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Case Report

# Vaping-associated constrictive bronchiolitis

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ABSTRACT

A woman in her 40s who vaped reported rapid onset of shortness of breath and cough. Pulmonary function testing showed severe obstruction and no substantial response to an inhaled bronchodilator, and chest computed tomography revealed extensive air trapping. A lung cryobiopsy was done after a comprehensive and unrevealing evaluation, which showed characteristics of airway inflammation and prominent bronchial-associated lymphoid tissue. With this knowledge and her vaping history, we diagnosed vaping-associated constrictive bronchiolitis. This phenomenon has not been well described. Clinicians should know to consider vaping when a patient with a vaping history presents with severe airway obstruction.

**Abbreviations**

| | |
|---|---|
| CT | computed tomography |
| ECMO | extracorporeal membrane oxygenation |
| $FEV_1$ | forced expiratory volume in 1 second |
| FVC | forced vital capacity |

## 1. Introduction

Constrictive bronchiolitis or bronchiolitis obliterans is an irreversible obstructive lung disease commonly seen in patients who have received lung transplants or allogeneic bone marrow transplants [1]. However, constrictive bronchiolitis has also been associated with other causes such as connective tissue disorders, inhaled toxins, and environmental exposures [1]. In May 2000, 8 workers in a plant that manufactures microwave popcorn were diagnosed with constrictive bronchiolitis [2]. Workers at the plant were subsequently found to have 3.3 times the rate of obstruction on spirometry than expected [3]. Diacetyl, a ketone used in artificial butter flavoring, was believed to be the cause [3], which led to a diagnosis termed *popcorn lung* [4].

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Vaping is a leading 21st century public health challenge. The rate of vaping was estimated to have increased from 1.5% to over 20.8% among American adolescents from 2011 to 2018 [5]. A 2015 study from Harvard University showed that diacetyl and 2 other diacetyl analogues were present in 47 of 51 vapes/e-liquid flavors tested in a random sample of over 7000 available flavors [6]. Because diacetyl is a common component of e-cigarettes, the likelihood exists that it could cause constrictive bronchiolitis for persons who vape, just as it caused popcorn lung. We present a case of vaping-associated constrictive bronchiolitis, a condition that is not well described in the literature.

## 2. Case presentation

A woman in her 40s came to our outpatient pulmonary clinic with abrupt onset of worsening shortness of breath and dry cough. She had a history of vaping. She was treated for an acute asthma attack with a 5-day course of oral corticosteroids and azithromycin, which did not substantially improve her symptoms.

When her symptoms worsened, the patient went to an emergency department elsewhere and was admitted to the hospital. She received intravenous corticosteroids, nebulized bronchodilators, and intravenous antibiotics (levofloxacin and azithromycin) for presumed community-acquired pneumonia, although a chest radiograph did not show consolidation. After several days, she was discharged home despite no substantial improvement in her symptoms.

The patient's symptoms persisted, and she returned to our outpatient pulmonary clinic for another appointment. Before that appointment, she was hospitalized several additional times. She could walk only short distances before oxygen desaturation developed, and she became dizzy and light-headed. She had required oxygen since her first hospitalization. She said that her home and work environments had not changed before her initial respiratory symptoms began. She also said that she had not had any occupational exposures. She smoked cigarettes for 4 years and had a 20-pack-year history. She transitioned to vaping after she quit smoking. However, she also stopped vaping after the onset of her initial, severe respiratory symptoms.

A comprehensive diagnostic workup was done as part of the patient's pulmonary review at our pulmonary clinic.

### 2.1. Imaging

A high-resolution computed tomography (CT) chest scan was ordered that included contrast and inspiratory and expiratory views. Mosaic attenuation, characterized by areas of heterogenous lung density, were seen in an inspiratory coronal slice (Fig. 1A, arrows) and was more pronounced in the upper lobes. Little change in the hypoattenuated areas was seen in an expiratory view at the same level (Fig. 1B), although a relative increase in attenuation could be seen in the hyperattenuated areas compared with the same areas on the inspiratory view. These findings indicated limited airflow consistent with air trapping in the hypoattenuating regions, a condition that has numerous differential diagnoses. Other findings on the chest CT were diffuse cylindrical bronchiectasis predominantly in the mid and lower lobes, with mild bronchial wall thickening.

### 2.2. Pulmonary function testing

Pulmonary function testing showed severe obstruction with a forced expiratory volume in 1 second ($FEV_1$) of 24% of predicted (forced vital capacity [FVC], 62%; $FEV_1$/FVC ratio, 31.8) without substantial bronchodilator response. Residual volume was correspondingly increased at 208% of predicted, consistent with substantial air trapping as seen on the CT images.

### 2.3. Echocardiography

Echocardiography with agitated saline did not show any signs of a cardiac shunt. Left and right ventricular function were within normal limits, and no valvular abnormalities were present.

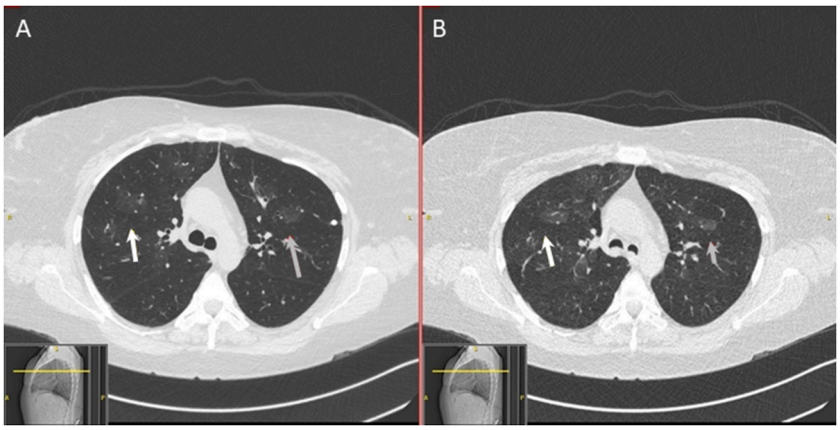


**Fig. 1.** High-Resolution Computed Tomography Scan of the Thorax. A, An inspiratory image shows areas of mosaic, heterogenous attenuation. The arrows denote areas of hypoattenuation with surrounding hyperattenuation. B, An expiratory image shows airtrapping with more prominent hyperattenuated areas (normal lung).

**Table**
Results of serologic testing.

| Test | Value | Interpretation |
|---|---|---|
| Antinuclear Ab, serum | <0.2 | Negative |
| c-ANCA/p-ANCA | NA | Negative |
| Myeloperoxidase Ab | 0.3 | Negative |
| Proteinase 3 Ab | <0.2 | Negative |
| Beta-2 GP-1 Ab IgM | <9.4 | Negative |
| Beta-2 GP-1 Ab IgG | <9.4 | Negative |
| Anti-CCP | <15.4 | Negative |
| Antiphospholipid Ab IgM | 37.6 | Weak positive |
| Antiphospholipid Ab IgG | <9.4 | Negative |
| DNA double-stranded Ab, IgG | 17.4 | Negative |
| SS-A/Ro Ab, IgG | <0.2 | Negative |
| SS-B/La Ab, IgG | <0.2 | Negative |
| SM Ab, IgG | <0.2 | Negative |
| RNP Ab, IgG | <0.2 | Negative |
| Scl-70 Ab, IgG | <0.2 | Negative |
| Jo-1 Ab, IgG | <0.2 | Negative |
| Rheumatoid factor | <0.2 | Negative |
| Allergen testing | | Negative |
| *Aspergillus fumigatus*, IgE | <0.35 | Negative |
| *Aspergillus fumigatus*, IgG | <0.35 | Negative |
| Avian panel | | Negative |
| Hypersensitivity pneumonitis panel | NA | Negative |
| Cystic fibrosis screen | | |
| Sweat chloride | NA | Negative |

Abbreviations: Ab, antibody; anti-CCP, anti–cyclic citrullinated peptide; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; GP-1, glycoprotein 1; Ig, immunoglobulin; Jo-1, histidyl-tRNA synthetase; NA, not applicable; p-ANCA, perinuclear antineutrophil cytoplasmic antibodies; RNP, ribonucleoprotein; Scl-70, scleroderma; SS-B/La Ab, anti–Sjögren-syndrome–related antigen B autoantibodies; SS-A/Ro, anti–Sjögren-syndrome–related antigen; SM, smooth muscle.

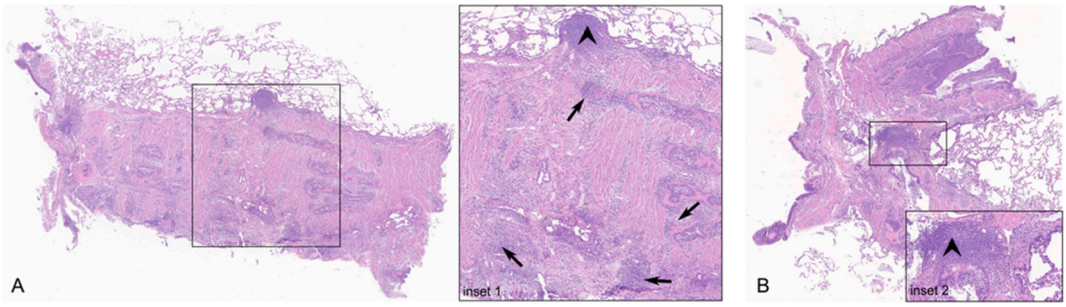


**Fig. 2.** Histopathologic Characteristics of the Transbronchial Cryobiopsy. A and B, Low-power views of stained lung tissue sections (hematoxylin-eosin) revealed transmural chronic inflammation. High-power views (insets 1 and 2) revealed edema and chronic lymphocytic inflammation throughout the bronchial wall (arrows). Lymphoid follicles are shown magnified in inset 2 (arrowheads). The adjacent alveolated lung parenchyma is unremarkable and not inflamed. Small, noncartilaginous airways were not seen in the specimen.

### *2.4. Serologic findings*

The patient underwent evaluations for vasculitis, other autoimmune diseases, hypersensitivity pneumonitis, cystic fibrosis, and infections. All test results were within normal ranges (Table).

### *2.5. Bronchoscopy and lung cryobiopsy*

The patient also underwent a bronchoscopy and cryobiopsy. Bronchoalveolar lavage was grossly cloudy. Cell counts revealed $10.4 \times 10^6$ total nucleated cells with 80% neutrophils, 17% alveolar macrophages, and 2% other cells. The sample was negative for any malignancy. The transbronchial cryobiopsy showed evidence of transmural chronic inflammation and prominent, bronchial-associated lymphoid tissue, consistent with chronic bronchitis (Fig. 2). The adjacent alveolated lung parenchyma was unremarkable. Small airways were not present in the specimen and therefore could not be evaluated. There was no evidence of neoplastic proliferations or granulomatous processes in the biopsy specimen.

### *2.6. Outcome and follow-up*

The patient continues to be seen in the pulmonary clinic. Her symptoms have not improved much, but they have remained stable except during episodes of respiratory tract infection when her symptoms have intermittently worsened. Spirometry findings have remained stable, with a mild decrease in diffusion capacity. She continues to use inhalers (corticosteroid, long-acting muscarinic ago-

nist, and long-acting beta agonist) and supplemental oxygen with some respite in the severity of her symptoms. She was evaluated by the lung transplant team with a plan to continue to follow-up at this point.

## 3. Discussion

The initial differential diagnosis in this case included many potential causes for fixed bronchial constriction (eg, postinfectious, autoimmune, inhaled lung toxicities, and, less likely, neoplasia [neuroendocrine hyperplasia]). Atypical pneumonia is a rarely reported cause of obliterative bronchiolitis. Findings from the rheumatologic workup were negative, and there were no other symptoms suggestive of a systemic autoimmune process. Ultimately, the cryobiopsy specimen revealed injury to the bronchi in a pattern of chronic exposure. The chest CT showed diffuse air trapping on expiratory views along with bronchiectasis, which suggested an airway process. Ultimately, based on the CT findings, the fixed airflow limitation on pulmonary function testing, and airway inflammation from the cryobiopsy specimen, a diagnosis of constrictive bronchiolitis from vaping best fit the clinical picture.

Diacetyl, which has been associated with constrictive bronchiolitis, exists in many e-cigarette flavors [6]. In the literature, however, only a few cases have described vaping-associated constrictive bronchiolitis. In 2019, a report described the case of a 17-year-old boy with an "intractable cough, progressive dyspnea, and hypoxia" after vaping flavored e-liquids and tetrahydrocannabinol [7]. He developed progressive hypoxia, first requiring mechanical ventilation with later escalation to venovenous extracorporeal membrane oxygenation (ECMO) for refractory hypercapnia. His chest CT showed tree-in-bud nodularity consistent with acute bronchiolitis. His symptoms continued even after discontinuation of ECMO, and his exercise tolerance remained limited. Pulmonary function testing showed persistent fixed airway obstruction and air trapping. The authors thought the clinical picture most likely represented constrictive bronchiolitis from an inhalation injury due to the flavored e-liquids [7].

In 2022, a small case series was published that included 4 patients with constrictive bronchiolitis and a history of vaping [8]. All 4 patients had progressive shortness of breath paired with obstructive lung function and air trapping on high-resolution chest CT. Two of the patients had fibrosis in the small airways with bronchiolar narrowing and lumen irregularities shown on endobronchial optical coherence tomography. All 4 patients underwent video-assisted thoracoscopic surgical biopsy. The predominant histologic finding was subepithelial fibrosis with luminal narrowing and patchy bronchiolar obliteration consistent with constrictive bronchiolitis [8]. In addition, 2 of the 4 patients had nodular airway–centered fibrosis and/or extensive peribronchiolar metaplasia.

In conclusion, when a case of constrictive bronchiolitis is encountered, a thorough investigation of exposures such as inhalation or vaping should be obtained and considered in the diagnosis.

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## CRediT authorship contribution statement

**Liam Carey:** Conceptualization, Data curation, Writing – original draft. **Kimberly Johnson:** Supervision, Validation, Writing – review & editing. **Julian Villalba:** Investigation, Writing – review & editing. **Misbah Baqir:** Conceptualization, Formal analysis, Supervision, Writing – review & editing.

## Declaration of competing interest

None.

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