilia (30%), elevated CRP and RF (1000 IU/ml), and IgE levels (1160 IU/ml) in the serum were observed. Chest radiograph and computed tomography on admission showed reticulonodular pattern at both lung fields. Pulmonary function tests assumed a restrictive pattern and a low diffusing capacity. Bronchoalveolar lavage revealed a marked eosinophilia (50%). Transbronchial lung biopsy indicated eosinophilic pneumonia. In this case we aimed to describe a rare case of CEP probably caused by exposure to isocyanate.

Keywords: Chronic eosinophilic pneumonia, Eosinophilia, Isocyanates.

Introduction
Chronic eosinophilic pneumonia (CEP) was first described in 1969 in a patient with a history of rhinitis and asthma, with dyspnoea, fever, peripheral eosinophilia and broncho-alveolar lavage (BAL) eosinophils.1 It is characterized by peripheral blood eosinophilia and abnormal eosinophil accumulation in the lungs.2 Although it is believed to be a hypersensitivity reaction etiology is not yet exactly clarified.1 The disease most frequently occurs between the ages of 30 and 40 with a twofold increased prevalence in females.1,3 No specific genetic predisposition has been identified. Coughing, dyspnoea, fever, and weight loss are the most common symptoms, while sputum, fatigue, wheezing and nocturnal sweating are infrequently observed in patients with CEP. Almost half of the patients have atopy, allergic rhinitis or nasal polyps and 30-50 percent of the patients have a history of asthma. The condition may result in pulmonary insufficiency if the diagnosis or treatment is delayed.1,3,5

Ninety percent of the patients demonstrate peripheral eosinophilia. Increased number of eosinophils can also be detected in sputum or bronchial lavage fluid. In the bronchoalveolar lavage fluid (BALF), eosinophils comprise more than 25 percent while neutrophil and lymphocyte ratios are usually within the normal range. Some cases may initially be considered as interstitial lung disease. However, detection of a high eosinophil ratio in BALF is a significant evidence in the diagnosis of CEP.3,6,7 Serum IgE level elevates in two-thirds of the patients, rheumatoid factor and immune complexes may be positive. Erythrocyte sedimentation rate often increases. Thrombocytosis and anaemia may also be observed.1,3

Pulmonary function tests may be normal in mild cases, but generally there is restrictive ventilatory defect, with reduced diffusing capacity of the lung for carbon monoxide (DLCO). There are also signs of obstruction in cases with concurrent asthma. In the majority of cases, chest radiographs show patchy peripheral consolidation. Lesions have a tendency to localize in the middle and lower zones. A photographic negative image of pulmonary oedema, characteristic for CEP, can only be observed in 50 percent of the cases. High resolution CT (HRCT) of the thorax shows peripherally located, patchy infiltration bilaterally. Ground-glass opacity is frequently seen. Less frequently, cavities within the peripheral consolidation may be observed.1,3,7 A marked response to steroids is observed during the management of CEP.1 Symptoms alleviate within a day or two and disappear in about 10 days. In this case report we aimed to emphasize CEP's possible association with isocyanate exposure.

Case Report
A 43-year old male patient presented with coughing for the past 4 years, sputum, dyspnoea and weight loss. The patient was a building painter for 30 years and had a 5 pack year smoking history and also had an unremarkable medical history with the exception of bronchitis. Physical examination revealed decreased breath sounds and extensive rales in both lungs with digital clubbing of the hands and feet. In laboratory examinations haemoglobin
level was 16.5 g/dl and platelet count was 345,000 /mm³, sedimentation rate was 22 mm hour. Leukocytosis (12.3 $10^3/\mu$L), hypereosinophilia (30%), elevation of CRP (4.46 mg/dl) and rheumatoid factor (1000 IU/ml) were also observed. Serum IgE level increased (1160 IU/ml), whereas serum antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA) were negative. Eosinophilia was also observed in bone marrow biopsy and aspiration specimens.

Chest X-Ray revealed scattered reticulonodular infiltration in both lungs, more prominent in the lower zones and peripheral fields. HRCT showed diffuse thickening of the septa, sub-pleural bullae and fibrotic strands in both lungs, more prominent in the apical, posterior and basal segments. Honeycomb appearance was present in the postero-basal region (Figure-1A). Computed tomography of the paranasal sinuses revealed hypoplasia of both frontal sinuses, an increase in soft tissue in the right maxillary sinus, and polypoid appearance of the left maxillary sinus. Pulmonary function tests were measured as Forced Vital Capacity (FVC): 72%, Forced expiratory volume in 1 second (FEV1): 75%, FEV1/FVC: 108%, DLCO 50%, DLCO/VA (diffusing capacity of the lung for carbon monoxide/alveolar volume) 58%. The arterial blood gas analysis on admission was as follows: PO2: 79 mmHg,

Figure-1: High-resolution chest tomography before-treatment (A), after-treatment (B) in case.

Figure-2: A high abundance of eosinophils were observed during the cytological examination of the bronchial lavage fluid (A). Bronchial biopsy revealed eosinophils in the epithelium together with eosinophils and marked fibrosis in the sub-epithelial areas (H&E 200) (B).
PCO2: 38.8 mmHg, SO2: 96.3%.

Copious amounts (more than 50 percent) of eosinophils were identified in the BALF, as well as histiocytes, epithelial cells that do not feature atypia, and lymphocytes (Figure-2A). Examination of the bronchial biopsy sample revealed inflammatory infiltration of the stroma with eosinophils. Areas of fibrosis were also present in the stroma (Figure-2B).

The diagnosis of CEP was established in the patient with these findings and methylprednisolone treatment (0.5 mg/kg/day) was administered. Within days (approximately one week), improvement in the clinical features was observed. Eosinophil count returned to normal values. Also, pulmonary function parameters improved in part. (FVC 82%, FEV1 88%, FEV1/FVC 104%, DLCO 69%, DLCO/VA 66%). HRCT confirmed resolution of consolidation areas in three weeks. However fibrosis, apical bullae and honeycomb appearance persisted (Fig 1B). Bronchoscopy was repeated in first year follow up and no evidence of eosinophil activation in peripheral blood or lung tissues was seen.

**Discussion**

CEP is a disease with unknown etiology. However, an increase in the production of interleukin (IL)-5 seems to be one of the critical pathophysiological features of eosinophilic pneumonia. Several reports have shown that IL-5 had been present in BAL fluid (BALF), and the level of IL-5 had reduced after resolution of pulmonary eosinophilia.

It was reported that occurrence of CEP is associated with Schizophyllum commune and radiotherapy. The etiology of CEP is not clear yet, but hypersensitivity or autoimmune processes have been implicated. Especially a marked eosinophilia, high serum IgE level, presence of atopy-rhinitis-nasal polyps-asthma in the history along with a prompt and dramatic response to steroids collectively support this hypothesis. In our case, having more than 50% eosinophils in the bronchial lavage fluid, high serum IgE level, nasal polyp and a history consistent with asthma, even though a definite diagnosis was never made, supported the hypothesis that the disease may be of allergic-immunologic-hypersensitivity origin. On the other hand, the contribution of occupational hazards to this sensitivity is unknown. Isocyanates are low-molecular-weight chemicals implicated in allergic asthmatic-type reactions. Our patient was exposed to isocyanates in the past 30 years of house painting. The relationship between isocyanates, occupational asthma, respiratory sensitization and hypersensitivity pneumonitis is well established and occupational exposure to isocyanate was reported to be the cause of eosinophilic bronchitis. However, as far as we are aware, the relationship between isocyanates and CEP has not been previously reported. Therefore the role of contact with occupational hazards, such as isocyanates in the ethiopathogenesis of CEP needs to be explored.

CEP is a rare disease and sometimes it can be challenging to establish the diagnosis, especially when eosinophilia is absent. Fibrosis develops in half of the cases of CEP, but apical bullae and honeycomb appearance are rarely observed. In cases that the diagnosis of CEP cannot be established, it is usually suggested that rapid and dramatic response to steroids can be ruled in favour of CEP. However, this assumption may sometimes be misleading because CEP may, albeit rarely, present with pulmonary fibrosis and honeycomb appearance of lung, both of which show limited response to steroids. The radiological appearance in our case was not typical. The patient did not seek medical attention despite long-lasting complaints and therefore the diagnosis was delayed. There were fibrosis, apical bullae and honeycomb appearance evident in the radiographs. Though steroid therapy was initiated, limited clinical and radiological improvement was achieved. Our aim in presenting this case was to emphasize the fact that when the diagnosis or treatment is delayed, patients may present with end-stage interstitial lung disease and that the response to steroids in such a circumstance is very poor.

In conclusion, with its unknown etiology, it is warranted to investigate the relationship between CEP and occupational hazards, such as isocyanates. Experimental animal studies or epidemiological studies have to be planned to establish a possible link between isocyanate and CEP. In cases advanced pulmonary signs such as fibrosis and honeycomb appearance dominate the radiological features; CEP needs to be differentiated from many other lung diseases. When the diagnosis of CEP cannot be established well, it is usually suggested that rapid and dramatic response to steroids can be ruled in favour of CEP. On the other hand, a limited response to steroid treatment does not necessarily rule out the presence of CEP.

**References**

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