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Constrictive bronchiolitis secondary to exposure to flavoring agents: a little known occupational hazard

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TO THE EDITOR:

Bronchiolitis is a generic term applied to a heterogeneous group of diseases that affect the small airways (internal diameter ≤ 2 mm), resulting in inflammation and/or fibrosis.[1] This diversified entity has several presentations with varied etiologies and evolutionary prognoses. The classification is usually based on the underlying histopathological pattern, which generally correlates with the clinical and radiological presentations.[2] The most common patterns are respiratory bronchiolitis, acute bronchiolitis, follicular bronchiolitis, diffuse aspiration bronchiolitis, diffuse panbronchiolitis, and constrictive bronchiolitis.[2] Constrictive bronchiolitis, also called obliterative bronchiolitis, has been proposed to have a pathogenic mechanism of an aberrant response resulting from injury and inflammation of epithelial cells and subepithelial structures of the small airway, leading to excessive fibroproliferation and reduction of its lumen.[3] Among the causes are autoimmune diseases, post-infectious viral sequelae, graft-versus-host disease after hematopoietic stem cell transplantation, bronchiolitis obliterans syndrome after lung transplantation, drug toxicity, inflammatory bowel diseases, paraneoplastic pemphigus, and exposure to and inhalation of volatile chemicals.[2,3] Exposures to chemical agents include those of occupational origin, and among them, we highlight exposure to diacetyl (2,3-butanedione) and 2-3-pentadione. The association of diacetyl, used in the food industry as a flavoring agent because its flavor and aroma are similar to butter, with constrictive bronchiolitis was initially described in 2002 in the microwave popcorn industry.[4] Since then, several other cases have been diagnosed, not only in this activity but also in flavoring manufacturing, snack food production, pet food production, coffee roasting, and packaging facilities.[5] Animal studies indicate that the respiratory epithelium suffers directly from diacetyl and 2-3-pentadione toxicity after inhalation. Persistent tissue damage can lead to aberrant airway epithelium repair causing intraluminal fibrosis resulting in constrictive bronchiolitis.[6]

Two men aged 21 and 36 years (patients A and B, respectively) with no known comorbidities and no history of smoking were referred to our hospital for evaluation. Both worked in a factory that produced flavors for food and cosmetics in the metropolitan region of São Paulo and developed progressive dyspnea on exertion, coughing, and wheezing after the start of exposure. Patient A presented symptoms 1 year after starting the job, being removed from exposure 1 year after the onset of symptoms, and patient B developed symptoms after 2 years of exposure and was removed 6 months later.

The work involved mixing concentrated flavoring agents with powdered products as diluents. Mixing was performed manually, followed by grinding and sieving, and then the product was packed in a 20-m^2 room. The room contained a mill, a mixer, a sieve, and a balance, with four to five workers being present simultaneously. During the work period, they used N95 particulate filtering facepiece respirators with daily changes. During a visit to the workplace, poor natural ventilation and lack of exhaust ventilation were found in the processes. The clothes of the workers worn while working had strong odors of the flavoring agents used and were dirty with dust. It was verified that in areas adjacent to the room where they worked, hundreds of flavoring agents were stored with the most diverse aromas and flavors, including that of butter.

The chest HRCT of both patients showed signs of thickening of the airway walls, bronchiectasis, mosaic attenuation, and lung hyperinflation (Figure 1). Functional assessment with pulmonary function testing by plethysmography and measurement of DL_{CO} revealed the presence of marked fixed obstructive ventilatory disorder with evidence of air trapping and small airway disease shown by high specific airway resistance, elevation of RV and of the RV/TLC ratio in both patients. Patient A had a marked reduction in DL_{CO}, whereas that was within normal limits in patient B.

Investigation of autoimmune diseases and viral serology for HIV, hepatitis B, and hepatitis C yielded negative results. Patient B had undergone a bronchoscopy with transbronchial biopsy in an external service; however, there was a complication (pneumothorax). Anatomopathological findings were inconclusive because of scarcity of material.

The diagnosis of constrictive bronchiolitis secondary to diacetyl exposure was established based on clinical history, functional assessment, imaging findings, and occupational anamnesis. Both patients were not further exposed. Patient A was initially started on treatment with corticosteroids (prednisone, 1 mg/kg per day) for 15 days and subsequent reduction over three months as he showed no improvement in clinical or functional parameters. Treatment with long-acting bronchodilators and azithromycin three times a week was instituted for both patients, with slight clinical improvement, but with no improvements in pulmonary function test results. Both patients were referred for evaluation for

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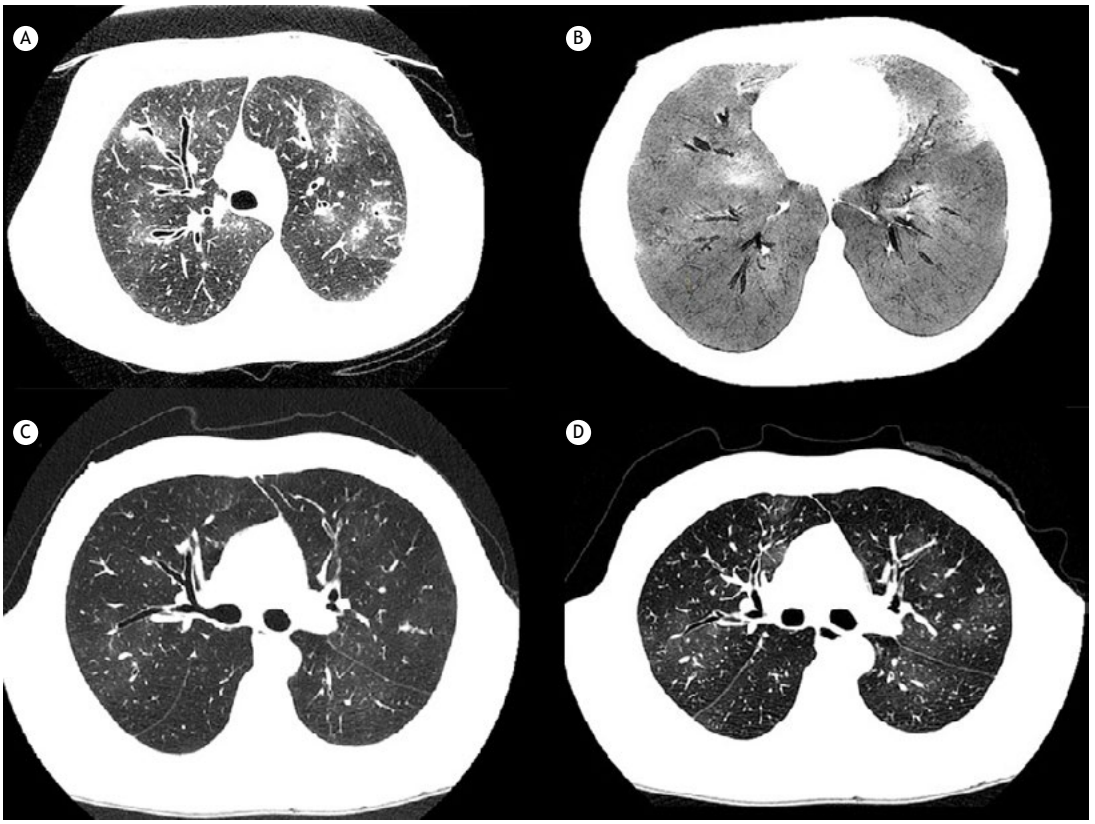

Figure 1. Axial chest HRCT scans (in A and C) of patients A and B, respectively, demonstrating diffuse bronchial wall thickening and mosaic attenuation pattern. There are areas of decreased lung attenuation associated with vessels of reduced caliber representing air trapping and regional oligemia. Minimum intensity projection reformation (in B) better depicts those areas in patient A. Expiratory acquisition (in D) confirms air trapping in patient B.

lung transplantation. At the moment of this writing, patient A is on the waiting list, while patient B is still being evaluated.

The attempt to investigate the existence of other workers affected by that type of exposure in the same factory was faced with resistance from those responsible for it; they provided some data such as spirometry tests, but those data were insufficient for an adequate analysis due to the poor quality of the tests.

Constrictive bronchiolitis secondary to exposure to flavoring agents is a potentially serious but preventable disease. The first Brazilian case series on exposed workers in a cookie factory was published in 2012,[7] but there has been a lack of national literature since then. In the northern hemisphere, several epidemiological surveillance studies in companies related to the use of flavoring agents have diagnosed multiple cases.[5]

The most commonly reported symptoms are dyspnea on exertion and dry cough that can manifest months or years after exposure onset.[5] The most common functional change in spirometry is obstructive respiratory disorder, but results can be normal or reveal restrictive or mixed disorders.[5,8] Chest HRCT demonstrates mosaic attenuation, which is consistent with air trapping.[5,8] In the majority of cases, diagnosis can be established by analyzing the history of exposure, presence of symptoms, and pulmonary function test results. Early withdrawal from exposure can halt disease progression.[5]

The motivation of this letter is to highlight that during evaluation of patients with bronchiolitis, attention should be paid to occupational causes, and the identification of a sentinel case should be seen as a signal for the investigation of other workers at risk, indicating the need for the adoption of exposure control measures such as local exhaust ventilation. Finally, the presence of diacetyl and other flavors in e-cigarettes and vaping solutions has recently been identified.[9] This fact should be viewed with concern, given the possibility of development of a similar pattern of bronchiolitis obliterans among individuals with chronic exposure to e-cigarette aerosols of solutions containing flavoring agents.[10,11]

AUTHOR CONTRIBUTIONS

GCA: study conception; data collection; and drafting of the manuscript. RFM: manuscript revision. All of the authors approved the final version of the manuscript.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Ryu JH, Myers JL, Swensen SJ. Bronchiolar disorders. Am J Respir Crit Care Med. 2003;168(11):1277-1292. https://doi.org/10.1164/rccm.200301-053SO
2. Ryu JH, Azadeh N, Samhouri B, Yi E. Recent advances in the understanding of bronchiolitis in adults. F1000Res. 2020;9:F1000 Faculty Rev-568. https://doi.org/10.12688/f1000research.21778.1
3. Barker AF, Bergeron A, Rom WN, Hertz MI. Obliterative bronchiolitis. N Engl J Med. 2014;370(19):1820-1828. https://doi.org/10.1056/NEJMra1204664
4. Kreiss K, Gomaa A, Kullman G, Fedan K, Simoes EJ, Enright PL. Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. N Engl J Med. 2002;347(5):330-338. https://doi.org/10.1056/NEJMoa020300
5. Nett RJ, Harvey RR, Cummings KJ. Occupational Bronchiolitis: An Update. Clin Chest Med. 2020;41(4):661-686. https://doi.org/10.1016/j.ccm.2020.08.011
6. Hubbs AF, Kreiss K, Cummings KJ, Fluharty KL, O'Connell R, Cole A, et al. Flavorings-Related Lung Disease: A Brief Review and New Mechanistic Data. Toxicol Pathol. 2019;47(8):1012-1026. https://doi.org/10.1177/0192623319879906
7. Cavalcanti Zdo R, Albuquerque Filho AP, Pereira CA, Coletta EN. Bronchiolitis associated with exposure to artificial butter flavoring in workers at a cookie factory in Brazil. J Bras Pneumol. 2012;38(3):395-399. https://doi.org/10.1590/S1806-37132012000300016
8. Kreiss K. Occupational causes of constrictive bronchiolitis. Curr Opin Allergy Clin Immunol. 2013;13(2):167-172. https://doi.org/10.1097/ACI.0b013e32835e0282
9. Allen JG, Flanigan SS, LeBlanc M, Vallarino J, MacNaughton P, Stewart JH, et al. Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes. Environ Health Perspect. 2016;124(6):733-739. https://doi.org/10.1289/ehp.1510185
10. Jonas A. Impact of vaping on respiratory health. BMJ. 2022;378:e065997. https://doi.org/10.1136/bmj-2021-065997
11. Hariri LP, Flashner BM, Kanarek DJ, O'Donnell WJ, Soskis A, Ziehr DR, et al. E-Cigarette Use, Small Airway Fibrosis, and Constrictive Bronchiolitis. NEJM Evid. 2022;1(6). https://doi.org/10.1056/EVIDoa2100051