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A Case of Chronic Cough in a Winemaker

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ABSTRACT

Background: Fungi have been known to cause a variety of respiratory conditions, ranging from mold-associated asthma to allergic bronchopulmonary mycosis and invasive disease. More recently some fungal species have been implicated in a non-asthmatic chronic cough syndrome.
Case presentation: A 59-year-old male presented to the pulmonary clinic with chronic nonproductive cough. Workup included pulmonary function tests with methacholine challenge, sputum cultures, CT scans of the chest and therapeutic trial with proton pump inhibitors. Sputum cultures repeatedly showed *Saccharomyces cerevisiae* and patient had elevated specific IgA and IgG. Bronchoscopy was unremarkable, except for tracheal mucosa biopsies revealing acute and chronic inflammation. A one-month course of steroids provided temporary relief of chronic cough, but symptoms returned once steroids were discontinued. He also experienced temporary relief away from home. Upon further evaluation, the patient described his hobby of wine making which was believed to be the source of *Saccharomyces cerevisiae*. Once he stopped wine making at home and cleared his cellar, his symptoms stopped and have not returned since.
Conclusion: We describe a rare presentation of non-asthmatic chronic cough associated with exposure to *Saccharomyces cerevisiae*. This is the first report of fungi associated chronic cough without asthmatic features outside of Japan and the first one associated with *Saccharomyces cerevisiae*. This report provides further evidence linking fungi with chronic cough syndrome without the features of asthma or allergic bronchopulmonary mycosis.

1. Introduction

Fungi have long been implicated in various cough syndromes. As far back as 1698 Floyer described a patient with an asthmatic attack after exposure to fermenting wine [1]. Since then, asthma has been associated with fungal sensitivity, especially to *Alternaria alternata* and *Cladosporium herbarum*, [2,3] and allergic bronchopulmonary mycosis (ABPM) has been described in association to multiple fungi species, most commonly *Aspergillus fumigatus* [1,3].

Non-asthmatic cough syndromes have also been described including eosinophilic bronchitis and atopic cough [4]. The concept of *fungal associated chronic cough* has been proposed by Ogawa et al. based on the observation that airway colonization by basidiomycetous fungi was more common in patients with unexplained chronic cough compared to those in which the cause of chronic cough could be identified [5]. A subsequent randomized controlled study showed improvement in cough scores after eradication of basidiomycetous with itraconazole [6]. A subset of these patients, described as having allergic fungal cough, presented inducible cough on exposure to antigen of a basidiomycetous fungi [7]. This same group has described cases of atopic cough in response to *Trichosporon asahii*, *Pichia guilliermondii*, and *Streptomyces albus* [7].

Saccaharomyces cerevisiae (*S. cerevisiae*) is a yeast commonly used for wine and beer fermentation and bread leavening. Although it has rarely been reported as the cause of respiratory disease in humans, literature has identified at least five cases of invasive lung disease [8] and one case of allergic bronchopulmonary disease with eosinophilic bronchitis [4].

We report the case of a 59-year-old patient who presented with

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Abbreviations

ABPM	allergic bronchopulmonary mycosis
FVC	forced vital capacity
FEV1	forced expiratory volume in 1 second
TLC	total lung capacity
RV	residual volume
BAL	bronchoalveolar lavage
K/μL	thousand per microliter
PAS	periodic acid-Schiff stain

chronic cough and had *S. cerevisiae* isolated repeatedly from sputum. The patient had a hobby of wine production at home and symptoms resolved after clearance of the wine cellar. To our knowledge, this is the first report of *S. cerevisiae* as a cause of chronic cough not associated with asthma or eosinophilic bronchitis and the first report of fungi associated allergic chronic cough outside of Japan.

2. Case report

A 59-year-old Caucasian gentleman from Illinois with past medical history significant for hyperlipidemia, prostatitis, and former tobacco use was referred to our pulmonary clinic by a local pulmonologist on September 2016 for evaluation of chronic cough of one year. He first experienced irritation in his throat and upper airway after drinking homemade wine, causing him to have a persistent dry cough, most commonly during the day. No one else in the family suffered from similar symptoms. He did not have nighttime coughing episodes, nor did he experience sputum production, secretions, dyspnea, hemoptysis or chest pain. He denied constitutional symptoms including fevers, chills, or weight loss. Physical examination was unremarkable, without distinct pulmonary findings. A review of his medications was done and no culprit was identified. He worked in an office without exposure to chemicals or fumes and only had a remote history of tobacco use (1 pack daily for 5 years, quit 30 years ago). He had no history of past or current illicit drug use. Family history was noncontributory.

He underwent extensive initial workup by local pulmonologist. Two-view chest x-ray did not reveal acute cardiopulmonary disease. In December 2015, pulmonary function testing revealed a mildly reduced forced vital capacity (FVC) (3.65L, 76% of predicted) but were otherwise normal: forced expiratory volume in 1 second (FEV1) was 3.16L, 86% of predicted; with an FEV1/FVC ratio of 0.86. Total lung capacity (TLC) was 5.81L, 87% of predicted; residual volume (RV) was 2.16L, 92% of predicted. Diffusion capacity was 89% of predicted. Methacholine challenge test was negative. CT scan of chest was unremarkable except for multiple small nonspecific mediastinal and hilar lymph nodes and minimal lingular atelectasis. Fungal enzyme immunodiffusion assays and antibodies obtained were negative for Coccidioides, Histoplasmosis, Blastomyces, and Cryptococcus. Two sputum cultures obtained in November and December 2015 were positive for *S. cerevisiae*. Further evaluation of *S. cerevisiae* with antibody testing revealed elevated specific IgA and IgG (22.2U [negative <20U] and 48.8U [negative <20U, positive >35U], respectively).

In February 2016, he was prescribed a tapering course of prednisone for 30 days (starting at 60 mg daily) as well as a bronchodilator, which nearly resolved his symptoms but they recurred once the steroids were discontinued. He was also prescribed antihistamines and anti-reflux medications (proton-pump inhibitor) for two months with no improvement in his symptoms.

Repeat CT scan of chest without contrast in May 2016 revealed stable nonspecific mediastinal lymph nodes, but no other relevant findings. The first bronchoscopy was performed on 5/20/16 by the local pulmonologist and only a bronchoalveolar lavage (BAL) of the RML and RLL were performed. There was no transbronchial biopsy obtained at this time as patient had significant cough. There was, however, a tiny polypoid lesion on the right lateral branch take off. Cultures and cytology of bronchoalveolar lavage (BAL) were negative. There was no cell count or differential obtained. Repeat antibody evaluation in June 2016 showed similar level of *S. cerevisiae* specific IgA and IgG (21.4U and 43.1U, respectively) but normal total IgE 5.9kU/L (normal 0–100kU/L). White blood cell count was normal at 5.7k/μL with 0.9% eosinophils.

In July 2016, the patient developed daily diarrhea after each meal. Since *S. cerevisiae* antibodies have been documented in patients with Celiac [9] or Crohn's disease [10], he was evaluated by gastroenterology. In September 2016, he had an upper endoscopy and colonoscopy. Upper gastrointestinal endoscopy was normal, without evidence of esophagitis or reflux. A random biopsy of the colon was obtained and a 3-mm transverse colon polyp was excised, revealing benign fragments of colonic mucosa without colitis or granulomas.

He first presented to us in September 2016, and after initial evaluation we repeated bronchoscopy which revealed a minimal amount of secretions, diffuse airway mucosal erythema and an unchanged polypoid appearing lesion on the right lower lobe lateral basal segment. Two biopsies of the polypoid lesion and two random biopsies of the tracheal wall were obtained which were significant for acute and chronic inflammation without eosinophils; no virus or malignancy were observed; Periodic Acid-Schiff (PAS) stain was negative for fungal organisms. Cytology of BAL was negative for malignant cells and cell count differential showed 32% lymphocytes and 68% macrophages. Cultures and stains for bacteria, mycobacteria, pneumocystis jirovecci and fungus were negative.

He was again evaluated in late September when he revealed significant improvement in symptoms during a trip to Florida for over a week. This prompted a more thorough questioning to which patient revealed he had been making wine as a hobby in his home basement for 15 years, with most of his fermentation being before the holidays. He agreed to stop making wine; he cleared his basement and had no further exposure to wine-making or supplies. One month later his chronic cough had resolved and he remains symptom free 3 months later. Sputum cultures were not repeated to document resolution.

3. Discussion

Chronic cough is a common complaint in the outpatient setting and up to 46% of cases remain unexplained or refractory to treatment [11]. We present the case of a patient with chronic cough and no initial apparent cause. Extensive initial workup was performed based on American College of Chest Physician's guidelines [12] but failed to provide an explanation for the cough: chest x-ray, CT scan and pulmonary function tests including methacholine challenge test were normal; patient had no response to proton pump inhibitor and antihistamine trials, no eosinophilia in BAL, tracheal mucosal biopsy or peripheral blood. Mucosal biopsies did not show any infection. No evidence was found to support the diagnosis of common causes of chronic cough including asthma, gastroesophageal reflux disease, upper airway cough syndrome, chronic bronchitis, lung infections or tumors. Patient was not a smoker, and not on angiotensin converting enzyme inhibitors. Only relevant findings were *S. cerevisiae* cultured repeatedly from sputum and

elevated specific IgA and IgG.

Various fungi can cause a myriad of respiratory diseases, including ABPM, bronchial asthma, eosinophilic pneumonia, eosinophilic bronchitis, and atopic cough [4]. *S. cerevisiae* is well known in the food industry as bakers' yeast as well as an important entity in the fermentation of wine and beer. As a pathogen, it has been implicated in invasive disease including lung disease [8] and in one case of chronic cough with eosinophilic bronchitis [4]. An increase in *S. cerevisiae* antibodies has been found in individuals with pulmonary sarcoidosis as well as interstitial lung disease. It is believed fungal pathogens can survive in immunocompetent patients via the formation of biofilms, establishing a relationship between fungi and the hosts [13]. Our patient had no evidence of either condition.

ABPM, eosinophilic bronchitis, hypersensitivity pneumonitis and atopic cough were considered initially in the differential diagnosis given their association with fungi. ABPM is diagnosed based on clinical, serologic and radiological criteria, including: asthma, infiltrates on chest X-ray, peripheral blood eosinophilia, elevated total serum IgE, cutaneous reactivity to antigen, elevated specific IgE and IgG, and the presence of central bronchiectasis [1]. Our patient did not meet any of the major criteria making this diagnosis unlikely. A case of chronic cough diagnosed as allergic bronchopulmonary mycosis with eosinophilic bronchitis due to *S. cerevisiae* presenting similar to our patient has been reported [4]. This patient had a chronic, dry cough without peripheral blood leukocytosis or eosinophilia. As in our case, the patient did not show signs of airway obstruction on pulmonary function tests (no report of methacholine challenge was given), no eosinophilia in BAL initially but did have elevated lymphocytes, and sputum cultures repeatedly revealing *S. cerevisiae* as well as positive specific antibodies. Unlike our case, however, chest X-ray did reveal a consolidation of the right lung field and had mildly elevated total IgE. The patient also had positive skin testing and positive bronchoprovocation tests which we did not perform in our patient. Sputum showed eosinophils after bronchoprovocation test. Transbronchial biopsy showed extensive eosinophilic infiltration into the bronchial mucosa. In the patient we describe however, mucosal biopsy did not show eosinophils excluding the diagnosis of eosinophilic bronchitis. The case exhibits some features suggestive of hypersensitivity pneumonitis such as exposure history and lymphocytosis in BAL. However, other important features such as radiologic changes, restrictive pattern in lung function test and decreased diffusion capacity were absent [14]. Our patient did have cough but the absence of dyspnea, hypoxemia or constitutional symptoms argues against this diagnosis.

The Japanese Cough Research Society has defined criteria for atopic cough: non-productive chronic cough without wheezing or dyspnea, evidence of atopy, no bronchial reversibility or hyperresponsiveness, increased cough receptor sensitivity to capsaicin, resistance of cough to bronchodilators, normal chest x-ray and spirometry [15]. The laboratory tests, radiological tests, biopsy results and pulmonary function tests together with the response to steroids and correlation of symptoms to changes in environment support the diagnosis of atopic cough syndrome. However, our patient does not have evidence of atopy (history of allergies, elevated specific or total IgE, or sputum eosinophilia) and capsaicin challenge and bronchodilator trial were not performed. Recently, Ogawa et al. [5] introduced the concept of fungal associated chronic cough in patients with a) chronic cough, b) presence of fungus in sputum, c) response to antifungal. They also describe a subset of patients having allergic fungal cough marked by positive reaction to bronchoprovocation test or lymphocyte stimulation test and frequent recurrence of cough in addition to the previously mentioned criteria [5]. Out of the five patients in this subset, three had positive specific IgG and two had elevated total IgE, none had elevated specific IgE or eosinophilia [7]. Our case shares several factors with the previously described cases including chronic cough, throat irritation, presence of fungus in sputum as well as elevated specific immunoglobulins with normal total IgE and no eosinophilia or evidence of bronchial obstruction. While reported cases have been treated with antifungals and responded well, our patient was treated only with steroids temporarily with a good response and the syndrome resolved completely when exposure was eliminated.

One limitation of our case is the absence of bronchoprovocation testing which would have proven a reaction to *S. cerevisiae* as the cause of the cough. However, symptoms were worse at home, improved away from home and resolved after removal of wine making equipment from his basement, thus eliminating exposure. This pattern strongly suggests an allergic cough response related to an antigen present in the wine making process. The repeat positive sputum cultures as well as positive specific IgG and IgA to *S. cerevisiae* make this the most likely cause.

4. Conclusion

Our case adds to the literature implicating fungal species in cases of unexplained chronic cough without asthmatic features. It is especially relevant as we describe a species that had not been related to this syndrome before as well as being the first reported case outside of Japan and describing a different treatment approach. Our report highlights the need of further research into the association of environmental fungi with chronic cough syndromes, as well as the importance of exploring environmental exposures in patients presenting with chronic cough.

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