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CASE REPORT

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Hypersensitivity pneumonitis: an overlooked cause of cough and dyspnea

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ABSTRACT

Hypersensitivity pneumonitis (HP) is an immune-mediated pulmonary disorder involving inflammation of the lung interstitium, terminal bronchioles, and alveoli caused by the immune response to the inhalation of an offending environmental airborne agent. It can manifest as exertional dyspnea, fatigue, weight loss, and progressive respiratory failure if left untreated. Because of its protean features, it can be misdiagnosed as other common obstructive lung conditions such as asthma. If triggers are not avoided, it can progress to irreversible pulmonary fibrosis. In this article, we present the case of a 51-year-old male who presented to our hospital with recurrent bouts of dyspnea and cough, initially diagnosed as an asthma exacerbation. He received a final diagnosis of HP after investigation of his workplace revealed airborne spores and surface molds from multiple fungal species, serology revealed eosinophilia, and computed tomography showed bronchiectasis. Avoidance of occupational exposure resulted in significant improvement of his respiratory symptoms after two months.

Abbreviations: HP: Hypersensitivity pneumonitis

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Hypersensitivity pneumonitis; asthma; dyspnea; interstitial lung disease

1. Introduction

Hypersensitivity pneumonitis (HP) is an immune-mediated pulmonary disorder affecting the lung interstitium, alveoli and bronchioles. It is caused by repeated inhalation and sensitization to a variety of environmental airborne antigens which may provoke an exaggerated immune response in the lung parenchyma of susceptible individuals [1,2]. HP may present with acute or subacute to chronic symptoms. Acute HP is characterized by flu-like symptoms, including chills, fever, sweating, myalgias, and headache that begin a few hours after antigen exposure, and respiratory symptoms of cough, chest tightness, and dyspnea are frequently noted [2]. Subacute and chronic HP may manifest with an insidious onset of cough, exertional dyspnea, fatigue, and weight loss that occur over several weeks to months, and over months to years, respectively [2]. Because the clinical presentation varies widely and because the findings are non-specific, the disorder is often initially misdiagnosed as a more common pulmonary condition. Specifically, acute HP, with wheezing and cough with response to steroid, is often initially thought to be asthma or chronic obstructive pulmonary disease (COPD), whereas chronic HP is often confused with non-specific interstitial pneumonia, usual interstitial pneumonia, or cryptogenic organizing pneumonia [3]. Misdiagnosis may delay proper treatment of HP and failure to identify offending antigens, which may in worst case result in irreversible damage to the lungs.

2. Case presentation

A 51-year-old Caucasian male presented to the emergency department of our hospital with a two-week history of shortness of breath and disabling cough. The cough was productive of thick, whitish sputum, and was aggravated by exertion and exposure to cold air. He reported a history of frequent 'bronchitis' episodes and chronic mild dyspnea for the past two years, and was previously diagnosed with mild persistent asthma. He had required short courses of oral corticosteroids three times in the past 12 months, but this was his first presentation to the hospital and he had never been intubated. Pulmonary function tests 11 months prior had revealed a forced vital capacity (FVC) of 4.38 L (103% predicted), a forced expiratory volume in 1 second (FEV_1) of 3.59 L (104% predicted), and a FEV_1:FVC ratio of 82%. Symptoms during this exacerbation were not alleviated with inhaled albuterol and ipratropium bromide, and he had been placed on cefuroxime five days prior for acute bronchitis by his primary care physician. He noted using his inhaler every two hours for the past 24 hours without relief. He denied any fever, sore throat, fatigue, malaise, nausea, vomiting, weight changes, or recent sick contacts. He reported a family history of asthma in his mother and two daughters, and asbestos-related lung malignancies in both of his parents. There was no history of smoking or illicit drug use. There was no personal history of asbestos

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exposure, immunodeficiency, lung malignancy, or allergy to pollen, dust, or mites. He noted having a pet dog for years, but no other animal or hobby exposures. He was however employed at a workplace with a large walk-in refrigerator for the past 15 years and reported presence of considerable mold growth in the coolers. He also noted that other colleagues with exposure to the cooler had similar symptoms. Although he denied any recent travel history, he reported transient improvement of his dyspnea and cough when he traveled to another state for a week away from his job site.

On physical exam, he was afebrile and hemodynamically stable. He had a resting oxygen saturation of 94% on room air, which initially declined to 87% while ambulating. Pulmonary exam was notable for high-pitched end-inspiratory wheezes throughout his lungs and expiratory wheezes at his bases bilaterally. Peak expiratory flow rate (PEFR) on admission was 550 L/min (weight-based expected PEFR is 545 L/min), which increased to 775 L/min the following morning after steroid administration.

Laboratory studies included the following: white blood count (WBC): 5700/μL (4800–10 800/μL), with 18% eosinophils (normal: 0–6%), total eosinophil count: 1030/μL (150–300/μL), total IgE: 440 IU/mL (<154 IU/mL). Chest x-ray revealed non-enlarged, asymmetric hilar opacities, but no acute cardiopulmonary abnormalities (Figure 1(a)). Computed tomography (CT) scan of the chest revealed mild bronchitis with mucoid impaction in several bronchi and several widened bronchi surrounded by inflammation and positive signet ring sign suggesting mild bronchiectasis (Figure 1(b)).

A preliminary admission diagnosis of asthma exacerbation due to bronchitis was made due to prior history of mild persistent asthma, and he was started on prednisone, and nebulized albuterol and ipratropium bromide. He showed mild improvement within the next two days and was discharged home on a tapered prednisone regimen and a possible discharge diagnosis of allergic bronchopulmonary aspergillosis in the face of bronchiectasis, elevated IgE and eosinophilia. However, serology for *Aspergillus fumigatus* antibody and *Aspergillus* galactomannan antigen were subsequently found to be negative. Local health authorities were asked to investigate the patient's workplace, and they identified spores and molds on surface samples within the coolers. Multiple species were detected including *Aspergillus, Cladosporium, Nigrospora*, and basidiospores. A final diagnosis of HP was determined after the new workplace safety findings of airborne spores and surface molds. He was instructed to avoid the coolers at his workplace, which were then sterilized. He reported marked improvement in his symptoms after two months, at which time the repeat *Aspergillus* serology was found to again be negative, as well as serology for *Thermoactinomyces* and *Micropolyspora*.

3. Discussion

HP was first described in 1700 by Bernardino Ramazzini, who observed shortness of breath and cachexia in grain workers after repeated exposure to grain dust [3]. However, the first detailed description of HP appeared in 1932, after a study described dyspnea, productive cough, night sweats, and weight loss in workers who were stripping bark from maple logs. Further investigation isolated the fungus *Cryptostroma corticale* from the dust accompanying the maple bark, and it was postulated that the workers' symptoms were due to an immune reaction to airborne spores [4,5].

Despite decades of advances in our understanding of HP, no universal disease definition yet exists [6,7]. Many experts describe HP as a disease that primarily affects the lungs but may also include constitutional symptoms including fever and weight loss. HP is

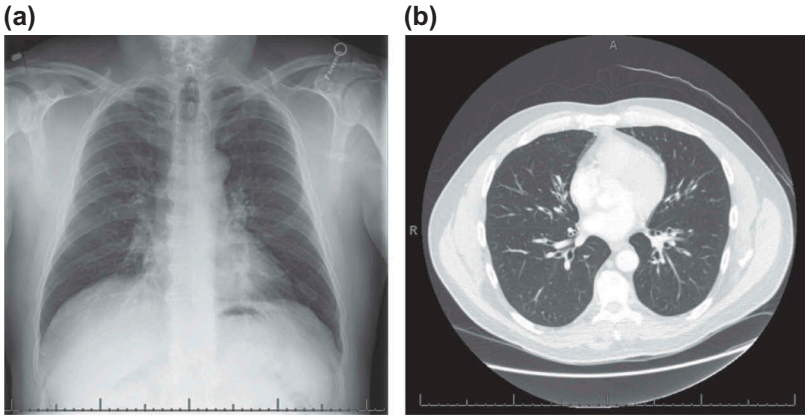

Figure 1. (a) Chest x-ray shows non-enlarged but asymmetric hilar opacities. (b) Axial view demonstrates mild bronchitis with mucoid impaction in several bronchi and several widened bronchi surrounded by inflammation and positive signet ring sign, suggestive of mild bronchiectasis.

believed to be caused by an offending airborne antigen to which the host mounts an exaggerated immune response. Symptoms typically appear or worsen hours after antigen exposure. Studies propose a 'two-hit' hypothesis to describe the development of HP, stating that genetic susceptibility comprises the 'first hit' and increases the risk of HP after the 'second hit' arrives in the form of antigen exposure [2]. Typically, these offending antigens originate from occupational exposures, but may also come from hobbies, recreational activities, and contaminated air systems [4]. Over 300 etiologies of HP have been reported [8,9] and have traditionally been divided into three major antigen categories: microbes, proteins from animals or plants, and low-molecular weight chemicals. Avian proteins and microbial agents comprise the most commonly reported causes of HP [2,4,6]. Specific examples of diagnoses along the HP spectrum are listed in Supplemental Table 1. As it pertains to our case report, workers exposed to ventilation systems and water-related contamination (forced-air systems, humidifiers, whirlpools, spas) may be exposed to antigens of various species including *Thermoactinomyces*, *Cladosporium*, and *Mycobacterium avium* [10,11].

A large epidemiological study reported an incidence of HP of approximately 1 per 100 000 people in the UK [12]. However, the exact prevalence of HP is unknown given that cases often go undetected or are misdiagnosed. In addition, there is no standardized method to assess the disorder, given the lack of defined diagnostic criteria and diagnostic modalities used [4].

Symptoms in HP have been conventionally classified into acute, subacute, and chronic-predominant stages, but significant overlap is frequently noted (Table 1) [2]. Acute HP is characterized by a rapid onset of flu-like symptoms, including chills, fever, sweating, myalgias, and headache that begin a few hours after exposure, and usually involves cough, chest tightness, and dyspnea [2]. Subacute and chronic HP both manifest with an insidious onset of cough, exertional dyspnea, fatigue, and weight loss. One scheme differentiates the two: subacute disease occurs over weeks to four months with episodic flare-ups, while chronic disease occurs over four months to years and consists of fibrosis, emphysema, or both [4,13]. During symptomatic episodes, pulmonary function tests (PFTs) typically show restrictive disease, but an obstructive pattern may also be present [6]. Tachypnea, tachycardia, and bibasilar crackles are often present on physical exam, and hypoxemia and respiratory failure may occur in severe cases [4].

Chest radiograph and CT scan findings vary based on stage of disease, with mostly nonspecific findings [15]. Ground glass opacities are most common in acute HP, and a reticulonodular pattern has been inconsistently documented [7]. Radiographic findings in subacute HP include ground glass opacities, centrilobular nodules, and air trapping [7]. More consistency is noted in imaging studies of chronic HP as upper-lobe and middle-lobe predominance of fibrotic changes, including reticular opacities and honeycombing, are almost invariably present [6,7]. Additional findings in chronic HP may include irregular subpleural linear opacifications, traction bronchiectasis, air trapping, lobar volume loss, and patchy emphysema [7]. Centrilobular nodules and ground-glass attenuation have been noted to be reversible in patients who avoid exposure to the offending agent, although honeycombing and emphysema usually indicate irreversible damage [16,17]. Notably, patients with chronic HP may have an

Table 1. Clinical features of hypersensitivity pneumonitis.

Category	Acute	Subacute	Chronic
Clinical duration	4–48 hours	Weeks to four months	Four months to years
Symptoms	Fever, chills, diaphoresis, cough, chest tightness, dyspnea, hypoxemia, generalized body aches and myalgias, headache	Exertional dyspnea, cough, fatigue, weight loss, episodic flares	Exertional dyspnea, cough, fatigue, weight loss
Immuno-pathophysiology	Alveolitis from neutrophilic infiltration, immune complex deposition with fibrin, tiny granulomas	Classic histologic triad of subacute HP: interstitial infiltrate, bronchiolitis, formation of poorly-formed granulomas. Triad is present in up to 75% of cases [14]. Interstitial infiltrate is typically composed of plasma cells and lymphocytes	Lymphocytic infiltration and fibrosis, neutrophil-mediated destruction, often includes eosinophil and mast cell infiltration
High-resolution CT chest findings	Ground glass opacities (most common), reticulonodular pattern, confluent alveolar opacification	Ground glass opacities centrilobular nodules, air trapping	Irregular subpleural linear opacifications, traction bronchiectasis, air trapping, lobar volume loss, Interstitial fibrosis, honeycombing pattern, patchy emphysema
Prognosis	Good	Typically good	Poor (especially with presence of extensive fibrosis)
Treatment	Avoidance of offending agent. Systemic corticosteroids if symptoms progress despite antigen avoidance. Lung transplant in severe cases of chronic HP.		

Symptoms, pathophysiology, natural history, and treatment are presented based on different stages of HP.

imaging pattern similar to that of nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP) [7,18].

Bronchoalveolar lavage is a sensitive test to detect alveolitis, with the most typical pattern showing a significant lymphocyte-rich alveolitis (>20% of total cells recovered, but more often >50%) [6,19,20]. In rare cases, clinicians may pursue surgical transbronchial biopsy to verify clinical diagnosis in patients refractory to therapy [6]. Laboratory tests are neither sensitive nor specific, but a mild leukocytosis, lymphocystosis, and eosinophilia may be present in some cases [21,22].

Because diagnosis of HP is often challenging, a clinical prediction model was developed by Lacasse et al. to aid clinicians. Criteria include exposure to a known offending antigen, positive precipitating antibodies, recurrent symptomatic flares, inspiratory crackles, symptoms that occur four-to-eight hours after antigen exposure, and weight loss [21]. Interestingly, documenting exposure to a known offending antigen alone has a high odds ratio of 38.8 [21]. The probability of HP is 98% in patients who satisfy all six criteria in the model [6,21]. Our case report patient satisfied only three criteria (exposure to known antigen, recurrent symptoms, and symptoms that occur soon after antigen exposure). Although he did not have positive serologic testing, it is important to note that the sensitivity and specificity of serum-specific antibody testing is very low [23], with one study citing a 25% detection rate in diagnosed HP patients [24]. Additional studies are needed to validate this diagnostic prediction system, but it offers promise towards more uniform, defined diagnostic criteria in the future.

Despite this initiative towards better prediction models, diagnosis of HP remains difficult and may be missed due to lack of specific clinical features and awareness among health-care providers. The clinical presentation and natural history are highly variable. Many patients with mild or sub-clinical HP escape detection or are misdiagnosed as suffering from viral upper respiratory illness or asthma [25], either of which may have nonspecific findings that mimic HP. On the other end of the spectrum, severe subacute and chronic HP may mimic interstitial lung diseases such as usual interstitial pneumonia. Misdiagnosis has critical therapeutic and prognostic implications as it may delay proper treatment of HP, and result in significant morbidity, unnecessary hospitalizations, and irreversible fibrosis to the lungs. Key discriminatory findings between asthma and hypersensitivity in this case include normal spirometry, completely normal peak flow testing despite ongoing symptoms, hypoxemia, significant eosinophilia, elevated IgE level, and bronchiectatic changes on imaging. Any one of these should make physicians consider an alternative diagnosis [26].

Avoidance of exposure to the suspected or confirmed agent is the mainstay of HP management. If HP continues to progress despite avoidance of antigen exposure, treatment with systemic corticosteroids is considered. In chronic HP, progressive pulmonary fibrosis is typically irreversible and does not respond to treatment [4]. In these cases, lung transplantation may be considered [6]. Generally, patients with acute or subacute HP without fibrotic changes have a good prognosis as they respond well to avoidance of the inciting exposure. However, once fibrosis occurs in chronic HP, prognosis is not favorable [27].

4. Teaching points

(1) Diagnosis of HP is challenging due to lack of specific clinical features, absence of universal diagnostic criteria, low awareness among clinicians, and variable clinical presentation.
(2) Although HP is infrequent, it should always be kept in the differential diagnosis of dyspnea and cough, especially in a patient with a suspected source of exposure to an offending environmental agent, hypoxemia, eosinophilia, and normal peak flows.
(3) HP may mimic viral upper respiratory illness or asthma exacerbation. Misdiagnosis has critical therapeutic and prognostic implications as it may delay proper treatment of HP and result in significant morbidity, unnecessary hospitalizations, and irreversible fibrosis to the lungs.
(4) HP can initially be treated conservatively with avoidance of the offending agent. Some cases of HP may require systemic corticosteroids and consideration for lung transplantation if severe fibrosis is present.

Disclosure statement

No potential conflict of interest was reported by the authors.

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