E-Cigarette Use, Small Airway Fibrosis, and Constrictive Bronchiolitis

Lida P. Hariri, M.D., Ph.D.[1,2,3], **Bess M. Flashner, M.D.**[2,3], **David J. Kanarek, M.D.**[2,3], **Walter J. O'Donnell, M.D.**[2,3], **Alyssa Soskis, M.D.**[2,3,4], **David R. Ziehr, M.D.**[2,3], **Angela Frank, M.D.**[2,3], **Sreyankar Nandy, Ph.D.**[2,3], **Sarita R. Berigei, B.S.**[2,3], **Amita Sharma, M.D.**[3,5], **Douglas Mathisen, M.D.**[3,6], **Colleen M. Keyes, M.D.**[2,3], **Michael Lanuti, M.D.**[3,6], **Ashok Muniappan, M.D.**[3,6], **Jo-Anne O'Malley Shepard, M.D.**[3,5], **Mari Mino-Kenudson, M.D.**[1,3], **Amy Ly, M.D.**[1,3], **Yin P. Hung, M.D., Ph.D.**[1,3], **Flavia V. Castelino, M.D.**[3,7], **Harald C. Ott, M.D.**[3,6], **Benjamin D. Medoff, M.D.**[2,3], **David C. Christiani, M.D.**[2,3,8]

[1]Department of Pathology, Massachusetts General Hospital, Boston

[2]Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston

[3]Harvard Medical School, Boston

[4]Division of Pulmonary and Critical Care Medicine, Duke University Hospital, Durham, NC

[5]Department of Radiology, Massachusetts General Hospital, Boston

[6]Division of Thoracic Surgery, Massachusetts General Hospital, Boston

[7]Division of Rheumatology, Massachusetts General Hospital, Boston

[8]Harvard T.H. Chan School of Public Health, Boston

Abstract

BACKGROUND—Vaping, including the use of electronic cigarettes (e-cigarettes), has become increasingly prevalent, yet the associated long-term health risks are largely unknown. Given the prevalence of use, particularly among adolescents early in their lifespan, it is vital to understand the potential chronic pathologic sequelae of vaping.

METHODS—We present the cases of four patients with chronic lung disease associated with e-cigarette use characterized by clinical evaluation, with pulmonary function tests (PFTs), chest high-resolution computed tomography (HRCT), endobronchial optical coherence tomography (EB-OCT) imaging, and histopathologic assessment.

RESULTS—Each patient presented with shortness of breath and chest pain in association with a 3- to 8-year history of e-cigarette use, with mild progressive airway obstruction on PFTs and/or chest HRCT findings demonstrating evidence of air trapping and bronchial wall thickening. EB-OCT imaging performed in two patients showed small airway–centered fibrosis with bronchiolar narrowing and lumen irregularities. The predominant histopathologic feature on surgical lung

biopsy was small airway–centered fibrosis, including constrictive bronchiolitis and MUC5AC overexpression in all patients. Patients who ceased vaping had a partial, but not complete, reversal of disease over 1 to 4 years.

CONCLUSIONS—After thorough evaluation for other potential etiologies, vaping was considered to be the most likely common causal etiology for all patients due to the temporal association of symptomatic chronic lung disease with e-cigarette use and partial improvement in symptoms after e-cigarette cessation. In this series, we associate the histopathologic pattern of small airway–centered fibrosis, including constrictive bronchiolitis, with vaping, potentially defining a clinical and pathologic entity associated with e-cigarette use. (Funded in part by the National Institutes of Health.)

Introduction

The use of electronic cigarettes (e-cigarettes), part of behavior commonly known as "vaping," is widespread in many cultures worldwide but has poorly understood health risks. There has been a large increase in e-cigarette use, especially among younger adults and adolescents, with 9% of the U.S. population overall and 27.5% of high school students reporting that they engage in vaping.[1] The recent e-cigarette or vaping-associated lung injury (EVALI) epidemic shed light on some of the potential dangers associated with vaping; young patients developed acute respiratory distress syndrome in association with histopathologic acute bronchiolocentric lung disease, with many cases proving fatal.[1–4] In contrast with this acute syndrome, very little is known about the longer-term chronic health risks from vaping, despite the fact that e-cigarette users report chronic respiratory symptoms.[4–7] In a large, nationally representative survey of 402,822 participants, there was an increased odds ratio (1.73) of self-reported asthma among never tobacco-smoking, daily e-cigarette users compared with never e-cigarette users.[5] However, the underlying pathophysiology of these symptoms is not understood. Given the prevalence of use, particularly among adolescents, it is important to understand whether there are chronic sequelae of e-cigarette use that can be identified on microscopic examination of lung tissue obtained from individuals with a clinical presentation consistent with a vaping-related illness. In this article, we present four patients who presented with histologically confirmed small airway–centered injury with fibrosis, including constrictive bronchiolitis, in association with e-cigarette use.

Methods

We present four patients with chronic lung disease and a 3- to 8-year history of e-cigarette use. All patients underwent detailed clinical evaluation, with pulmonary function tests (PFTs), chest high-resolution computed tomography (HRCT), and surgical lung biopsy for histopathologic assessment. Spirometry was interpreted using the European Respiratory Society Global Lung Initiative predicted values.[8] Endobronchial optical coherence tomography (EB-OCT) imaging was performed for two of four patients, the methods of which were published previously.[9,10] Briefly, EB-OCT is a volumetric optical imaging modality with high-resolution (approximately 10 mm) that visualizes fine

microscopic features of peripheral lung tissue that is deployed at the time of fiberoptic bronchoscopy.[9,10]

Results

CASE PRESENTATIONS

Patient 1 was a 25-year-old otherwise healthy woman who vaped for 3 years before presenting with pleuritic chest pain, dyspnea, and fatigue. Patient 2 was a 50-year-old woman who vaped for 6 years before presenting with progressive dyspnea on exertion and pleuritic chest pain in the context of a recent, significant increase in vaping frequency. She had a history of systemic lupus erythematosus (diagnosed 16 years before presentation) with overlap Sjögren's syndrome, autoimmune hemolytic anemia (both diagnosed 8 years before presentation), and well-controlled gastroesophageal reflux disease (GERD), and her notable medications included 20 mg of methotrexate orally per week, 400 mg of hydroxychloroquine orally per day, and 40 mg of omeprazole orally daily. Patient 3 was a 65-year-old woman with a history of mild asthma/chronic obstructive pulmonary disease (COPD) overlap syndrome. She had a 4-year vaping history and developed subsequent dyspnea on exertion. Patient 4 was a 63-year-old man who had been vaping for 8 years and developed cough and chest pressure. All patients denied experiencing fever, chills, wheezing, arthralgias, and arthritis, and they had no history of infectious, occupational, or known environmental or allergic exposures. None of the patients reported characteristic EVALI symptoms such as weight loss, fever, or gastrointestinal symptoms. Each patient had other etiologies of their chest pain and dyspnea evaluated at the discretion of their treating clinician, each of whom concluded that the symptoms were pulmonary in etiology. Detailed case histories are provided in Table S1 in the Supplementary Appendix.

The four patients all used different types of vaping devices and vape fluids (Table 1). Patient 4 vaped fluid containing propylene glycol (PG) and vegetable glycerin (VG) alone and denied using fluid containing flavorants, nicotine, tetrahydrocannabinol (THC), or cannabidiol. Patients 1 through 3 all vaped nicotine, and patient 3 also used THC vaping products. All patients endorsed vaping usage more than 4 days per week. All patients were former cigarette smokers and vaped in the context of smoking cessation. Patient 1 had a smoking history of 5 pack-years (1 pack per day [PPD] for 5 years, from 18 to 22 years of age), then switched to vaping 3 years before presentation. Patient 2 smoked 2 PPD for 34 years (from 11 to 44 years of age), then switched to vaping 6 years before presentation. Patient 3 smoked 1 PPD for 40 years (from 19 to 58 years of age), quit smoking 7 years before presentation, and began vaping 3 years after smoking cessation. Patient 4 smoked 0.5 to 1 PPD for 40 years (from 21 to 60 years of age) and quit 3 years before presentation. He concurrently vaped and smoked cigarettes for 5 years before smoking cessation and then only vaped for the subsequent 3 years until presentation.

PFT AND SEROLOGY

Data from PFTs over time (when available) are shown in Table S2. In three of four patients, the rate of loss of forced expiratory volume in the first second (FEV_1) appeared to be more rapid near the time of presentation than for previous testing. Serologic testing revealed

antinuclear antibody (ANA) positivity in patients 1, 2, and 4; patients 1 and 4 had an ANA positive result at a titer of 1:160 (speckled) and patient 2 had an ANA positive result at 1:320 (homogeneous). In keeping with patient 2's known history of Sjögren's syndrome, she had a positive SS-A (Ro) antibody result. Patient 1 also had a positive antibody test result for *Aspergillus flavus*. All other serologic testing results were negative (Table S1).

RADIOLOGIC FINDINGS

Findings on chest HRCT are detailed in Figures S1 and S2 and Table S1. All patients demonstrated mild bronchial wall thickening and lower lobe predominant mosaic attenuation, suggestive of air trapping. Patient 1 also demonstrated multiple bilateral solid, part-solid, and cystic lung nodules in both upper lobes and the superior segment of the right lower lobe, which was concerning for multifocal lung carcinoma. Patient 4 also showed bilateral, basilar predominant, subpleural-sparing peripheral ground-glass opacities with associated reticulations and cystic changes. Patients 2 through 4 had evidence of mild centrilobular emphysema in the upper lobes that was distinct from the other imaging findings. Patients 3 and 4 each also had a cystic and ground-glass nodule that was being followed for suspicion of malignancy on screening computed tomography (CT) imaging.

EB-OCT IMAGING FINDINGS

Patients 3 and 4 underwent EB-OCT imaging (Fig. 1), which demonstrated regions of small airway–centered fibrosis affecting distal bronchioles, with microscopic luminal narrowing and irregularities, and foci of scarring that appeared to obliterate the lumen. The subpleural lung distal to regions of fibrosis had preserved alveolar parenchyma with patchy, mild interstitial fibrosis. Patient 4 also showed regions of prominent airway-centered cystic changes consistent with peribronchiolar metaplasia, hyperinflation, and emphysema-like changes (not shown).

HISTOLOGIC FINDINGS

All patients underwent video-assisted thoracoscopic surgery to assess disease pathology (Figs. 2 and S3). On histopathology, all patients showed constrictive bronchiolitis with subepithelial fibrosis between the basement membrane and smooth muscle layer of the small airways, with luminal narrowing, and regions of obliteration and respiratory epithelial nuclear and cytologic reactive changes indicative of injury. There were occasional intraluminal mucus plugs and scattered chronic inflammation, but no goblet cell metaplasia or significant chronic inflammatory infiltrate or lymphoid aggregates were seen. By immunohistochemistry, there was overexpression of MUC5AC in the respiratory epithelium of numerous bronchioles in all cases, predominantly seen in small airways with fibrosis (Fig. 3). In some cases, patchy mild interstitial fibrosis within alveolar walls and peribronchiolar metaplasia was present adjacent to small airways with fibrosis.

Patient 1 also showed dense, nodular fibrosis, with both keloid-like and elastotic features, consistent with the nodular lesion seen on HRCT. Patient 4 showed marked, multifocal, bronchiolocentric cystic peribronchiolar metaplasia, hyperinflation, and emphysematous-like changes associated with regions of small airway fibrosis, consistent with the cystic changes seen on HRCT. Patient 4 also had regions of nodular, small airway–centered fibrosis.

Patients 2 through 4 also had mild centriacinar emphysema and respiratory bronchiolitis, consistent with their known former smoking history, which was distinct from the described constrictive bronchiolitis and other small airway–centered fibrosis abnormalities. Patient 1 had no evidence of centriacinar emphysema or respiratory bronchiolitis. Patient 1 had patchy peribronchiolar granulomatous inflammation, which was not seen in patients 2 through 4. Both patients 3 and 4 had lung adenocarcinoma, consistent with the nodules seen on screening CT imaging. Patient 3 had a minimally invasive adenocarcinoma (total size, 1.1 cm; invasive size, 0.2 cm) with no nodal metastasis (pTmi, N0). Patient 4 had an invasive adenocarcinoma, acinar predominant (total size 1.5 cm; invasive size, 0.9 cm) with no nodal metastasis (pT1a, N0). The described nonneoplastic lung findings were seen in lung tissue at least 5 cm away from the adenocarcinomas. None of the patients showed evidence of vasculitis, infection, foreign or polarizable material, or asthmatic airway changes. Cultures were negative for organisms.

DIAGNOSIS AND CLINICAL FOLLOW-UP

In each of the four cases, we considered a broad differential diagnosis for causes of each patient's condition, but no other identified condition could fit the clinical, imaging, lung function testing, and histopathologic findings that had been gathered (Table 2). In the absence of other known diagnoses, vaping was considered to be the most likely common causal etiology.

After evaluation and biopsy, patients 1 through 3 ceased vaping, while patient 4 continued to vape. None received glucocorticoids, antibiotics, or other therapies directed at their pulmonary disease. For patient 3, her previously prescribed inhaled fluticasone (44 μg two puffs twice daily) was maintained for her baseline asthma/COPD overlap syndrome. The patients who stopped vaping had symptomatic improvement, as noted in Tables S1 and S2; these patients may also have had increases in their FEV_1 or improvement of disease on chest imaging. All patients had at least 1 year of clinical follow-up after presentation (range, 1 to 4 years), and none had new symptoms or evidence consistent with an alternative etiologic diagnosis on follow-up.

Discussion

E-cigarette use has become increasingly prevalent, especially among young individuals, yet the associated long-term health risks are largely unknown.[1] Large epidemiologic surveillance-based studies have shown that e-cigarette users may have self-reported asthma-like respiratory symptoms, but the physiological basis for these symptoms is unknown.[4–7] Constrictive bronchiolitis (also known as obliterative bronchiolitis or bronchiolitis obliterans) is a well-established pathologic sequelae of chronic small airway injury from inhalational chemical fume exposures.[11–14] Constrictive bronchiolitis and other small airway fibrotic syndromes can present with asthma-like symptoms due to fibrotic narrowing of the small airways.[15] Based on the reported histologic findings in EVALI, with most cases demonstrating primarily airway-centered acute lung injury, it has been postulated that this represents a form of airway-centered chemical pneumonitis from one or more inhaled toxic substances, with the major culprit in the vaping epidemic that occurred in May

to September of 2019 in the United States thought to be vitamin E acetate.[2] It has been hypothesized that patients who vape may be at risk for developing, distinct from the EVALI syndrome, chronic small airways disease as a result of accumulated, subclinical airway injury from vaping.[2] Here, we present evidence for this second "chronic form" of injury in four e-cigarette users with small airway–centered injury with fibrosis, including constrictive bronchiolitis, confirmed by EB-OCT imaging and histopathology.

Our evidence is circumstantial. All four patients were former smokers who experienced a slow onset of shortness of breath and/or chest pain that affected their quality of life after heavy vaping use over 3 to 8 years. For some patients, this was accompanied by mild airway obstruction, as evidenced by a decrease in FEV_1, on PFTs, and/or imaging findings demonstrating evidence of air trapping and bronchial wall thickening. On histopathology and volumetric EB-OCT imaging, the major defining feature was small airway–centered fibrosis, with all patients showing constrictive bronchiolitis with subepithelial fibrosis, patchy bronchiolar obliteration, airway epithelial injury, and associated MUC5AC overexpression. Patients 2 and 3 showed predominantly constrictive bronchiolitis, whereas patients 1 and 4 had findings of nodular airway-centered fibrosis and/or extensive peribronchiolar metaplasia in addition to constrictive bronchiolitis. All of the features seen can be broadly categorized as small airway–centered injury with fibrosis.

Adverse reactions to toxic agents, such as vaping, are often difficult to diagnose, requiring verification of a temporal relationship between the exposure and disease onset and exclusion of other etiologies of the disease pathology with a high degree of certainty.[16] Chronic lung disease related to inhalational exposure may be more difficult to identify, given the time lag between repeated exposure and disease manifestation. The four patients presented herein each had clear, symptomatic chronic lung disease, which developed in temporal association with their e-cigarette use. There was symptomatic and objective improvement (improved FEV_1 and/or imaging) after cessation for the three patients who quit vaping without therapeutic intervention or other lifestyle modifications. However, the improvement noted did not return the patients to their baseline function or imaging, as would be expected in small airway fibrosis and constrictive bronchiolitis (Tables S1 and S2). Taken together, we speculate that chronic vaping-induced lung injury was the most likely etiologic cause of disease in all four patients (Table 2).

The differential diagnosis of constrictive bronchiolitis includes inhalational chemical fume or drug exposures, postinfectious small airways disease, connective tissue disease (CTD)–related lung disease, posttransplantation, and other less common conditions (i.e., diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, inflammatory bowel disease).[11–14] Other potential etiologic considerations that can cause small airway fibrosis, distinct from constrictive bronchiolitis, include hypersensitivity pneumonitis, chronic aspiration, and combustible tobacco smoking-related lung disease. None of the patients had any other known inhalational or drug exposures other than current vaping and former smoking, did not have any history of infection before presentation and symptom onset, and had not undergone transplantation. Although patients 1 and 4 had a positive ANA at a titer of 1:160 (speckled), it is well established that this does not necessarily indicate a systemic CTD.[17] The rest of their clinical evaluations were negative for CTD, and no other autoantibodies

were positive. Up to 15% of patients may present with pulmonary manifestations of CTD before development of systemic signs and symptoms.[18] However, patients 1 and 4 in this study had 4 and 2 years of follow-up after presentation, respectively, and did not develop signs or symptoms of CTD over that time period, making CTD-related lung disease highly unlikely. Patient 2 had a long-standing, established diagnosis of Sjögren's syndrome. Rare cases of constrictive bronchiolitis have been described in Sjögren's syndrome, with reported cases demonstrating stable or worsening findings on follow-up CT imaging and PFTs.[19–22] However, CTD-related lung disease, including constrictive bronchiolitis, frequently has prominent associated chronic inflammatory infiltrates, which were not present in the biopsies. Our data suggest that occult CTD is an unlikely cause of these patients' condition.

Although patient 1 had positive serology for *A. flavus*, detection of serum precipitins has low sensitivity/specificity for hypersensitivity pneumonitis.[23] The patient had no known mold exposure, and the clinical, imaging, and pathologic features were inconsistent with hypersensitivity pneumonitis. None of the patients reported symptoms of reflux at the time of presentation or in clinical follow-up. Patient 2 had a known history of GERD but reported that this was well controlled with omeprazole. Although hypersensitivity pneumonitis and chronic aspiration in GERD can both cause small airway–centered fibrosis, they are not known to cause features of constrictive bronchiolitis. In addition, both hypersensitivity pneumonitis and chronic aspiration frequently have an associated histiocytic inflammatory infiltrate that was not seen on the biopsies. None of the patients had evidence of asthmatic airway changes on histology. Although patient 3 was being treated empirically for asthma before presentation, she had no bronchodilator response on PFTs obtained 4 years before presentation and no histologic evidence of asthma.

Constrictive bronchiolitis, seen in all four patients, is not a known pathologic sequela of cigarette smoking.[11–14,24–29] The findings in all patients were not clinically, radiologically, or pathologically consistent with known pathologic manifestations of smoking-related disease, which include emphysema, respiratory bronchiolitis (and respiratory bronchiolitis interstitial lung disease [ILD]), chronic inflammatory bronchitis, and smoking-related interstitial fibrosis in the lung parenchyma.[24–30] Although small airway fibrosis can be seen in association with smoking, it is distinct from constrictive bronchiolitis and typically has prominent goblet cell metaplasia, mucus plugging, and chronic inflammation with lymphoid aggregates, none of which were seen in the biopsies from any of the patients in this study.[24–29] Consistent with their former smoking history, three of four patients also had evidence of mild emphysema radiologically and pathologically, but these findings were distinct from the pathologic findings of constrictive bronchiolitis and small airway fibrosis. Notably, patient 1 had a short, 5 pack-year smoking history before vaping and no evidence of emphysema or other smoking-related lung disease radiologically or pathologically.

Marked overexpression of MUC5AC in the bronchiolar respiratory epithelium provides further support for vaping-associated small airways disease (Fig. 3), especially given that the overexpression was seen most prominently in fibrotic small airways. MUC5AC is a major gel-forming mucin in the mucus layer of human airways. In the normal, healthy airways of nonsmokers, MUC5AC expression is found only in the superficial epithelium of the proximal, cartilaginous bronchi, and no expression is seen in the bronchioles.[31] MUC5AC

overexpression has been reported in response to vape exposure in bronchial brushings and induced sputum samples from e-cigarette users compared with nonsmoking controls.[32,33] Increased MUC5AC expression has also been reported in response to vape exposure in human bronchial epithelial cell cultures in vitro and in murine respiratory epithelium in vivo.[32] MUC5AC overexpression is known to occur in COPD and asthma.[34–36]

However, in patients who had stopped smoking before biopsy, as noted in our patient cohort, MUC5AC expression has been shown to normalize to levels similar to those of never-smokers.[34,35] Our patient cohort had no histologic evidence of asthma. MUC5AC expression in ILD has a similar expression profile as healthy lungs, including in patients with CTD-ILD.[37] This provides additional supporting evidence that the pathologic findings in patient 2 are likely due to vaping exposure rather than Sjögren's syndrome–related lung disease.

The four patients each used different vaping devices and fluids, including brands and flavors. Due to this exposure heterogeneity and the small cohort size, we cannot determine whether there is a single component of the vaping fluid and/or device (or a combination thereof) that may be the culprit for the identified pathologic findings. It is notable that patient 4 only vapes the PG/VG base without known added nicotine, THC, or flavorants and demonstrates features of constrictive bronchiolitis and small airway–centered fibrosis with increased MUC5AC expression. Increased MUC5AC expression is known to occur in response to PG/VG exposure alone in both in vitro human bronchial epithelial cultures and in vivo mouse respiratory epithelium, with no further increase in expression with the addition of nicotine to PG/VG.[32] This raises the possibility that volatilized PG/VG alone may cause airway epithelial damage and/or fibrosis. However, chemical analysis of purchased e-liquids have demonstrated that the majority of e-liquids, pods, and disposable e-cigarettes that are labeled as "nicotine-free" do actually contain some nicotine.[38,39] Our data do not allow us to identify a single or combination culprit material.

All four patients were former smokers. Although constrictive bronchiolitis, seen in all four patients, is not a known pathologic sequela of cigarette smoking,[11] it cannot be determined whether all of the pathologic findings are the result of vaping alone or the combination of vaping after cessation of cigarette smoking. Further, large-scale studies will be needed to assess this in detail, which will be critical given the large effort to utilize vaping as a tool to facilitate combustible tobacco smoking cessation and recent Food and Drug Administration authorization to allow marketing of tobacco-flavored electronic nicotine delivery systems.[40]

There is heterogeneity in the case histories among the four patients presented, including the extent of prior smoking history, their past medical histories, and the vaping products that were used. Despite this heterogeneity, all patients had similar pathologic findings, including histologic evidence of constrictive bronchiolitis, with vaping as the common factor among these cases. Importantly, patient 1 was a young, otherwise healthy female with no prior medical history and a 5 pack-year smoking history. The only known exposure patient 1 had that could plausibly result in the histologic findings seen on her biopsy was her vaping exposure. The fact that the other three patients showed similar histologic findings, in the

absence of another known diagnosis, increases confidence that vaping is the common causal etiology.

Conclusions

We present four cases of chronic lung pathology in association with 3 to 8 years of e-cigarette use in patients who all used different vape devices and fluid flavors/brands, including one patient who only vaped PG/VG. The predominant histopathologic feature was small airway–centered injury with fibrosis, including constrictive bronchiolitis, with MUC5AC overexpression. All patients who ceased vaping had partial reversal of disease over 1 to 4 years. For all patients, after thorough evaluation for other potential etiologic causes of the disease, vaping was considered to be the most likely common causal etiology due to the temporal association of symptomatic chronic lung disease with their e-cigarette use and improvement in symptoms after cessation of e-cigarette use. Further investigation of chronic lung disease manifestations from e-cigarette use is essential to understand the potential risk of vaping use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures

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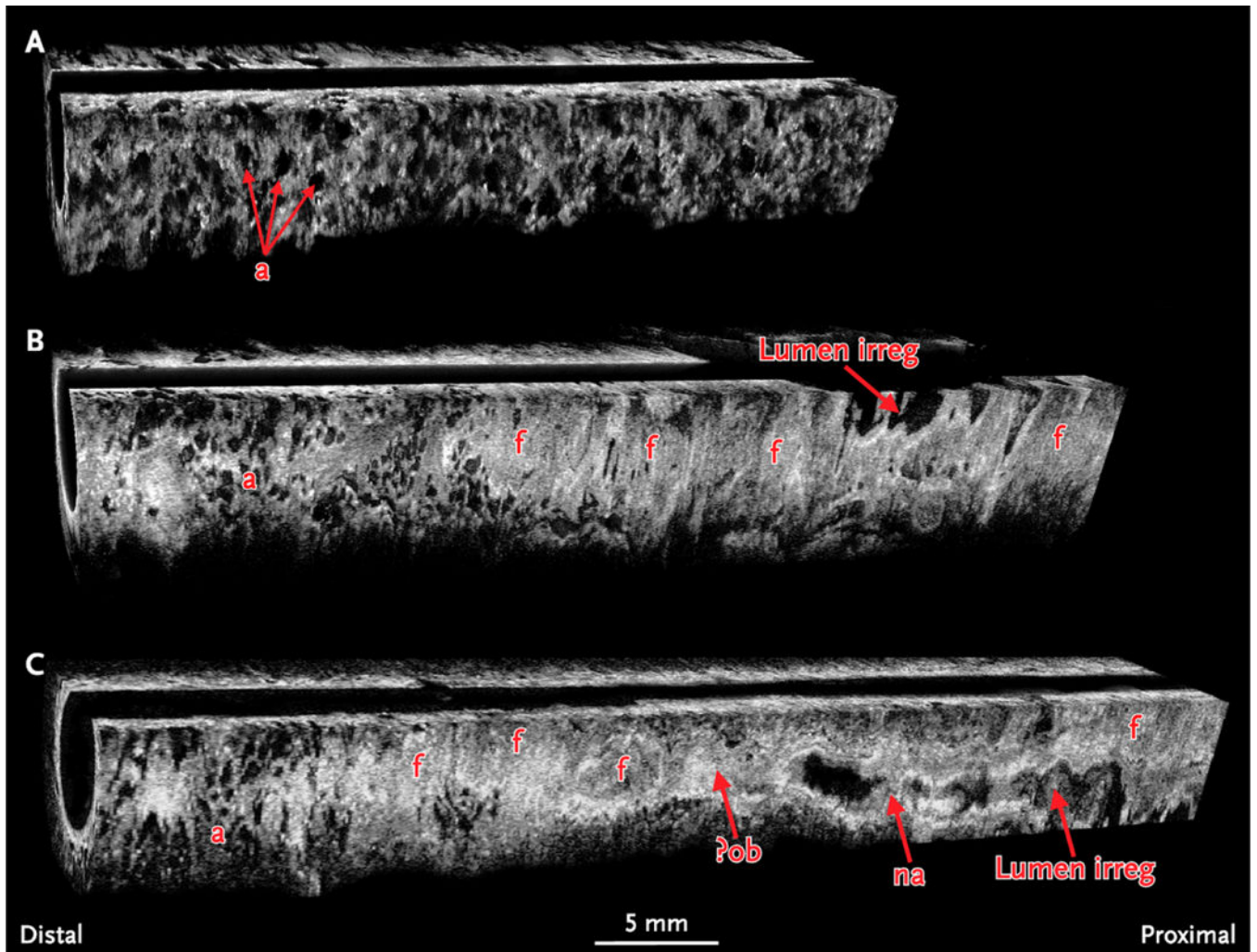
Figure 1.
Endobronchial Optical Coherence Tomography.

Panel A shows a normal peripheral bronchiole in a nonvaping patient control with attached, lattice-like lung parenchyma seen as signal-void (black), round, evenly spaced alveoli (a) and thin, signal moderate (gray) alveolar walls. Panels B and C show peripheral bronchioles from patients 3 and 4 with small airway–centered fibrosis (f), with microscopic luminal narrowing (na) and irregularities (Lumen irreg), and regions of scarring that may have luminal obliteration (?ob). The subpleural lung distal to regions of fibrosis had preserved alveolar parenchyma (a) with patchy, mild interstitial fibrosis. The distal end of each bronchiole is on the left and the proximal end is on the right. Scale bar, 5 mm.
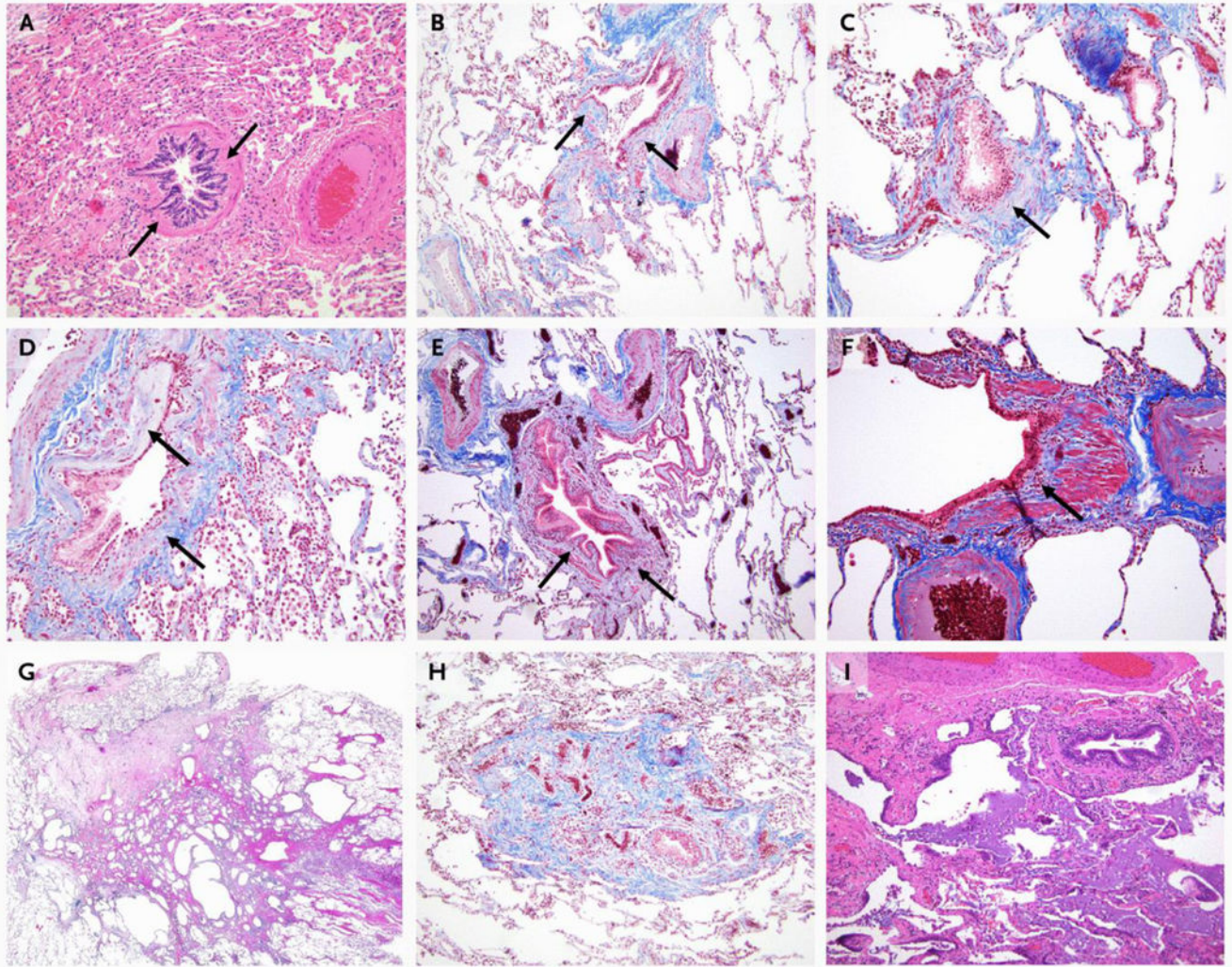
Figure 2.

Histopathology from Lung Biopsies.

Panels A through Fshow that all patients demonstrated histologic evidence of constrictive bronchiolitis with subepithelial fibrosis (arrows) and lumen narrowing. Panels B through E show some patients had focal extension of fibrosis into adjacent parenchyma. Panel E shows some patients had associated mild peribronchiolar metaplasia. Panel G shows patient 1 also had dense, nodular fibrosis, consistent with the nodular lesion seen on HRCT. Panels H and I shows patient 4 also had nodular airway-centered fibrosis around bronchioles (Panel H) and marked, cystic peribronchiolar metaplasia with hyperinflation and emphysematous-like changes in regions of small airway fibrosis (Panel I), consistent with the cystic changes seen on HRCT. Original magnification and staining are as follows: 200× in Panel A (patient 1; hematoxylin and eosin [H&E]), Panels Cand D (patient 3; trichrome), and Panel F (patient 2; trichrome); 100× in Panel B (patient 3; trichrome), Panel E (patient 4; trichrome), Panel H (patient 4; trichrome), and Panel I (patient 4; H&E); and 20× in Panel G (patient 1; H&E).
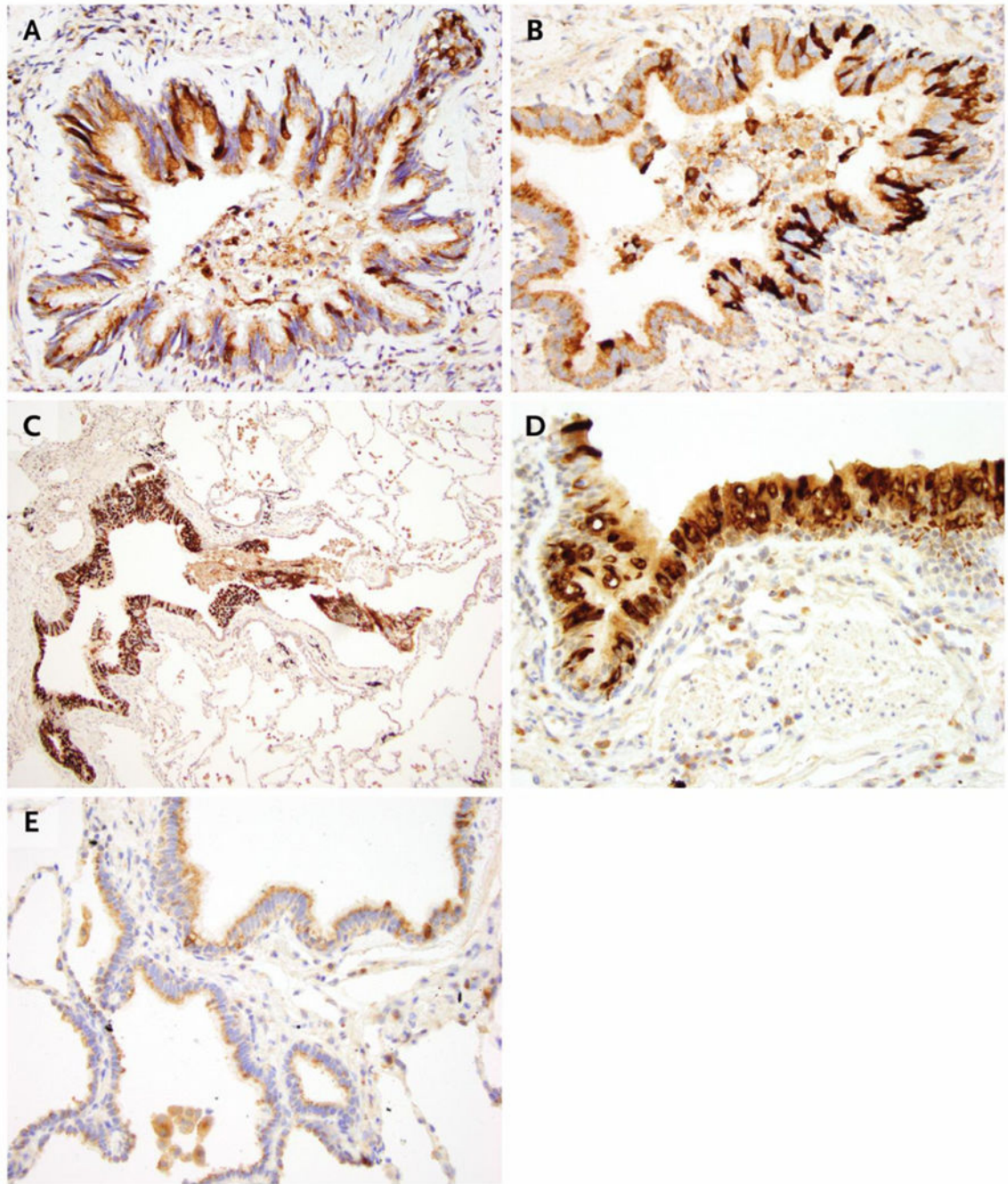
Figure 3.

MUC5AC Immunohistochemistry.

Panels A to D show that, by immunohistochemistry, there was overexpression of MUC5AC in the respiratory epithelium of numerous bronchioles in all vaping patients. Panel E shows MUC5AC expression in a nonvaping, former-smoker patient as a control, which has very little MUC5AC expression compared with the vaping patients. Original magnification is as

follows: 400× in Panel A (patient 1), Panel B (patient 2), Panel D (patient 4), and Panel E (nonvaping, former-smoker control); and 100× in Panel C (patient 3).

Table 1.

Patient Vaping History.[*]

Patient	Duration of Vaping in yr	Nicotine Use and Concentration	THC/CBD Use	Type of Vape Device	Flavor and Brand of Vape Fluid	No. of Days on Average per Week of Vaping	No. of Pods Vaped per Day
1	3	Yes, unknown	None	Unknown	Flavored, but unknown flavor/brand	7	0.5–1
2	6	Yes, 5 mg	None	Viper	Teleos, Captain Crunch, JUUL	7	0.5–1
3	4	Yes, unknown	Yes	Vuse	Tobacco or menthol	4	0–0.5
4	8	None	None	Uwell Caliburn	Propylene glycol and vegetable glycerin alone (no flavors or nicotine)	7	0.5–1

[*] CBD denotes cannabidiol and THC tetrahydrocannabinol.

Table 2.

Etiologic Considerations in the Case Cohort.*

Etiologic Consideration	Relevant Clinical Details from Case Cohort	Typical Histologic Findings	Diagnostic Consideration of Each Etiology in Case Cohort
Smoking-related small airways disease	Patient 1: 5 pack year smoking history (1PPD × 5 yr) Patient 2: 68 pack year smoking history (2PPD × 34 yr) Patient 3: 40 pack year smoking history (1PPD × 40 yr) Patient 4: 30 pack year smoking history (0.5–1PPD × 40 yr)	- Emphysema, respiratory bronchiolitis (and respiratory bronchiolitis ILD), chronic inflammatory bronchitis, and smoking-related interstitial fibrosis in the lung parenchyma - Small airway fibrosis, typically with prominent goblet cell metaplasia, mucus plugging, and chronic inflammation with lymphoid aggregates. - Constrictive bronchiolitis not a known pathologic sequelae of smoking	Smoking-related small airways disease excluded in patients 1–4 due to the following: - Constrictive bronchiolitis seen in patients 1–4 not known to occur in association with smoking - Lack of prominent goblet cell metaplasia, mucus plugging, and chronic inflammation with lymphoid aggregates known to occur in small airways disease from smoking - Short smoking history in patient 1 - Review of histopathology by 5 pulmonary pathologists who all concur that the findings were not consistent with combustible tobacco-related lung disease
Vaping-associated inhalational injury	Patients 1–4: vaping exposure in temporal association with symptom onset, with symptom improvement after vaping cessation in patients 1–3 (patient 4 continued to vape)	- Unknown; hypothesized that chronic small airways disease may develop over time in patients as a result of accumulated, subclinical airway injury from vaping - May see features similar to other inhalational exposures, such as constrictive bronchiolitis and/or small airway injury with fibrosis	Vaping-associated inhalational injury is a common causal etiology among patients 1–4
Other inhalational or drug exposures	Patients 1–4: no other known inhalational or drug exposures	- Constrictive bronchiolitis and/or small airway injury with fibrosis	Other inhalational- and drug-related injury excluded in patients 1–4 due to lack of known exposures
Post-infectious small airways disease	Patients 1–4: no known infection prior to presentation or symptom onset	- Chronic inflammatory bronchiolitis - Constrictive bronchiolitis and small airway injury with fibrosis	Post-infectious etiology excluded in patients 1–4 due to lack of clinical history of infection prior to presentation or symptom onset
CTD-related lung disease	Patient 2: known Sjögren's disease Patients 1 and 4: positive ANA, no rheumatologic symptoms Patient 3: no rheumatologic symptoms	- ILD, organizing pneumonia, bronchiectasis - Small airway injury with fibrosis can be seen - Constrictive bronchiolitis very rare (seen most commonly in rheumatoid arthritis) - Typically has associated chronic inflammatory infiltrates	CTD-related lung disease excluded due to the following: - Patient 2: temporal association with vaping in setting of prior stable PFTs over 8 years; improvement of symptoms and PFTs with vaping cessation; rarity of constrictive bronchiolitis in association with Sjögren's disease and lack of associated chronic inflammatory infiltrates - Patients 1, 3 and 4: lack of rheumatologic symptoms on follow-up 4, 1 and 2 years after presentation, respectively
Chronic aspiration	Patient 2: known history of GERD, well-controlled on omeprazole at presentation Patients 1, 3, and 4: no known history of GERD	- Small airway injury with fibrosis, typically with associated histiocytic inflammation - Constrictive bronchiolitis not a known pathologic sequelae of chronic aspiration	Chronic aspiration excluded due to the following: - Constrictive bronchiolitis seen in patients 1–4 not known to occur in association with chronic aspiration - Patient 2: GERD well-controlled on omeprazole at presentation; lack of histiocytic inflammation frequently present in chronic aspiration - Patients 1, 3, and 4: no known history of GERD

* ANA denotes antinuclear antibody, CTD connective tissue disease, GERD gastroesophageal reflux disease, ILD interstitial lung disease, PFT pulmonary function test, and PPD packs per day.