Hypersensitivity Pneumonitis with Recurrence—A Case Presentation and Review of the Literature

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A 76-year-old farmer suffered from fever, general malaise, and headache after he had trimmed the bushes near his farm. A chest radiograph revealed diffuse reticulonodular lesions, and thoracic high resolution computed tomography (HRCT) demonstrated patches of ground-glass opacity and reticulonodular centrilobular opacities. Based on the exposure history and HRCT findings, hypersensitivity pneumonitis was highly suspected. The symptoms subsided dramatically and the pulmonary infiltrates subsided gradually after corticosteroid prescription. Recurrence of hypersensitivity pneumonitis was noted two months after he had returned to his normal living and working environment. ***(Thorac Med 2000; 15: 165-171)***

Key words: hypersensitivity pneumonitis, extrinsic allergic alveolitis.

Introduction

Hypersensitivity pneumonitis (HP) is an allergic lung disease caused by an inhaled agent, particularly an organic antigen. Numerous inciting agents have been described, including agricultural dusts, bio-aerosols, and certain reactive chemical materials. The radiographic and pathologic abnormalities can be classified into acute, subacute, and chronic stages. Early recognition and removal from exposure can avert the ongoing pulmonary inflammation which can lead to irreversible pulmonary fibrosis.

Case Presentation

A 76-year-old man, a farmer, with a 2-week history of fever, headache, general malaise and dyspnea, was referred to our hospital. He had bilateral tardy ulnar palsy, and C-spine radiculopathy was suspected. His past surgical history included transposition surgery 5 years ago due to tardy ulnar palsy of the right side and an operation for a herniation of an intervertebral disc. He smoked socially. He felt a general malaise, fever and chill with severe headache after he had trimmed some bushes near his farm about 2 weeks previous. The bushes he had trimmed were contaminated with a moldy outgrowth. During the trimming process, his working environment was quite dusty and the air he breathed became unpleasant. He had done this trimming periodically every year, and never felt

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uncomfortable before. Since he felt uncomfortable this time he went home for a rest. The feeling of discomfort feeling wosened, and fever, chill, headache and general malaise developed.

He visited local medical clinics several times in the following two weeks, but the symptoms persisted despite medication. Then, he was brought to Changhua Christian Hospital for further evaluation. At Changhua Christian Hospital, laboratory data and the chest radiograph yielded negative results. Under the impression of a fever of unknown origin, he was observed at the emergency department. On the 4th hospital day, dyspnea and wheezing were noted, and the follow-up chest radiograph showed bilateral pulmonary infiltration (Fig.1). Under the impression of acute pulmonary edema, diuretics were prescribed. The symptoms showed no improvement despite medical treatment. The patient was transferred to our hospital 2 days later.

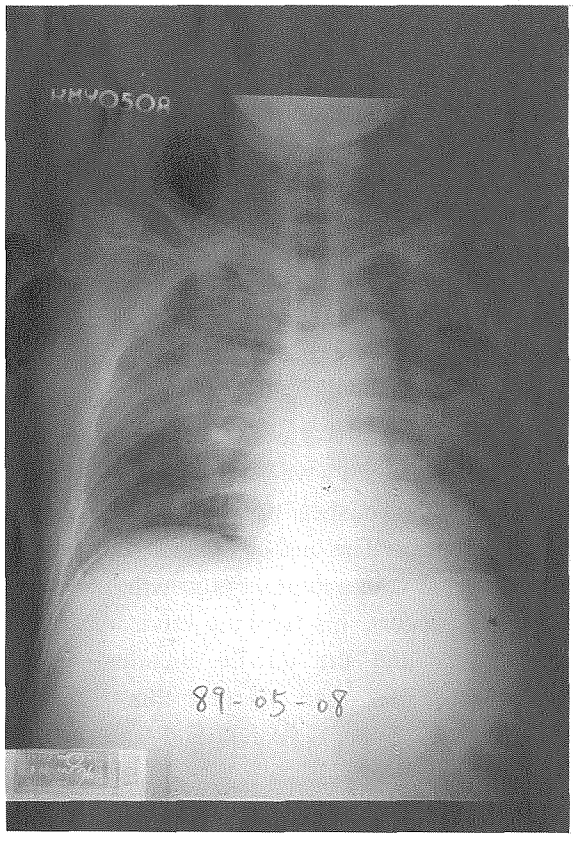

Fig 1. The chest radiograph showed bilateral pulmonary infiltration simulating acute pulmonary edema, but still reticulonodular lesions could be found.

At our emergency room, his body temperature was 38.9 ^{0}C; blood pressure, 154/86 mmHg; pulse rate, 90/min; and respiratory rate, 20/min. On physical examination, bilateral inspiratory crackles with mild wheezing were heard. Neither anemia (Hb 14.1 g/dL) nor leukocytosis (WBC 6180/cumm with normal differential counts: N/L/M/E 74/20/4/1) was found. Blood biochemical tests revealed elevated lactate dehydrogenase (1322 I.U./L), uric acid (8.8 mg/dl), total bilirubin (1.74 mg/dl), direct bilirubin (0.59 mg/dl), alkaline phosphatase (485 U/L), and a decrease of albumin (3.3 g/dl). The results of the arterial blood gas analysis while the patient breathed-in room air were as follows: pH, 7.538; pO_2, 46.5 mmHg; and pCO_2, 25.0 mmHg. The chest radiograph showed diffuse reticulonodular lesions in both lungs. A thoracic high resolution CT revealed several ground-glass patches with several reticulonodular centrilobular opacities and mild fibrotic changes, enlarged lymph nodes in the pre-tracheal, aorta-pulmonary window and subcarinal regions, and a minimal amount of bilateral pleural effusion (Fig.2).

Miliary tuberculosis, atypical pneumonia such as legionellar pneumonia, hypersensitivity pneumonitis in subacute form, and drug-induced lung disease were suspected. After admission, the 1hr-erythrocyte sedimentation rate (ESR) was 71 mm; the 2hr-ESR, 101 mm; and C-reactive protein (CRP), 160.1 mg/L. Sputum was sent for acid-fast stain, Gram's stain, mycobacterial culture, bacterial culture, fungal culture, and legionella culture; the results were all non-revealing. Blood cultures were performed for three sets and no microorganism was cultured out. Serum and urine were sent for legionella antibody and antigen detection, and negative findings were later reported. Blood levels of imunoglobulin E (IgE), IgG, and IgA were within normal limits. The mast allergy test was negative. The pulmonary function test showed a restrictive

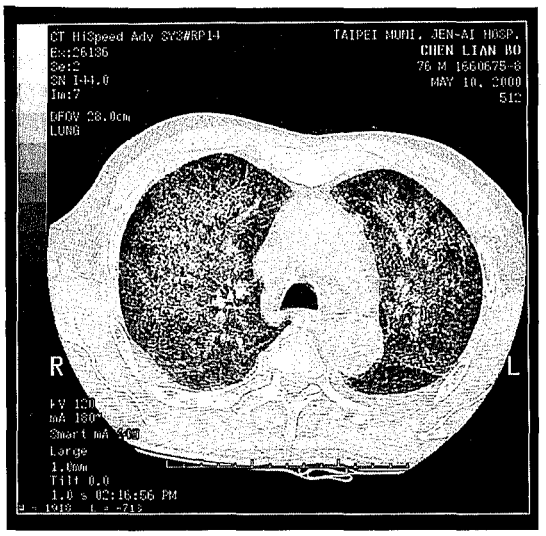

Fig 2. Ground-glass patches with several reticulonodular centrilobular opacities were disclosed in thoracic high resolution CT.

ventilatory defect with FVC 1.93 L (65.2% pred.), FEV1 1.8 L (98.9% pred.), FEV1/FVC 93.3%, and TLC 4.02 L (82% pred.). The patient had no previous drug history, the sputum acid-fast stain showed negative findings, a normal blood leukocyte count (WBC 6180/cumm with normal differential counts: N/L/M/E 74/20/4/1) was found, and high ESR and CRP were noted. Bacterial infection and drug-induced lung diseases were excluded initially due to normal leukocyte and differential blood counts and the absence of a drug history; although the acid-fast stain of the sputum showed negative findings, miliary TB still was included in the diagnostic list. Because of persistent hypoxemia, supplemental oxygen therapy with up to 6 liters/minute was given to keep SpO_2 around 90%. Hyperthermia with relative bradycardia was noted. Since subacute hypersensitivity pneumonitis and miliary tuberculosis could not be ruled out, solumedrol (methyl-prednisolone) 40 mg intravenous drip every six hours, and anti-TB medications [Rifater 5# (rifampicin 600 mg + isoniazid 400 mg + pyrazinamide 1250 mg) and EMB 2# (ethambutol 800 mg)], were given on the 2nd hospital day. The symptoms subsided dramatically after corticosteroid treatment and the anti-TB medications were discontinued on the 4th hospital day. The levels of ESR and CRP declined. The patient was discharged with oral prednisolone 20 mg Bid after one-week hospitalization, and was followed at an outpatient clinic. Ten days after discharge, the 1hr-ESR was 22 mm; the 2hr-ESR, 49 mm; CRP, 15.7 mg/L; and IgG, 1412 mg/dL. The pulmonary function test showed normal ventilatory functioning with FVC 2.44 L (81.9% pred.), FEV1 2.42 L (130.1% pred.), FEV1/FVC 99.2%, and TLC 4.91 L (99.4% pred.). Nearly complete resolution of the pulmonary lesions was found in the chest radiograph. Oral prednisolone was discontinued and the total period of steroid treatment was 2 weeks.

Three and half months later, the patient was admitted again, due to recurrence of hypersensitivity pneumonitis. The patient reported a fever, chills, headache, and malaise for 2 days. Diffuse fine crackles were heard on auscultation; body temperature was 39.7 °C; pulse rate, 84/min; respiratory rate, 24/min; and blood pressure, 166/84 mmHg. The results of arterial blood gas analysis in room air were as follows: pH 7.467; pO_2 61.5 mmHg; and pCO_2 28.5 mmHg. Slight anemia (Hb 12.8 g/dL) and a normal white blood cell count of 9830/cumm with a differential count of N/L/M/E 75/14/8/2 were found. Blood biochemistries revealed elevated creatinine (1.8 mg/dl) and uric acid (12 mg/dl). The 1hr-ESR was 96 mm; the 2hr-ESR, 112 mm; and CRP 55.9 mg/L. The levels of IgE, IgG, and IgA were within normal limits. The mast allergy test was negative. The pulmonary function test showed restrictive ventilatory impairment with FVC 1.12 L (37.2% pred.), FEV1 1.12 L (60.2% pred.), FEV1/FVC 100%, and TLC 4.49 L (90.9% pred.). The chest radiograph showed diffuse reticulonodular lesions (Fig.3). The thoracic HRCT revealed diffusely thickened intralobular septa with a reticular pattern, and fine reticulonodules involving bilateral lungs, which spared the right middle lobe and subpleural regions; mixed chronic and subacute hypersensitivity pneumonitis was considered. The clinical features were quite similar to those noted of thee last visit. Under the impression of hypersen-sitivity pneumonitis with recurrence, intravenous

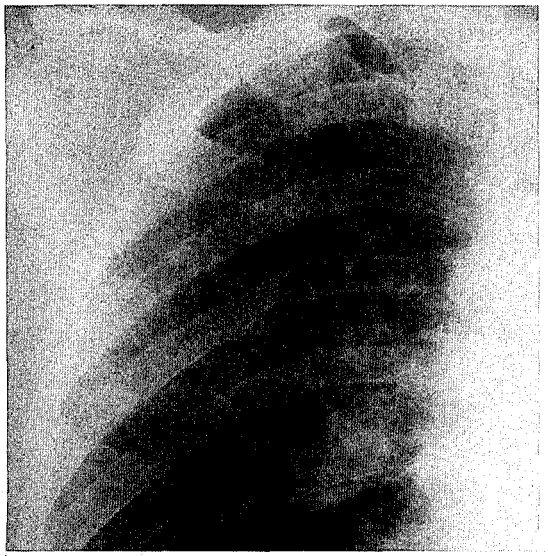

Fig 3 Close-up view of the chest radiograph in the episode of recurrence, the diffuse reticulonodular lesions were similar to the pictures disclosed in the first hospitalization (Figure 1).

solumedrol (methyl-prednisolone) 40 mg intravenous drip every six hours was prescribed. Again, the symptoms subsided dramatically after corticosteroid treatment. After hospitalization for 2 weeks, the patient was discharged with oral prednisolone 20 mg Bid and followed up at our outpatient clinic. The patient was suggested to move away from his home and farm to avoid continuous exposure to the etiologic antigen in order to prevent the development of a chronic form hypersensitivity pneumonitis.

Discussion

Hypersensitivity pneumonitis, or extrinsic allergic alveolitis, belongs to a group of immunologically-mediated pulmonary diseases caused by a variety of antigens. Over 300 etiologic antigens causing hypersensitivity pneumonitis have been reported. [1] Those antigens can be divided as organic (high molecular weight complete antigens) and inorganic (low molecular weight haptens). [2] The majority of etiologic antigens are derived from occupational exposure, such as in farming, breeding birds, mushroom packing, sugar cane harvesting or bathtub finishing. Most of the antigens do not proliferate (e.g., avian glycoprotein in bird droppings) or do not proliferate in physiologic temperature (e.g., Saccharopolyspora rectivirgula in farming dusts). [3] The most frequent allergens are thermophilic actinomycetes, which are found in warm humid environments (such as soil, hay, or forced heating and cooling systems). The prevalence of the disease varies by region, climate, and farming practices, and ranges from about 2 to 9% of exposed individuals. [1] Many different disease names have been reported, such as farmer's lung, bird fancier's disease, malt worker's disease, bathtub finisher's lung, bagassosis, sequoiosis, suberosis, mushroom worker's lung, late respiratory systemic syndrome, isocyanate disease, ventilation pneumonitis, Sax lung, or Japanese summer house hypersensitivity pneumonitis. Farmer's lung, which is the best-known hypersensitivity pneumonitis syndrome, results from the inhalation of fungal organisms (thermophilic actinomycetes) that grow in moist hay. Pathologic examination of the affected lung reveals antigen-mediated granulomatous inflammation of the lung parenchyma, alveolar walls, and terminal airways.

There are three stages related to hypersensitivity pneumonitis: the acute, subacute, and chronic. In the classic acute form, the affected person usually presents with fever, a general malaise, cough, and dyspnea 4 to 6 hours after heavy antigen exposure. The flu-like symptoms are often confused with the common cold, and bacterial and viral pneumonitis; patients usually are identified with delay. Symptoms abate after a few hours to a few days if exposure is avoided. The chronic form is characterized by productive cough, dyspnea, fatigue, and weight loss, due to prolonged exposure to the antigen. The very severe chronic form can progress to irreversible pulmonary fibrosis. Subacute disease is characterized by the gradual development of cough, dyspnea, fatigue, anorexia, and weight

loss. [4] The subacute form is an intermediate stage; it can lead to fibrosis if antigen exposure is not eliminated or it can resolve completely if proper treatment is prescribed. This condition should be suspected if flu-like symptoms occur after exposure to microbial spores, animal proteins, or certain chemicals. Prolonged illness may be associated with considerable weight loss, but symptoms usually tend to improve within 48 hours after removal from the causative agent.

On physical examination, lung auscultation may reveal diffuse dry crackles. The chest radiograph in acute or subacute forms may show a ground glass pattern or reticulonodular shadows; in the chronic form, diffuse reticulonodular infiltrates and fibrosis are characteristic. [4] Findings of hypersensitivity pneumonitis on thoracic HRCT depend on the stage of the disease. The acute form is rarely recognized, but shows bilateral air-space lesions and ill-defined small (1-3 mm diameter) nodules. The thoracic HRCT is performed much more commonly in the subacute stage, weeks to months following the first exposure to the antigen. Characteristic appearances of the subacute stage of hypersensitivity pneumonitis on HRCT are ill-defined centrilobular nodules, less than 5 mm in diameter, and patchy areas of ground-glass opacity. In the subacute stage, small nodules and areas of ground-glass opacity represent potentially treatable or reversible lesions. These findings often undergo dramatic improvement when patients with subacute disease are removed from exposure and treated with corticosteroid. The chronic stage of HP is characterized by the presence of fibrosis, which may develop months or years after the initial exposure. In patients with the chronic form, HRCT can show irregular reticular opacities representing fibrosis, traction bronchiectasis, or frank honeycombing, mimicking idiopathic pulmonary fibrosis. The findings of pulmonary fibrosis often show a middle lung zone predominance or an even distribution throughout the upper, middle, and lower lung zones. Relative sparing of the lung bases, seen in a majority of the chronic cases, can sometimes differentiate it from IPF, in which the fibrosis usually predominates in the lung bases. [5]

Pulmonary function tests in hypersensitivity pneumonitis often show a restrictive defect with a loss of lung volume. Airflow limitation can also be seen. By and large, there is often a mixed pattern of ventilatory impairment. [6] The lung biopsy in the acute form reveals interstitial infiltrates of plasma cells, lymphocytes, and neutrophils; granulomas with central necrosis and multinucleated giant cells formed by fused macrophages are often present. In the chronic form, the lung biopsy shows interstitial fibrosis destroying the lung architecture. [7] There is no single pathognomonic test for hypersensitivity pneumonitis. Specific precipitating antibodies (precipitins) to the causal agents in the serum are helpful in making the diagnosis. However, these antibodies are only a marker to exposure, not to disease. Negative results in the context of strong clinical evidence may suggest the disease and cannot exclude the diagnosis. [2, 3, 8]

No single mechanism can explain all of the pathologic features of hypersensitivity pneumonitis. In most experimental models, after antigen challenge, there is an increase in neutrophils in the alveoli and small airways, followed by an influx of mononuclear cells and granulomas formation. A variety of pro-inflammatory cytokines are released, and play an extensively important pathogenic role in the production of experimental granulomas, including interleukin-1 (IL-1), IL-2, IL-3, IL-12, interferon-□, granulocyte-macrophage colony-stimulating factor (GM-CSF), and CSF-1. The Gell and Coombs Type III and Type IV hypersensitivity reactions are probably not the best paradigm for explaining the immunological mechanisms that result in hypersensitivity pneumonitis. There is a lymphocytosis and generally CD8+ cells exceed the number of CD4+ cells in the BALF (bronchoalveolar lavage fluid). The patients appear to have some defect in the suppressor

function of CD8+ cells, suggesting an active modulation of granulomas formation. Individuals with more CD4+ cells are prone to develop fibrosis. Lymphocytes in BALF and bronchial biopsies have an increase in activation markers, such as Ia and CD25, on the cell surface. Macrophage activation has also been described. Increases in IL-8 and monocyte chemo-attractant protein-1 (MCP-1), a soluble form of intercellular adhesion molecules (sICAM), have been reported to occur in BALF. Activated macrophages and CD8+ cells incapable of suppressing these molecules are probably the immunogenetic mechanism driving the inflammation of hypersensitivity pneumonitis. [2,7]

In treating the acute and subacute phases, corticosteroids beginning with 1 mg/Kg prednisolone or its equivalent are often used to hasten recovery. [2] With avoidance from exposure and the administration of corticosteroids tapered over a several-week period, many individuals regain normal lung function if fibrosis has not already occurred. Avoidance of the etiologic antigen is the most important treatment. Masks, dust filters, respirators, and attention to the heating and air conditioning systems are all important. The patient may need to change occupations or move away from the living environment to eliminate the exposure completely. It is important to recognize the diagnosis as early as possible since fibrotic change can occur and is irreversible. There is no evidence that long-term steroid usage protects against lung damage from chronic exposure. [2, 11]

Conclusion

Hypersensitivity pneumonitis is an important occupational lung disease, which is caused by a variety of antigens. Early recognition with exposure avoidance can prevent irreversible processes. The disease is a *sequelae* of antigen exposure and no single diagnostic test, not even a lung biopsy, is pathognomonic for hypersensitivity pneumonitis. The diagnosis of hypersensitivity pneumonitis should be relatively straightforward, based on a consistent exposure history, physical examination, pulmonary function tests, chest radiograph, HRCT of the chest, temporal relationship to an antigen known to cause hypersensitivity pneumonitis, and precipitins to the causal antigens in the serum.

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過敏性肺炎—病例報告與文獻回顧

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過敏性肺炎，或稱外因性過敏性肺泡炎，是一種免疫反應性肺疾病。許多抗原可引起過敏性肺炎，包括微生物(黴菌、原蟲、細菌等)、動物性蛋白、昆蟲蛋白及某些低分子量無機化學物。臨床及病理上過敏性肺炎可分為三期：急性期、亞急性期及慢性期。急性期常表現發燒、咳嗽、全身不適等類似感冒的症狀。長期暴露在過敏抗原下(慢性期)，可導致體重減輕與肺纖維化。適度的治療與避免暴露過敏原方可根治肺部發炎。 持續性過敏原暴露可能導致瀰漫性不可逆的肺纖維化。

過敏性肺炎的診斷並無特殊的檢查方法。血清中存在對過敏原具特異性抗體(precipitins)對診斷雖有幫助，但陰性反應並不能排除診斷。急性及亞急性期胸部影像檢查可呈現毛玻璃樣型態或細微顆粒影像；慢性期可見瀰漫性網狀結節樣肺浸潤及肺纖維。肺功能檢查通常呈現侷限型通氣障礙及肺瀰散量低下。肺部巨噬細胞被活化及抑制型淋巴球(CD8+ lymphocyte) 無法抑制活化型巨噬細胞，可能是導致過敏性肺炎發炎反應的免疫機轉。

在急性及亞急性期，類固醇的使用可加速肺損傷的復原。避免致病抗原的繼續暴露，是預防慢性不可逆肺纖維化的唯一也是最重要的準則。*(胸腔醫學 2000; 15: 165-171)*

關鍵詞：過敏性肺炎，外因性過敏性肺泡炎

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