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Case report

Biopsy-proven recurrent, acute, familial hypersensitivity pneumonitis: A case report and literature review

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ABSTRACT

Hypersensitivity pneumonitis (HP) is characterized by inflammation of the lung parenchyma that is induced by exposure to an inhaled organic antigen. We present a case of recurrent, acute HP caused by repeated transient exposure to a down sleeping bag in a patient with a family history of chronic bird-associated hypersensitivity pneumonitis. The patient's recurrent symptoms, changes in physiology, and radiographic findings coincided with repeated exposure to this source. It was later confirmed that the patient's sister had also developed chronic HP from recurrent exposure to household birds. This case highlights recent studies implicating gene-exposure interactions in the development of HP.

1. Case

A previously healthy 36-year-old male non-smoker presented with rapidly worsening dyspnea during a home renovation in 2008. His family history included a sister with a diagnosis of chronic and progressive hypersensitivity pneumonitis (HP) secondary to a longstanding bird exposure in her home. Pulmonary function tests (PFTs) showed a borderline restrictive pattern with a forced vital capacity (FVC) of 83%-predicted and diffusion capacity of the lung for carbon monoxide (DLCO) of 52%-predicted. Chest computed tomography (CT) showed diffuse ill-defined, ground glass, centrilobular nodules (Fig. 1A). Bronchoscopy was negative for infectious and malignant etiologies, and transbronchial biopsies were non-diagnostic. There were 1% lymphocytes on bronchoalveolar lavage (BAL). Connective tissue disease serology and serum precipitins for Aspergillus were negative. A surgical lung biopsy confirmed a diagnosis of HP (Fig. 2A/B). He was treated with prednisone with near complete resolution of symptoms and normalization of physiological (FVC 106%, DLCO 88%) and radiological abnormalities (Fig. 1B). The patient denied exposure to mold, birds, hot tubs, and other likely antigens, with a clear underlying precipitant not identified.

He remained asymptomatic until 2015 when he presented with dyspnea and cough within several hours of his first visit to a friend's ranch. FVC and DLCO had declined to 86% and 59%, respectively, and chest CT showed worsening diffuse centrilobular nodularity and mosaic attenuation (Fig. 1C). Bronchoscopy was negative for infectious etiologies and malignancy, with 85% lymphocytes on bronchoalveolar lavage (BAL). Endobronchial biopsies confirmed a diagnosis of HP (Fig. 2C). A precipitant was not identified at that time, but the patient was advised to not visit the ranch again. His symptoms and lung function improved following two weeks of prednisone 30mg daily with a subsequent 2-month taper.

He was referred to an interstitial lung disease (ILD) clinic as well as an allergist and immunologist after re-visiting the ranch on two subsequent occasions, with both episodes associated with worsening symptoms and physiology, and improvement with prednisone. He underwent skin testing, with no reaction to tree pollens or commercially available mold spores (Alternaria, Aspergillus, Cladosporium, Penicillium, or Fusarium). He experienced a third episode of worsening respiratory symptoms while camping at a location distant from the ranch and reported use of a down sleeping bag. Upon further questioning, he confirmed that he had used the same sleeping bag during all prior visits to the ranch.

2. Discussion

HP is characterized by inflammation of the lung parenchyma caused by exposure to an organic inhaled antigen [1]. The diagnosis of HP can

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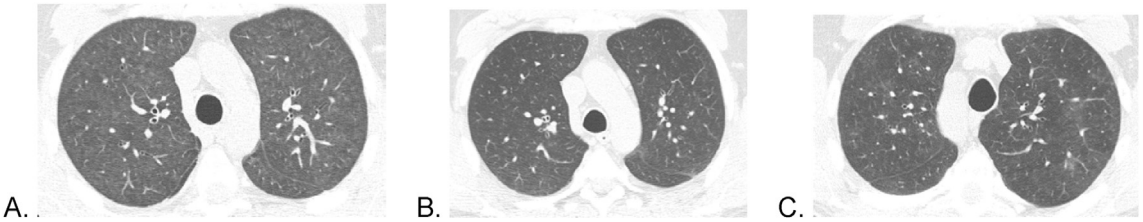

Fig. 1. Lung windows from axial chest CT demonstrating diffuse ill-defined centrilobular nodules at the time of presentation (**A**). A subsequent axial chest CT after treatment with prednisone demonstrated near complete resolution of previously identified centrilobular nodularity (**B**). Axial CT demonstrating new patchy areas of ground glass attenuation (**C**).

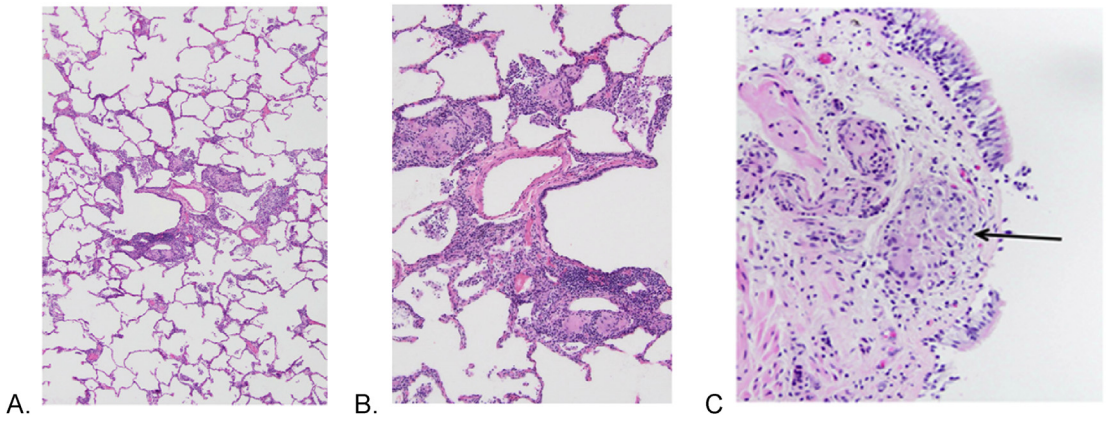

Fig. 2. Low power (**A**) and high power views (**B**) of the video-assisted thoracoscopic surgery lung biopsy in 2008 showing a typical pattern of HP with centrilobular chronic interstitial inflammation and multiple granulomas. Endobronchial biopsy in 2015 showing a small endobronchial granuloma (arrow; **C**).

be challenging due to the lack of a diagnostic gold standard and the frequent inability to identify an underlying antigen [2,3]. Ground-glass, ill-defined nodules, and air trapping are seen on chest CT in acute and subacute HP, with reticulation, volume loss, and traction bronchiectasis present in chronic HP. HP is pathologically characterized by a bronchiolocentric granulomatous lymphocytic alveolitis, which can evolve into fibrosis in chronic cases [4]. Diagnostic models for HP using clinical and radiological variables have been proposed [5,6]; however, these models have not been adequately validated for clinical use in chronic HP. Patients with acute and subacute disease may fully recover with antigen avoidance and often corticosteroid therapy. Patients with chronic HP are frequently treated with systemic corticosteroids and additional immunosuppressive agents, but often have irreversible and progressive pulmonary fibrosis despite therapy [7].

Previous cohorts of familial HP have been reported, predominantly including Japanese patients with summer-type HP (SHP) with many of these individuals having a common home residence and exposure history [8,9]. SHP is the most common form of HP in Japan, typically occurring in the western part of Japan where summer temperatures and humidity are high [9]. In one recent publication, 50 Japanese patients with familial SHP from 23 families were reported between 1982 and 2011 [8]. All of these families lived in traditional Japanese wooden houses that were damp. 41 of 49 cases (84%) occurred in the summer months, and all patients presented within 2 months of the first case of HP within the family. Another retrospective study of 114 patients diagnosed with chronic HP identified 20 patients (17.5%) who had a family history of pulmonary fibrosis [10]. Of these, only 1 patient had a relative with chronic HP, with other relatives having idiopathic interstitial pneumonias (17 cases), idiopathic pulmonary fibrosis (12 cases), rheumatoid arthritis (3 cases), and systemic sclerosis-associated interstitial lung disease (1 case) [10]. Some previous studies of SHP that show clustering within families have also presented in non-biologic family members (*e.g.*, husband and wife).

Only a minority of exposed individuals develop HP, and genetic susceptibility likely increases this risk [1]. Additional cohort studies have implicated multiple gene polymorphisms in HP, including polymorphisms in genes related to human leukocyte antigens [11–13], tumor necrosis factor-α [14],and telomere length [13]. Telomere length and gene polymorphisms in MUC5B also appear to correlate with disease severity and prognosis in HP [15].

This patient was diagnosed with recurrent acute HP associated with repeated exposures to a down sleeping bag, and in the context of a well-documented family history of chronic and progressive HP that was secondary to a longstanding bird exposure. While the 2008 VATS biopsy was typical of subacute HP, the 2015 bronchial biopsy showed an endobronchial granuloma, an uncommon finding in HP that may suggest an unusual degree of sensitization. This family may have a genetic predisposition to HP, but with different gene variants and/or exposures leading to recurrent episodes of acute HP in one sibling, and chronic HP in another. Future studies are needed to identify potential gene-environment interactions that predispose to HP in some exposed individuals and not in others.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmcr.2018.05.007.

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