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Moldy Hazelnut Husk and Shell-Related Hypersensitivity Pneumonitis: A Possible Novel Occupational Causative Agent

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Summary

Hypersensitivity pneumonitis (HP) is a complex immune-mediated interstitial lung disease (ILD) triggered by inhalation exposure to environmental or occupational antigens in genetically susceptible individuals. Novel exposure sources and antigens are frequently identified. However, the causative agent remains unidentified in nearly half of HP cases. Early diagnosis for nonfibrotic-HP and quitting the exposure may prevent the disease progression to fibrotic forms and related complications. Here, we present two cases of HP associated with mold exposure in hazelnut husks, leaves, and shells in hazelnut agriculture.

1. Introduction

Hypersensitivity pneumonitis (HP) is a complex immune-mediated interstitial lung disease (ILD) triggered by inhalation exposure to environmental or occupational antigens in genetically susceptible individuals [1, 2]. In the United States of America, the one-year cumulative incidence rates of HP range from 1.28 to 1.94 per 100,000 people [3]. Novel exposures and antigens have been frequently identified (environment, workplace, hobbies) since the first paper on HP as Campbell published Farmer's Lung in 1932 [1, 4, 5]. However, the causative agent remains unidentified in nearly half of HP cases [1, 2]. Because of the difficulties related to diagnosis and identifying antigen exposure, the final diagnosis of HP requires a multidisciplinary approach that includes pulmonology, radiology, pathology, and occupational-environmental medicine specialists [6, 7]. Turkey is the world's leading producer and exporter of hazelnuts [8]. Italy and Spain are two other important hazelnut-producing countries. But it is seen that all processes in hazelnut farming are more mechanized in other hazelnut-producing countries, unlike Turkey. Hazelnut is an agricultural product grown in Turkey's eastern Black Sea Region. Harvest is usually picked up by non-mechanized way (manually) in this region. After waiting for the drying processes, the nuts are given to the haymaker to separate from the husk. Both these processes are risky regarding mold and dust exposure. This region is also known for the highest rainfall and high

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humidity levels. Here, we present two cases of HP associated with mold exposure in hazelnut husks, leaves, and shells in hazelnut agriculture.

1.1. Case 1

A 64-year-old nonsmoker woman working as a hazelnut farmer for the last four years presented with progressive dyspnea on exertion, weakness, and fatigue for one year. She described that she had worked in the hazelnut harvest and threshing. She revealed that while hazelnuts wait in the open or closed warehouses to be dried, a strong musty odor and dust from hazelnut husk and leaves occurred and were released into the environment. She had worked with other family members and sometimes helped neighbours while not wearing a mask. In occupational and environmental history, she worked as a cook between the years 2007 to 2017. Based on detailed occupational and environmental history, she had no other relevant exposure history of organic or inorganic dust, birds, or mold-related agents at work and home. She declared that her symptoms worsened while working in hazelnut farming every year from July to September. She had no clinical findings of connective tissue diseases, chronic diseases, or drug usage history. On physical examination, oxygen saturation (SaO_2) was 96% on room air, and basal inspiratory crackles were present on chest auscultation. There was no clubbing.

Her laboratory tests were obtained, including complete blood count, electrolytes, renal and liver function test results, and connective tissue disorders panel. Her fasting blood glucose level was 121 U/L, and others were normal. Rheumatology found no evidence of connective tissue disease.

Pulmonary function tests revealed decreased forced vital capacity (FVC) was 1.19 L (43% predicted); decreased FEV1, 1.13 L (49% expected); FEV1/FVC, 95%. But she was unable to cooperate diffusing capacity of the lung for carbon monoxide (DLCO). A chest high-resolution CT (HRCT) imaging demonstrated diffuse bilateral ground glass patchy opacities, mosaic patterns, and reticulations (Figure 1).

BAL differential count demonstrated 30% lymphocytes, 5% neutrophils, and 65% macrophages.

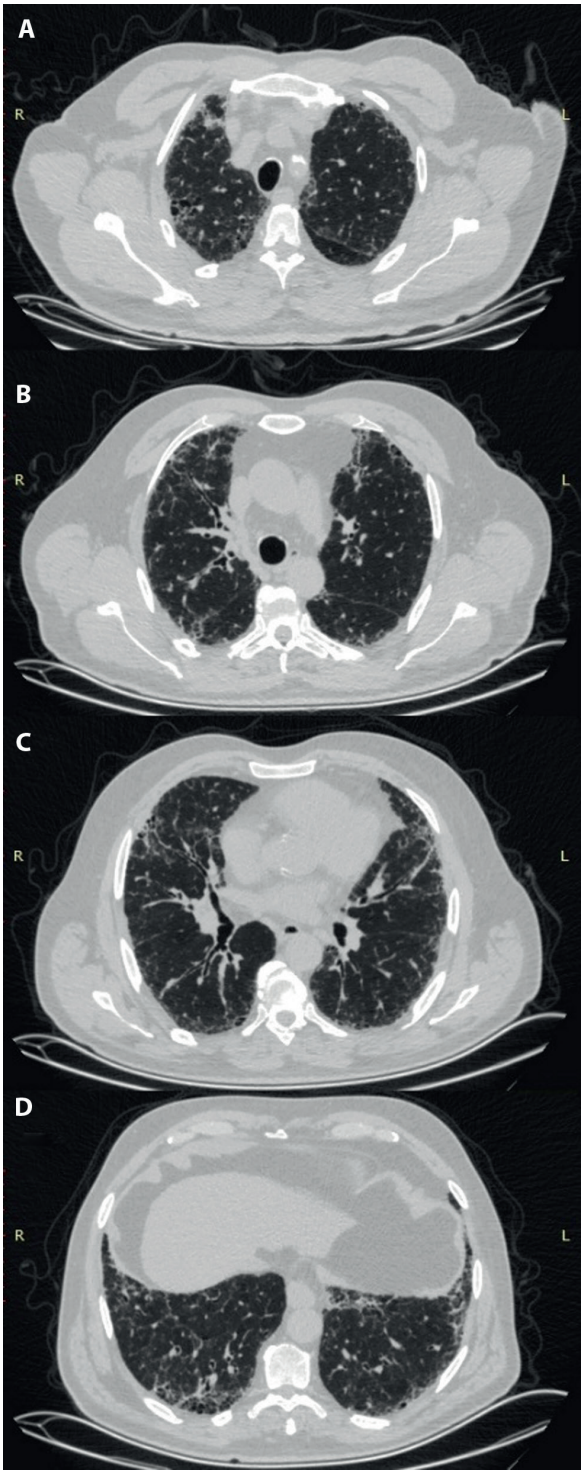

Figure 1. Figure 1A, 1B, 1C, 1D. Chest high-resolution CT imaging of Case 1 showing diffuse bilateral ground glass patchy opacities, mosaic pattern, minimal air-trapping, traction bronchiectasis, minimal honeycombing and reticulations.

The patient underwent a right lung lower lobe transbronchial cryo-biopsy. The pathological examination revealed focal mild interstitial and lymphocytic infiltrates, bronchiolization in alveoli, squamous metaplasia, mucus stasis, fibroblast plugs, and intact alveolar groups in between but without granuloma, which is compatible with HP. The pathological findings were evaluated as probable fibrotic-HP. The final diagnosis of HP related to possible molds contaminating hazelnut storages (husk and leaves) and the environment was decided according to the multidisciplinary discussion (MDD) conducted with the participation of pulmonologists, radiologist, pathologist, and occupational-environmental medicine specialists. Treatment with 0.5 mg/kg/d *p.o.* Prednisone was initiated with gradual tapering, and the patient was instructed to stop occupational exposure.

1.2. Case 2

A 65-year-old male ex-smoker patient was admitted to the hospital with complaints of progressive dyspnea on exertion and cough for two years. He had worked different jobs such as construction worker for one year, textile worker for five years, cleaner for six years, elevator installer for eleven years, and he retired 13 years ago. He also worked hazelnut farming only in the summertime for two months every year from younger ages without using personal protective equipment. The last time he was exposed to molds and dust related to hazelnut farming was the summer before he was admitted to hospital. He revealed that he was dealing with hazelnut harvest and threshing. He had no relevant exposure history of birds or other mold-related environments. The physical assessment results show that he has basal inspiratory crackles on auscultation and clubbing.

Pulmonary function tests revealed that FEV1/FVC: 75%, FVC 2.5 L (106% predicted); FEV 1, 3.19 L (95% expected), with low DLCO such as 57% (22.6), DLCO/VA 75% (4.01), spO2 was 94% mm Hg on room air. HRCT scan demonstrated diffuse bilateral ground glass patchy opacities, mosaic pattern, honeycombing, and interlobular septal thickening. Laboratory tests were normal. Because the BAL differential count was contaminated by bronchial cells (>5%), differential cell analysis could not be performed as it would not represent the diagnosis of ILD. The serological markers of connective tissue disorders were negative. The patient underwent a video-assisted wedge lung biopsy of the left upper lobe revealed poorly formed granuloma structures in the interstitium, subpleural microscopic honeycombing, traction bronchiectasis, fibrosis, lymphoid aggregates in the interstitium (Figure 2).

The pathological findings were evaluated as typical fibrotic HP. A diagnosis of HP related to possible molds contaminating hazelnut storages and environment made. Antifibrotic therapy and 0.5 mg/kg/d *p.o.* Prednisone treatment was initiated with gradual tapering, and she was advised to quit hazelnut farming.

2. Discussion

We demonstrated for the first time an association between molds contaminating hazelnut storages (husk and leaves) and HP in two cases working in hazelnut agriculture without any other related exposures. Only one case reported from Turkey has been collecting green and brown hazelnut leaves to fuel the house, diagnosed as fibrotic-HP [9]. Another study, including workers in a hazelnut processing factory, showed that a significant deterioration in restrictive and obstructive pulmonary functions was observed and concluded the research needs to investigate HP in hazelnut processing [10]. Although metalworking fluid HP and farmers' lungs are the leading occupational subtypes of HP, mold-related working products and processes or environments are being reported with increasing frequency [11, 12]. In hazelnut farming, HP can be related to contaminating molds and plant-derived materials. Pscheidt et al. said that fungi were isolated from kernels with mold and Penicillium spp., species of Aspergillus and Cladosporium, and Diaporthe rudis [13]. As an example of a plant-derived material exposure related to nuts, HP was reported in a worker exposed to dust from a tiger nut in a processing factory (a nut used in the production of horchata, a drink consumed in Spain and Mexico) [14].

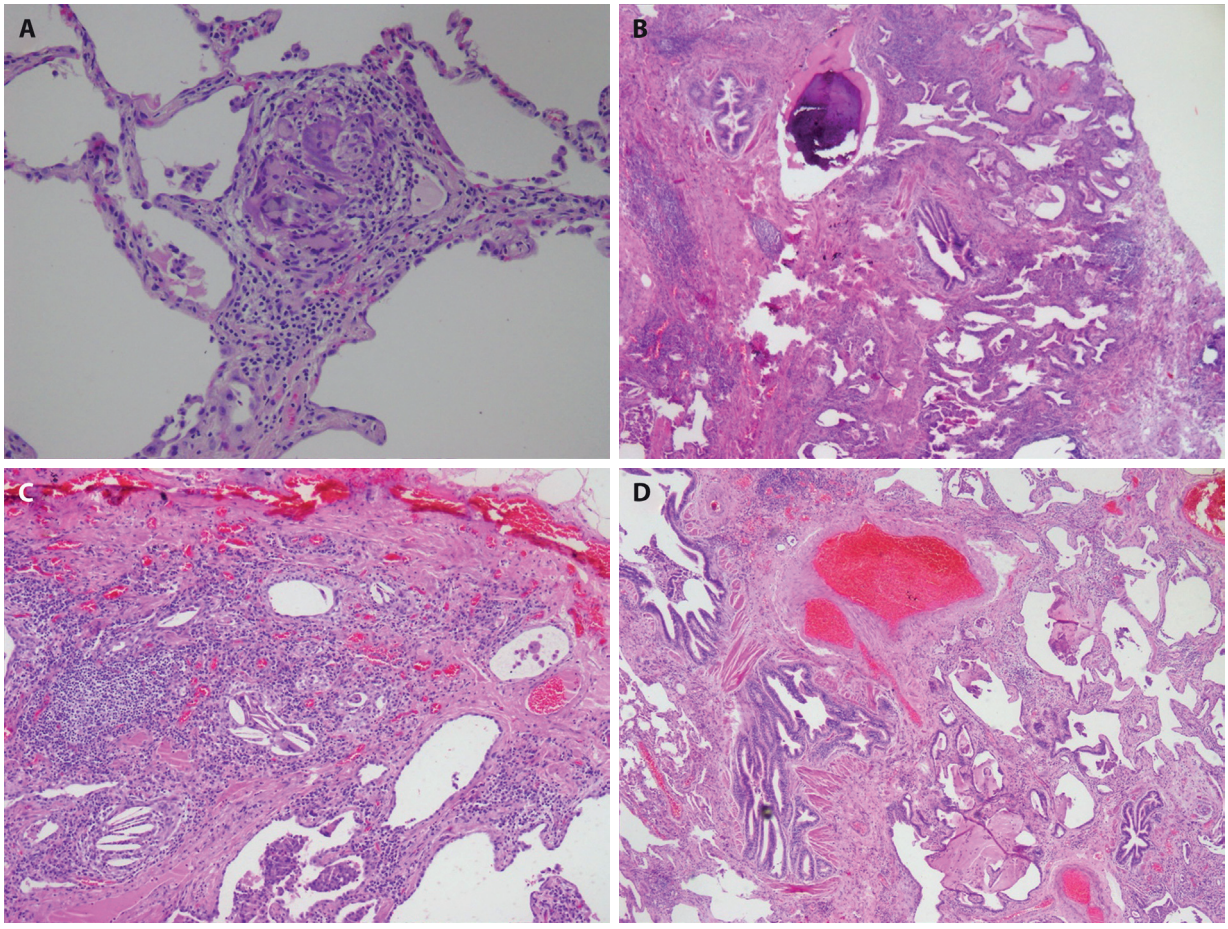

Figure 2. Figure *2*A. Video-assisted wedge lung biopsy of the left upper lobe of Case 2, showing poorly formed granuloma structures in the interstitium (10x10 hematoxylin and eosin), 2B, 2C, 2D displaying subpleural microscopic honeycombing, traction bronchiectasis.

In the first case, the diagnosis of HP was given by transbronchial cryo-biopsy with a BAL fluid lymphocytosis. She had only an exposure history of molds and dust contaminating hazelnut husk and leaves. HRCT findings are compatible with fibrotic-HP. She emphasized that her symptoms were worsening while working in hazelnut farming every year in the summer during the exposure period. A video-assisted lung biopsy of the left upper lobe confirmed the diagnosis of our second patient. He had no exposure to HP besides molds and dust contaminating hazelnut husks and leaves. Both patients declared that an intense musty odor and macroscopically moldy-black or green discoloration appeared on hazelnut husks and leaves due to humid climatic conditions and rain on the threshing. Both patients had fibrotic-HP, so we could not see clinical and radiological improvements after avoiding exposure to hazelnut-related molds.

In our chest diseases hospital, many of the ILD patients are consulted by our occupational and environmental outpatient clinic to identify possible causative agents or exposures that may be related to ILD by interviewing patients face to face with a modified questionnaire and also evaluated in the multidisciplinary discussion (pulmonologists, radiologists, pathologists, and occupational and environmental medicine specialists).

One of the main limitations of our case report is the lack of investigation of the molds for microbiological analyses on the husk and leaves due to the hazelnut harvest not coinciding. Also, the

unavailability of specific IgG to standard HP antigens test was one of the critical limitations. So, the findings of these two cases led the authors to investigate either HP in hazelnut farming for microbiological analyses.

In conclusion, we present two cases of HP related to occupational exposure to molds in hazelnut husks, leaves, and shells in hazelnut agriculture. The fact that hazelnut shells are easily molded due to humid climatic conditions and that it is a plant-derived product are possible reasons that increase the risk. Also, less mechanized or manual and traditional systems used in hazelnut farming are a substantial risk for exposure to molds and dust. During the waiting period for the hazelnuts to dry, mold growth is inevitable due to humidity and rainfall. After drying, giving the hazelnuts into the haymaker to separate from the husks is the other primary exposure to dust and molds. People engaged in hazelnut farming in this region do not receive regular occupational health services since they work as a family business in the summer. For this reason, we think it would be beneficial to ensure that employees have access to essential occupational health services, to provide training on the prevention of mold formation in hazelnuts, and to apply mechanized and modern systems.

Early diagnosis for nonfibrotic-HP and quitting the exposure may prevent the disease progression to fibrotic forms and related complications. The findings of two cases led us to investigate HP in hazelnut farming accompanied by case-control or cohort studies.

Declaration of Interests: None to declare.

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