OCCUPATIONAL BRONCHIOLITIS OBLITERANS IN FOOD FLAVORING

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Short running head: Occupational Bronchiolitis Obliterans

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Abbreviations:

ATS       American Thoracic Society
FEV1      Forced Expiratory Volume in the first second
NIOSH     National Institute for Occupational Safety and Health
ppm       Parts Per Million
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ABSTRACT

Recent studies reported severe occupational lung disease in workers exposed to materials used in food flavoring. In these cases, airborne dust from butter flavoring, as diacetyl, were causative. The Center of Disease Control and Prevention and the California Division of Occupational Safety and Health issued a recent report indicating among others, the need to identify cases and reduce risk for lung disease from occupational exposure to flavoring chemicals. We report four patients exposed to powders, vapors and mists in the food flavoring industry with chronic bronchiolitis obliterans, where the first clinical presentation could be that of asthma or reactive airways disease with deterioration to bronchiolitis obliterans.
INTRODUCTION

Bronchiolitis obliterans is a rare lung disease that attacks and causes fibrosis of the bronchioles (small airways less than 2-3 mm in diameter). The pulmonary interstitium is usually spared from damage. The small airways may be severely damaged before signs of respiratory complaints or spirometric changes. Various clinical syndromes are associated with bronchiolitis obliterans, including toxic environmental and industrial exposures (King 2003).

In 1985, the National Institute for Occupational Safety and Health (NIOSH) reported on two workers in the baking industry exposed to chemicals used in the mixing room. These workers were diagnosed with fixed obstructive lung disease, consistent with bronchiolitis obliterans, however specific etiology could not be determined (NIOSH 1986). Since 2000, there has been growing concern regarding workers in the flavoring industry (such as microwave popcorn workers), who are exposed to flavoring chemicals, most notable diacetyl, and the risk of developing bronchiolitis obliterans. Several clinical studies have demonstrated bronchiolitis obliterans in food processing workers who inhale flavoring vapors. Experimental animal, case-control, and cross-sectional epidemiological studies demonstrate that bronchiolitis obliterans is a result of exposure to food flavoring materials (van Rooy et al. 2007). Within the spectrum of chemicals, diacetyl was found to play a major role (Kreiss et al. 2002; Hubbs et al. 2004). The causative factor of bronchiolitis obliterans in food flavoring industry is believed to be diacetyl, although other chemicals have not been ruled out (Harber et al. 2006). The clinical manifestations commonly entail shortness of breath in a food flavoring worker without adequate ventilation and respiratory protection and fixed obstructive airways disease. Bronchiolitis obliterans can present to the clinician as interstitial lung disease and/or asthma. Recent onset of asthma may be the first presentation of bronchiolitis obliterans.
We report four patients who worked in food flavoring industry and developed bronchiolitis obliterans. One patient initially presented with asthma; the condition deteriorated to bronchiolitis obliterans. Bronchiolitis obliterans must be suspected in patients who present with obstructive airways disease and are exposed to industrial or non-industrial food flavoring chemicals. A detailed occupational and environmental history in an otherwise unexplained asthma may be the red flag for bronchiolitis obliterans.

PATIENTS AND METHODS

We have examined and treated four patients with a history of exposure to powders, vapors and mists while working in the food flavoring industry. After a detailed medical, occupational and environmental history, each patient underwent a physical examination, standard laboratory work complete blood count, chemistry panel, urine analysis, and evaluation of IgE-mediated environmental allergens. Diagnostic studies included chest x-ray, electrocardiogram, and computed tomography scan of the chest. One patient underwent a lung biopsy. Pulmonary function test was performed using criteria established by the American Thoracic Society (ATS) and under the guidance of a trained certified respiratory technologist. Methacholine stimulation test utilizing the ATS criteria was performed on one patient.

RESULTS

Table 1 summarizes relevant results and patients’ clinical presentations. A common denominator was fixed airway obstruction with a substantially reduced FEV₁ with insignificant or no response to bronchodilator and poor response to treatment. Of importance, patient 4 was initially diagnosed with occupational asthma (with positive methacholine challenge test) and responsive FEV₁ to bronchodilator. She was not seen for three years after the initial diagnosis of asthma. Her condition deteriorated. She was retested and demonstrated fixed obstructive airways disease. Based on her fixed obstructive airway disease, occupational history and lack of response
to treatment, she was diagnosed with bronchiolitis obliterans.

DISCUSSION

In 2000, eight former Missouri microwave popcorn workers, with exposure to butter flavoring agents containing diacetyl, soybean oil, salt, and food coloring, were diagnosed with bronchiolitis obliterans (Kreiss et al. 2002). A study of workers in diacetyl production plant from 1960 to 2003 indicated excess rate of bronchiolitis obliterans (van Rooy et al. 2005). Kanwal et al. (2006) demonstrated that chronic exposure to low levels of diacetyl may cause bronchiolitis obliterans in microwave popcorn workers.

In California, eight diacetyl-exposed workers between ages of 29 and 49 developed symptoms of cough, wheezing and shortness of breath that presented as early as one month after initial exposure to several years (Materna 2007). History of smoking was not evident and only one worker had pre-existing asthma. The workers were treated for asthma, bronchitis or allergic rhinitis without improvement in their condition. Investigators diagnosed three workers with bronchiolitis obliterans. In 2007, the United States Department of Health Services reported at least eight cases of bronchiolitis obliterans in California flavor manufacturing workers exposed to diacetyl (Bailey 2007). Bronchiolitis obliterans has also been reported in Dutch chemical workers producing diacetyl for food flavoring (van Rooy et al. 2007). According to the Center for Disease Control and Prevention, no safe level for diacetyl and many other flavoring agents have been established. Exposed workers may present with cough, wheezing and shortness of breath, with onset ranging from 1 month to 5 years after initial exposure. Initial diagnosis may be asthma, bronchitis, emphysema, or bronchiectasis (United States Center for Disease Control and Prevention 2007). NIOSH has evaluated workers at a California flavoring manufacturing plant (Kanwal and Kullman 2007). Diacetyl concentrations were highest in the production room, where workers filled boxes with butter flavored powders. Investigators reported three exposed
workers with bronchiolitis obliterans. NIOSH also evaluated workers exposed to airborne butter flavoring chemicals at Montana microwave popcorn plants (Kullman et al. 2007). Dust exposure was highest during bagging activities and when powdered flavoring were used. In work areas, diacetyl measured less than 0.01 ppm with peak air concentration of 0.14 ppm directly above a heated container of butter flavored oil. Some airborne dust particles were small enough to be inhaled into the lung. Two workers were found to have evidence of bronchiolitis obliterans. Researchers at the National Jewish Medical and Research Center identified a man whose only inhalation exposure was heavy, daily consumption of butter-flavor microwave popcorn for a number of years (Rose 2007). Clinical findings indicated the diagnosis of bronchiolitis obliterans and other known causes were ruled out. These investigators suggested that the patient’s exposure to microwave popcorn flavoring vapors (diacetyl) could be the cause of bronchiolitis obliterans. Based on these studies, it is clear that diacetyl concentrations as low as 0.01 ppm may be causative of bronchiolitis obliterans, however diacetyl may not be the only culprit.

We report four food-flavoring workers who developed bronchiolitis obliterans. Medical history did not indicate pre-existing chronic respiratory symptoms or illness; one patient had a history of childhood asthma that resolved early in adolescence. History of smoking was not evident in any of our patients. These patients reported occupational exposure to varying amounts of flavoring chemical fumes and dust, with duration of exposure ranging from a few months to years. The duration of exposure for our patients is variable and compatible with previous studies. Upon exposure, patients reported similar symptoms, including eye irritation, shortness of breath, chest pain, and sense of suffocation. The patients were given paper masks for respiratory protection, but described it as ineffectual. One patient was initially diagnosed with reactive airways disease with a positive methacholine challenge test and presented a few years later with fixed obstructive disease with no response to bronchodilator. The clinical course with initial
presentation of asthma is consistent with in vitro studies of Fedan et al. (2006), who demonstrated that exposure to diacetyl (a volatile ketone) in the airways of guinea pigs led to compromise and airways hyperreactivity to methacholine. Patient 4 also had a positive methacholine test, and her condition eventually deteriorated to bronchiolitis obliterans. In assessing workers’ compensation and other compensation entities, occupational physicians should be wary not to miss the diagnosis of bronchiolitis obliterans in patients with similar presentation, who may have been initially diagnosed with reactive airways disease. Our reports have demonstrated the importance of a detailed occupational history, industrial hygiene, and the red flag for bronchiolitis obliterans.
REFERENCES


Table 1. Summary of patients reported here with occupational exposure to diacetyl

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Duration of exposure</th>
<th>Symptoms</th>
<th>Pulmonary function test, FEV₁ (before → after)</th>
<th>Chest x-ray</th>
<th>Chest CT scan</th>
<th>Biopsy</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>Male</td>
<td>2 years</td>
<td>Suffocation, eye irritation</td>
<td>27% → 36%; 22% → 23%; 31% → 29%</td>
<td>Normal</td>
<td>Pending</td>
<td>N/A</td>
<td>Albuterol, Tiotropium, Fluticasone and Salmeterol</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>Male</td>
<td>5 months</td>
<td>Shortness of breath, chest pain, cough, eye irritation</td>
<td>16% → 17%; 13% → 17%; 12% → 14%</td>
<td>N/A</td>
<td>Incidental small pulmonary nodules at the right lung base</td>
<td>Bronchiolitis obliterans</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>Male</td>
<td>6 years</td>
<td>Cough</td>
<td>37% → 37%; 40% → 35%; 37% → 39%</td>
<td>Normal</td>
<td>Minimal pleural-based markings bilaterally</td>
<td>Pending</td>
<td>N/A</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>Female</td>
<td>10 years</td>
<td>Shortness of breath, watery eyes, nasal congestion</td>
<td>42% → 42%</td>
<td>Normal</td>
<td>Pending</td>
<td>N/A</td>
<td>Albuterol</td>
</tr>
</tbody>
</table>
