Bronchiolitis associated with exposure to artificial butter flavoring in workers at a cookie factory in Brazil*

Bronquiolite associada à exposição a aroma artificial de manteiga em trabalhadores de uma fábrica de biscoitos no Brasil

Zaida do Rego Cavalcanti, Alfredo Pereira Leite de Albuquerque Filho, Carlos Alberto de Castro Pereira, Ester Nei Aparecida Martins Coletta

Abstract

Objective: To report the cases of four patients with bronchiolitis caused by exposure to artificial butter flavoring at a cookie factory in Brazil. **Methods:** We described the clinical, tomographic, and spirometric findings in the four patients, as well as the lung biopsy findings in one of the patients. **Results:** All four patients were young male nonsmokers and developed persistent airflow obstruction (reduced FEV_1/FVC ratio and FEV_1 at 25-44% of predicted) after 1-3 years of exposure to diacetyl, without the use of personal protective equipment, at a cookie factory. The HRCT findings were indicative of bronchiolitis. In one patient, the surgical lung biopsy revealed bronchiolitis obliterans accompanied by giant cells. **Conclusions:** Bronchiolitis resulting from exposure to artificial flavoring agents should be included in the differential diagnosis of airflow obstruction in workers in Brazil.

Keywords: Diacetyl; Flavoring agents; Bronchiolitis.

Resumo

Objetivo: Relatar quatro casos de bronquiolite decorrente de exposição a aroma artificial de manteiga em uma fábrica de biscoitos no Brasil. **Métodos:** Descrevemos os achados clínicos, espirométricos e tomográficos nos quatro pacientes, assim como achados de biópsia pulmonar em um dos pacientes. **Resultados:** Os quatro pacientes eram homens jovens, não fumantes, e desenvolveram obstrução persistente ao fluxo aéreo (relação VEF_1/CVF reduzida e VEF_1 de 25-44% do previsto) após 1-3 anos de exposição a diacetil, sem a utilização de equipamentos de proteção individual, em uma fábrica de biscoitos. A TCAR mostrou achados indicativos de bronquiolite. Em um paciente, a biópsia pulmonar cirúrgica mostrou bronquiolite obliterante associada a células gigantes. **Conclusões:** A bronquiolite decorrente de exposição a flavorizantes artificiais deve ser considerada em trabalhadores com obstrução ao fluxo aéreo no Brasil.

Descritores: Diacetil; Aromatizantes; Bronquiolite.

Introduction

The etiology of bronchiolitis in adults is varied, including viral infections, smoking, inhalation of toxic substances, chronic lung and bone marrow transplant rejection, collagen diseases, and idiopathic forms.[1] In view of its clinical and spirometric characteristics, bronchiolitis is often confused with diseases that are more common, especially asthma and COPD. Although the clinical course of bronchiolitis is variable, progression to severe and incapacitating obstructive disease is common. In recent years, a severe form of bronchiolitis caused by inhalation of flavoring agents has been reported in food factory workers, especially in microwave popcorn production workers (hence the term "popcorn lung"), mainly in the USA, but also in Europe.[2-7] The objective of the present study was to report the clinical, tomographic, and spirometric findings in four young patients exposed to artificial butter flavoring at a cookie factory in Brazil, as well as the lung biopsy findings in one of the patients.

* Study carried out at the Barão de Lucena Hospital, Brazilian Unified Health Care System, Recife, Brazil.
Correspondence to: Zaida do Rêgo Cavalcanti. Rua do Futuro, 480/1902, Graças, CEP 52050-010, Recife, PE, Brasil.
Tel. 55 81 3423-1825. E-mail: zaidarc@globo.com
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Methods

This was a descriptive cases series. The data collection protocol and the contents of the written informed consent form were approved by the Research Ethics Committee of the Agamenon Magalhães Hospital, in the city of Recife, Brazil.

Results

Four previously healthy young male nonsmokers, whose ages ranged from 24 to 27 years at the time of the first medical visit and who worked at a cookie factory in the city of Recife, presented with a 1-3 year history of exposure to artificial butter flavoring, i.e., diacetyl (2,3-butanedione). All of them worked on the preparation of cookie dough, which consisted of a mixture containing artificial butter flavoring, vegetable fat, wheat flour, and sugar, among other ingredients, without heating. All of them reported smelling a strong odor while handling the artificial butter flavoring agent, and none reported wearing personal protective equipment, such as masks, which is contrary to the product label instructions.

Dry cough, progressive dyspnea, and wheezing were reported by all of them. Systemic symptoms, such as weight loss, fatigue, myalgia, and nasal irritation, were present in some cases (Table 1).

In the initial spirometry test, all of the patients showed a moderate to severe obstructive pattern, with reduced FVC (Table 2). Two cases showed significant responses to inhaled albuterol (cases 1 and 4). The spirometry tests performed 4 years later revealed persistence of the airflow obstruction pattern (Table 3). Neither TLC nor DLCO was determined, because the required equipment was unavailable in our region.

None of the patients showed clinical or functional improvement after withdrawal from the workplace.

Chest X-rays revealed lung hyperinflation in three cases, being normal only in case 1. Abnormal chest CT findings included lung hyperinflation, air trapping, bronchial thickening, and mosaic perfusion (Figure 1). Ground-glass opacity was found in case 4 only.

Hematologic test results revealed marked eosinophilia in the peripheral blood (eosinophils > 1,000 cells/mm^3) in case 2 only. Total IgE levels were found to be increased in all of the cases, the values ranging from 164 to 622 IU/mL (upper limit = 100 IU/mL). Specific IgE levels to house dust were found to be increased in cases 2 and 4, and all of the patients tested

Table 1 - Clinical characteristics of the patients exposed to artificial butter flavoring.

Characteristic	Case 1	Case 2	Case 3	Case 4
Male gender	Yes	Yes	Yes	Yes
Age at symptom onset	24	24	25	27
Year of hire	2005	2003	2007	2006
Year of symptom onset	2007	2006	2008	2007
Cough	Yes	Yes	Yes	Yes
Dyspnea	Yes	Yes	Yes	Yes
Wheezing	Yes	Yes	Yes	Yes
Fever	No	No	No	No
Nasal irritation	Yes	Yes	No	No
Skin irritation	No	No	No	No
Weight loss	Yes	No	No	No

Table 2 - Results of initial spirometry in the patients exposed to artificial butter flavoring.

Variable	Case 1	Case 2	Case 3	Case 4
FEV_1, L (% of predicted)[a]	1.32 (32)	1.82 (44)	1.11 (25)	1.36 (34)
FVC, L (% of predicted)[a]	2.72 (56)	2.97 (62)	2.92 (55)	2.92 (62)
FEV_1/FVC, %	48.52	61.27	38.01	46.57
Post-BD FEV_1, L	1.35	1.88	1.23	1.72
Post-BD FVC, L	3.12	3.09	2.90	3.04

BD: bronchodilator (400-μg dose of inhaled albuterol). [a]Reference values for Brazilians.[10]

Table 3 - Results of spirometry after a four-year follow-up period.

Variable	Case 1	Case 2	Case 3	Case 4
FEV_1, L (% of predicted)[a]	1.31 (32)	1.95 (47)	0.99 (22)	1.12 (28)
FVC, L (% of predicted)[a]	2.62 (54)	2.92 (61)	2.13 (40)	2.44 (52)
FEV_1/FVC, %	50.00	66.78	46.47	45.90
Post-BD FEV_1, L	1.21	1.81	1.04	1.23
Post-BD FVC, L	2.15	2.71	2.11	2.47

BD: bronchodilator (400-μg dose of inhaled albuterol). [a]Reference values for Brazilians.[10]

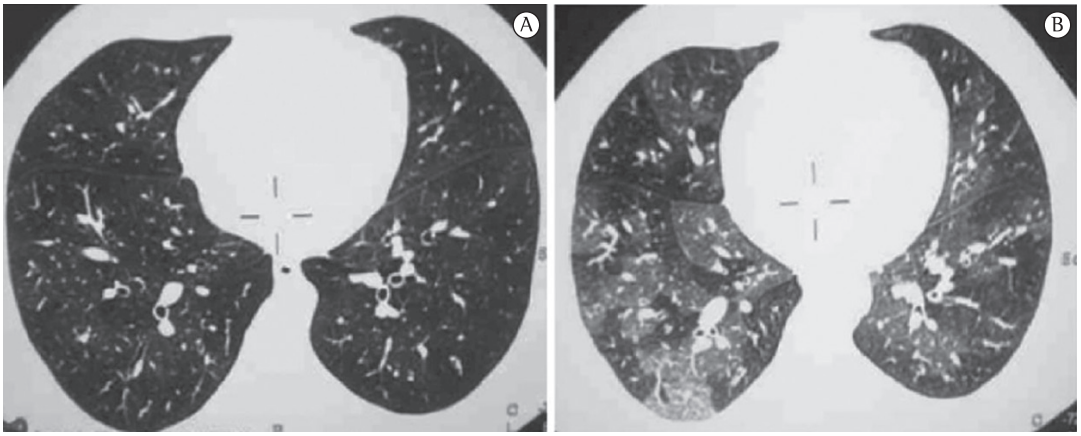

Figure 1 - Chest CT scans of case 2 during inhalation (in A), revealing lung hyperinflation and bronchial wall thickening, and during exhalation (in B), revealing a mosaic pattern.

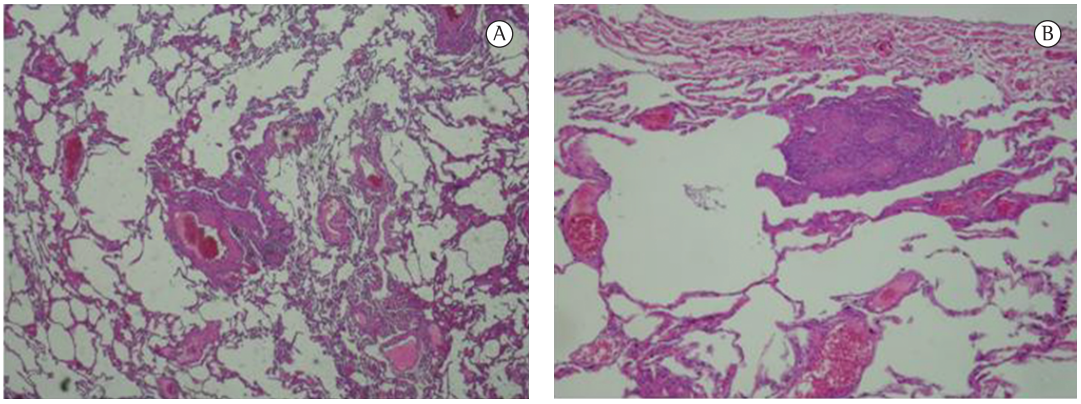

Figure 2 - In A, surgical lung biopsy specimen, with mild mononuclear cell infiltrate, slight distortion of the small airways, and areas of hyperinflation (H&E; magnification, ×100). In B, non-necrotic epithelioid granuloma with multinucleated giant cells in the subpleural region (H&E; magnification, ×100).

negative for specific IgE to mites. No skin tests were performed.

One of the patients (case 1) underwent open lung biopsy, which revealed a pattern consistent with bronchiolitis obliterans, characterized by slight distortion of the small airways with airway wall smooth muscle hyperplasia, mild mononuclear cell infiltrate, and areas of air trapping and hyperinflation (Figure 2A). In the subpleural region, there was a single non-necrotic epithelioid granuloma, together with multinucleated giant cells (Figure 2B).

Discussion

This report describes the first cases of bronchiolitis in workers handling artificial flavoring agents in Brazil. Our cases come from

a cookie factory located in the metropolitan area of Recife, Brazil. Worldwide, the first reports of flavoring-related bronchiolitis appeared in 1985,[8] when the etiologic agent had yet to be chemically identified. By 2007, flavoring-related bronchiolitis had been diagnosed in four states in the USA.[1] In that same year, the first three European cases, identified by a survey conducted in a chemical plant manufacturing diacetyl in the Netherlands, were published.[6]

The clinical, radiological, and functional characteristics of the patients described in the present study were very similar to those reported in the literature.[9] All of the patients were in charge of mixing the artificial flavoring agent with a previously prepared solution, this specific activity being the most commonly reported job in the previously described cases.[6] The workers sought treatment from a pulmonologist within 1-3 years after the initiation of exposure; in the literature, time to symptom onset has been reported to range from a few months to 5 years.[7] The predominant symptoms were progressive dyspnea and cough, which did not improve significantly on weekends and vacations; this characteristic facilitates the differential diagnosis with occupational asthma.[9] All of the patients were nonsmokers.

An obstructive spirometric pattern with reduced FVC was most common, which is consistent with air trapping, as seen on the CT scans. Two of the four patients showed a significant response to albuterol inhalation; this finding is in contrast with those of most reports,[7,9] although there are exceptions.[5]

In our case series, the HRCT findings, especially air trapping (found in all of the patients) and bronchial wall thickening, formed a pattern that is characteristic of bronchiolitis.[7,9] Ground-glass opacities, observed in one of the four cases, are rarely reported in the literature.[9]

According to the literature, few patients have undergone surgical lung biopsy.[9] Such patients have been characterized as having bronchiolitis obliterans or constrictive bronchiolitis, bronchiolar inflammation and fibrosis being present. Granulomas, found in the patient who underwent biopsy, have been observed in some cases,[2,5] leading pathologists to the diagnosis of granulomatous bronchiolitis or hypersensitivity pneumonitis. However, no other findings suggestive of hypersensitivity pneumonitis, such as evidence of pulmonary restriction, progression to fibrosis, and response to systemic corticosteroids, have been reported in the cases in the literature,[9] which is consistent with our own findings.

Typically, patients, especially the first cases of bronchiolitis in a given factory, are initially diagnosed as having asthma or COPD.[7,9] Three of our patients underwent empirical treatment with an inhaled corticosteroid and a systemic corticosteroid used in combination with a long-acting beta-adrenergic agonist, and there was no clinical or functional improvement in any of those patients, similarly to what has been described in the literature.[10] In those three individuals, the clinical and spirometric patterns remained unchanged after a mean follow-up period of 4 years.

An intriguing finding in the cases described here was increased total serum IgE levels, which was observed in all of the patients. In major case series and reviews of bronchiolitis, IgE levels are not even mentioned.[1-6,10] The increased serum IgE levels, together with a significant response to albuterol inhalation (in two of our patients), were also suggestive of asthma. However, radiological findings strongly suggestive of bronchiolitis, the absence of a history of asthma or allergic rhinitis in all of the patients, and the lack of clinical and functional response to corticosteroid treatment constituted strong evidence against that hypothesis. The high prevalence of parasitic infestation in our region could explain the increased IgE levels in our patients; however, this hypothesis was not investigated.

Only the first of our patients underwent lung biopsy. In the remaining patients, HRCT findings characteristic of bronchiolitis, together with shared occupational exposure, allowed us to establish the diagnosis.[7] Histopathological confirmation of bronchiolitis can be difficult, given the random distribution of the foci of disease in the lung tissue and along the airways.[9]

Flavoring chemicals are highly volatile, being easily inhaled after evaporation. Certain activities, such as mixing flavoring chemicals with other ingredients, are most commonly associated with cases of bronchiolitis. The possibility that cases of bronchiolitis also occur among individuals working in the production of foods other than microwave popcorn[9] was confirmed by our case series (our patients worked at a cookie factory). Despite the identification of diacetyl as the most

probable cause of lung disease in such patients, no preventive measures have been adopted. Preventive measures include engineering control measures (effective ventilation and improved work practices such as covering containers and minimizing spills) and respiratory protection measures (appropriate use of respirators with particulate filters and cartridges for protection against vapors).[2] Such exposure control measures, as well as active surveillance programs, have been implemented in some companies.[2,11]

In conclusion, we reported, for the first time in Brazil, four cases of bronchiolitis secondary to inhalation of artificial flavoring agents in workers at a cookie factory. Bronchiolitis resulting from exposure to artificial flavoring agents should be included in the differential diagnosis of airflow obstruction in workers in Brazil.

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About the authors

Zaida do Rego Cavalcanti
Pulmonologist. Barão de Lucena Hospital, Brazilian Unified Health Care System, Recife, Brazil.

Alfredo Pereira Leite de Albuquerque Filho
Pulmonologist. Barão de Lucena Hospital, Brazilian Unified Health Care System, Recife, Brazil.

Carlos Alberto de Castro Pereira
Pulmonologist. Federal University of São Paulo; and Director. Department of Respiratory Diseases, *Hospital do Servidor Público Estadual* – HSPE, São Paulo Hospital for State Civil Servants – São Paulo, Brazil.

Ester Nei Aparecida Martins Coletta
Professor of Pathology. Federal University of São Paulo; and Attending Physician. Department of Anatomic Pathology, *Hospital do Servidor Público Estadual* – HSPE, São Paulo Hospital for State Civil Servants – São Paulo, Brazil.