

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplemental Appendix

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E-cigarette use, small airway fibrosis, and constrictive bronchiolitis

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DJK, WJD, FVC, AS, DRZ, AF, and CMK cared for the patients. AS and JOS interpreted imaging studies. SN, SRB, and LPH collected and analyzed EB-OCT imaging data. DM, ML, HCO, and AM cared for the patients and performed surgical lung biopsies. LPH, MRM, YPH, and AL interpreted histopathology. LPH, BMF, BDM, and DCC wrote the report, which was reviewed by all authors.

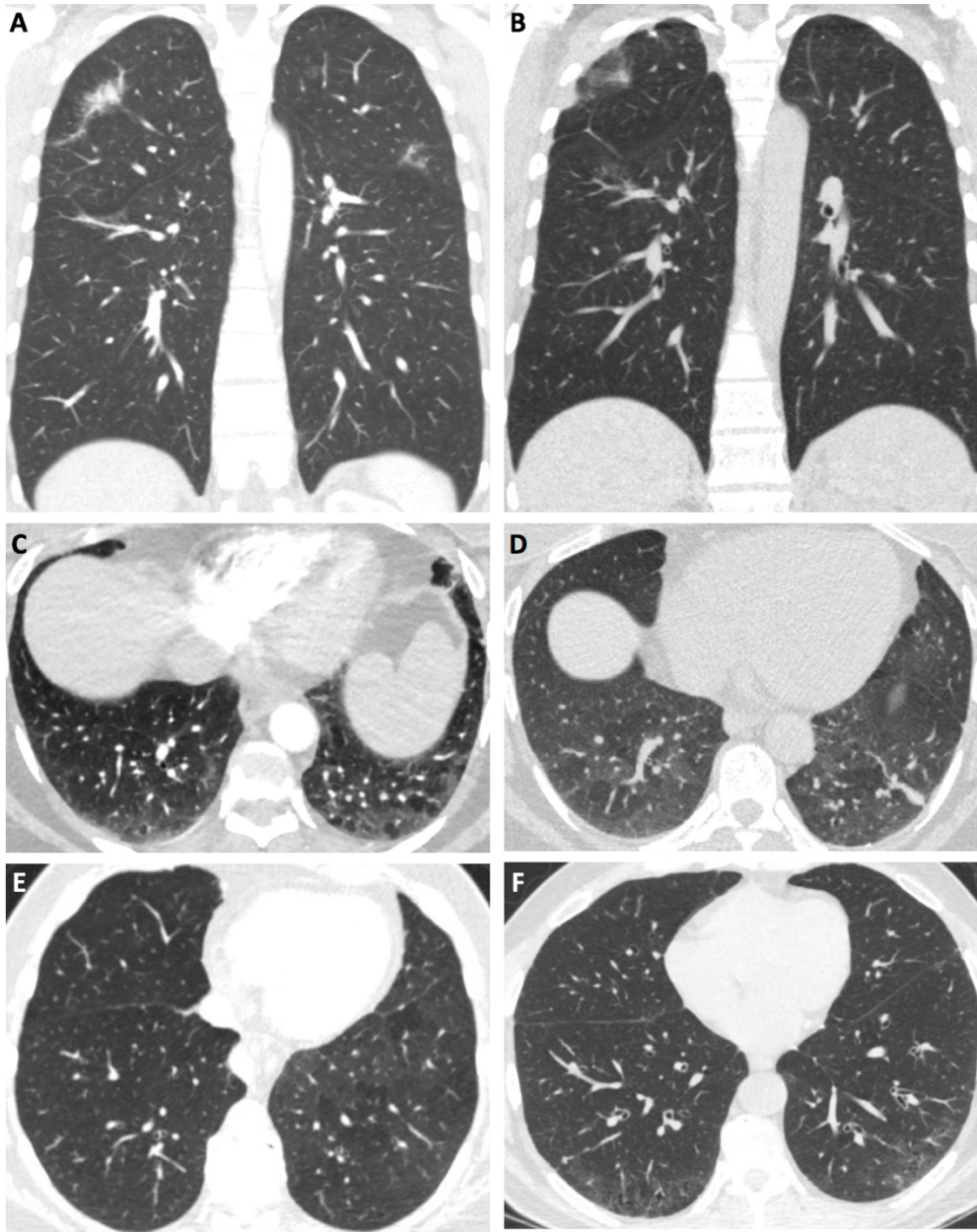


Figure S1. Chest computed tomography. (A) Patient 1 at presentation and (B) at 21 months follow-up, (C) Patient 2 at presentation and (D) 3 years follow-up, and (E) Patient 3 and (F) Patient 4 at presentation. Patients 1, 3 and 4 had mild bronchial wall thickening and lower lobe predominant mosaic attenuation, suggestive of air trapping. Patient 2 had mild bronchial wall thickening and lower lobe predominant lobular lucencies, also suggestive of air trapping. Patient 4 also showed bilateral, basilar predominant, peripheral ground glass with subpleural-sparing and associated traction bronchiectasis and peribronchiolar cysts. Patient 1 additionally demonstrated multiple bilateral solid, part-solid and cystic lung nodules in both upper lobes and superior segment of the right lower lobe, which was concerning for multifocal lung carcinoma but was diagnosed as a fibrotic lung nodule on histopathology. Patients 3 and 4 each additionally had a mixed cystic and part-solid nodule that was being followed for suspicion of malignancy on screening CT (see Figure S2), which were both diagnosed as adenocarcinoma on histopathology. Patient 1 had improvement of bronchial wall thickening and size of lung nodules on follow-up imaging performed 21 months after presentation (B), but lower lobe mosaic attenuation remained unchanged. (D) For Patient 2, on expiratory imaging studies performed 3 years after presentation, there are several persistent areas of low attenuation in the middle and bilateral lower lobes on expiration studies, consistent with air trapping and small airways disease.

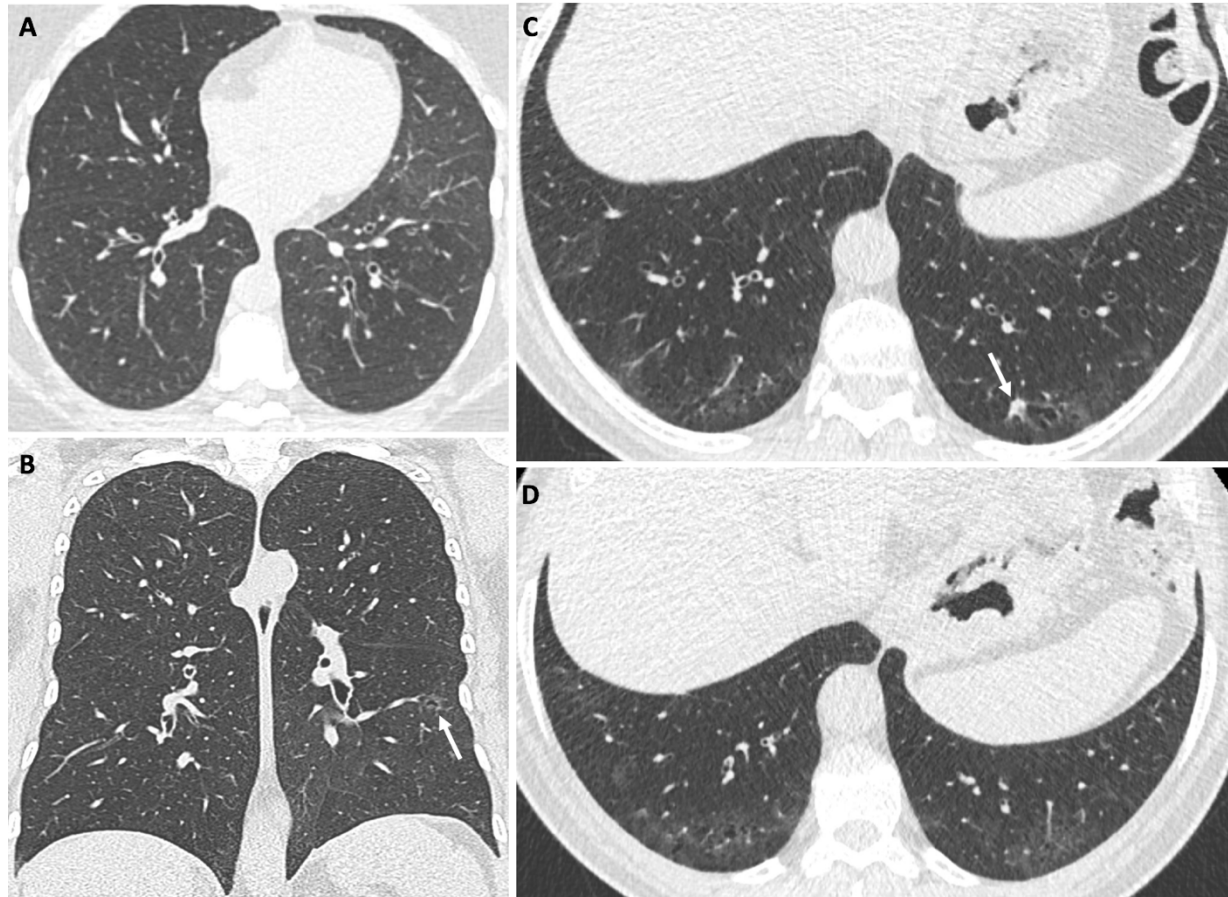


Figure S2. Additional chest computed tomography (CT) imaging. (A-B) CT images from Patient 3 at presentation showed mild bronchial wall thickening and lower lobe predominant mosaic attenuation, suggestive of air trapping. (C-D) CT images from Patient 4 at presentation also showed mild bronchial wall thickening as well as bilateral, basilar predominant, peripheral ground glass with subpleural-sparing and associated peribronchiolar cysts. Patients 3 and 4 each additionally had a mixed cystic and part-solid nodule (arrows) that was being followed for suspicion of malignancy on screening CT, which were both diagnosed as adenocarcinoma (minimally invasive adenocarcinoma (pTmiN0) and acinar predominant invasive adenocarcinoma (pT1aN0), respectively) on histopathology.

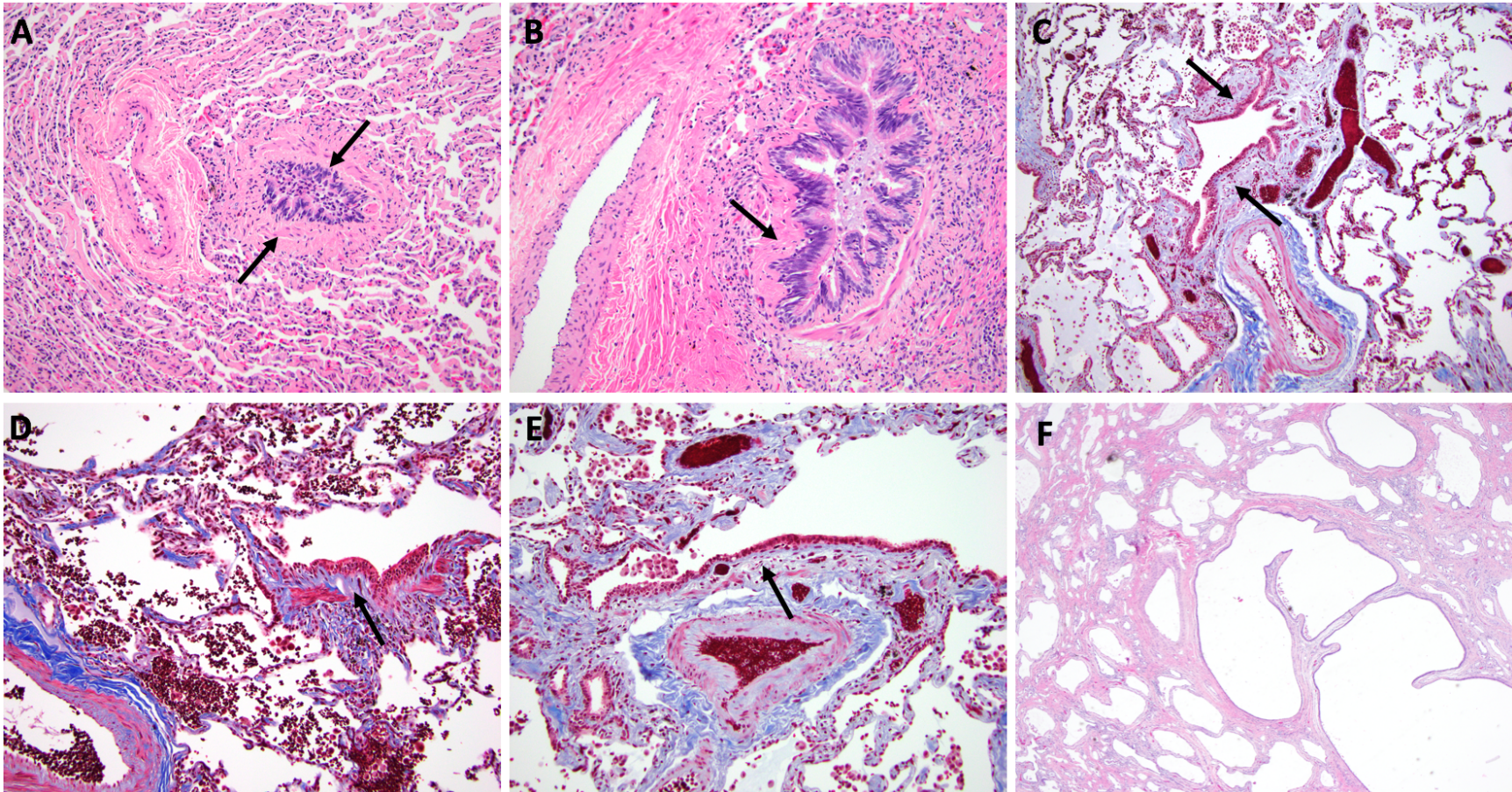


Figure S3. Additional histopathology from lung biopsies. (A-E) All patients showed histologic evidence of small airway fibrosis and constrictive bronchiolitis, with subepithelial fibrosis (arrows) and lumen narrowing and/or irregularity. (F) Patient 1 additionally showed dense, nodular fibrosis with associated architectural simplification, consistent with the nodular lesion seen on chest CT imaging. (A) Patient 1, H&E, magnification: 200x, (B) Patient 1, H&E, magnification: 200x, (C) Patient 4, trichrome, magnification: 100x, (D) Patient 2, trichrome, magnification: 200x, (E) Patient 4, trichrome, magnification: 200x, (F) Patient 1, H&E, magnification: 40x.

Table S1. Patient demographics and clinical findings.

Patient #- Age/Sex	Pulmonary symptoms	Notable medical history	Occupation/ Exposures	Smoking history	Serology	Radiographic findings	Quit vaping	Follow up after quitting
#1-25/F	Dyspnea, fatigue, pleuritic chest pain	None	Teacher and graduate student; No known environmental exposures	1 PPD for 5 years from ages 18 to 22, quit 3 years prior to presentation and then started vaping	ANA 1:160 (speckled); Negative dsDNA, SS-A (Ro), SS-B (La), Scl-70, Jo1; ESR 2, CRP 2.1; HP panel-positive <i>Aspergillus flavus</i> antibody	Multiple bilateral solid, part-solid and cystic lung nodules in the upper lung zones and superior segment of the right lower lobe; Mild bronchial wall thickening and lower lobe predominant mosaic attenuation.	Yes	4 year follow up: <u>Symptoms:</u> improved, but persistent; <u>HRCT:</u> partial resolution of ground glass lesions but persistent solid nodules and bronchial wall thickening; <u>PFTs:</u> FEV ₁ declines from 98 percent of predicted at presentation to 83 percent of predicted 4 years later..
#2-50/F	DOE, substernal chest pressure, pleuritic chest pain	SLE (2003), GERD, Sjogren's disease, autoimmune hemolytic anemia (2011)	Homemaker; No known environmental exposures	2 PPD for 34 years from ages 11 to 44, quit 6 years prior to presentation and then started vaping	ANA 1:320 (homogenous); Positive SS-A (Ro); Negative SS-B (La), ANCA, RF, RNP, Scl-70, dsDNA, Jo-1; ESR 27, CRP 1.8 HP panel negative	Mild bronchial wall thickening and lower lobe predominant mosaic attenuation.	Yes	3 year follow up: <u>Symptoms:</u> improved, but persistent; <u>HRCT:</u> persistent mild bronchial wall thickening and lower lobe predominant mosaic attenuation.; <u>PFTs:</u> FEV ₁ decreased from 94% to 85% of predicted over 8 years prior to presentation and increased to 90% of predicted 2.5 years after vaping ceased.
#3-65/F	DOE	Asthma/COPD overlap syndrome, Lung adenocarcinoma (minimally)	Program coordinator; No known environmental exposures	1 PPD for 40 years from ages 19 to 58, quit 7 years prior	ESR 30, CRP 8.1	Centrilobular ground glass nodules with mosaic attenuation and air trapping in the lower lobes;	Yes	1 year follow up: <u>Symptoms:</u> improved, but persistent; <u>HRCT:</u> partial resolution;

		invasive, resected), OSA, CKD, hiatal hernia, obesity		to presentation and then started vaping 3 years after smoking cessation		Bronchial wall thickening in the upper and lower lobes; Multiple pulmonary nodules including dominant part cystic ground glass nodule in the left lower lobe.		PFTs: FEV ₁ decreased from 116 percent of predicted 4 years prior to presentation to 91% at presentation and 92% of predicted after vaping ceased for 8 months..
#4-63/M	Morning chest pressure	Lung adenocarcinoma (resected), renal cell carcinoma (post nephrectomy), dysphagia	Engineer; No known environmental exposures	0.5-1 PPD for 40 years from ages 21 to 60. Concurrently smoked cigarettes and vaped for 5 years, then quit smoking and exclusively vaped for 3 years prior to presentation.	ANA positive 1:160 (speckled); Negative SS-A (Ro), SS-B (La), anti-Sm, RNP, Scl-70, RF, ANCA, CCP, dsDNA, Jo-1, myositis-3 panel; HP panel negative	Peripheral ground glass with associated reticulations and clustered cystic changes, bilateral, basilar predominant, and subpleural-sparing; Peribronchiolar cysts; Mild bronchial wall thickening, diffuse.	No	2 years follow-up: Patient did not stop vaping. FEV ₁ was 102 percent pf predicted at presentation.

Abbreviations: F: female, M: male, DOE: dyspnea on exertion, SLE: systemic lupus erythematosus, GERD: gastroesophageal reflux disease, COPD: chronic obstructive pulmonary disease; OSA: obstructive sleep apnea; CKD: chronic kidney disease, PPD: packs per day, HRCT: high resolution chest computed tomography, PFTs: pulmonary function testing, ANA: anti-nuclear antibody, dsDNA: double stranded DNA, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, HP: hypersensitivity pneumonitis, RF: rheumatoid factor, ANCA: antineutrophil cytoplasmic antibodies, CCP: cyclic citrullinated peptide

Table S2. Pulmonary function testing (PFTs). (% predicted by GLI).

Patient #- Age/Sex	PFTs at presentation	PFTs prior to presentation	Follow-up PFTs			
#1-25/F	At presentation: FEV1 3.44L (98%) FVC 4.14L (101%); FEV1/FVC 83% No bronchodilator response TLC 5.44L (99%) DLCO-Hgb 91% Rate of change in FEV1: No prior PFTs	None	9 month follow-up: FEV1 3.33L (95%) FVC 4.40L (108%); FEV1/FVC 75% No bronchodilator response TLC 5.44L (99%) DLCO-Hgb 91% Rate of change in FEV1 from presentation: -110 mL/9 months	18 month follow up: FEV1 3.19L (92%) FVC 4.47L (110%); FEV1/FVC 71% No bronchodilator response No lung volumes or DLCO testing Rate of change in FEV1 from presentation: -167 mL/year	4 year follow up: FEV1 2.83L (83%) FVC 3.85L (96%); FEV1/FVC 74% No bronchodilator response No lung volumes or DLCO testing Rate of change in FEV1 from presentation: -153 mL/year	
#2-50/F	At presentation: FEV1 2.17L (85%) FVC 2.93L (92%) FEV1/FVC 74% 11% Positive post-bronchodilator response No lung volumes or DLCO testing Rate of change in FEV1: -40 mL/year	8 years prior: FEV1 2.52L (94%) FVC 3.28L (104%) FEV1/FVC 77% No bronchodilator response No lung volumes or DLCO testing	6 month follow-up: FEV1 2.03L (80%) FVC 2.61L (82%) FEV1/FVC 77% 5% Positive post-bronchodilator response No lung volumes or DLCO testing Rate of change in FEV1 from presentation: -140 mL/6 months	7 month follow up: FEV1 2.35L (92%) FVC 2.89L (91%) FEV1/FVC 81% No bronchodilator response No lung volumes or DLCO testing Rate of change in FEV1 from presentation: +180 mL/7 months	1 year follow-up: FEV1 2.18L (86%) FVC 2.92L (92%) FEV1/FVC 75% 7% Positive post-bronchodilator response No lung volumes or DLCO testing Rate of change in FEV1 from presentation: +10 mL/year	2.5 years follow-up: FEV1 2.25L (90%) FVC 2.94L (94%) FEV1/FVC 77% 5% Positive post-bronchodilator response No lung volumes or DLCO testing Rate of change in FEV1 from presentation: +32 mL/year
#3-65/F	At presentation: FEV1 2.12L (91%) FVC 3.17L (106%) FEV1/FVC 67% TLC 6.32 (124%) DLCO 84% Rate of change in FEV1: -148 mL/year	4 years prior: FEV1 2.71L (116%) FVC 3.83L (130%) FEV1/FVC 71% TLC 5.94 (121%) DLCO 91%	8 month follow up: FEV1 2.08L (92%) FVC 3.03 (106%) FEV1/FVC 69% TLC 5.69 (116%) DLCO-Hgb 80% Rate of change in FEV1 from			

			presentation: -40 mL/8 month
#4- 63/M	FEV1 3.21L (102%) FVC 4.71L (115%) FEV1/FVC 68% No bronchodilator response TLC 6.35L (103%) DLCO 75% Rate of change in FEV1: No prior PFTs	None	None

Abbreviations: F: female, M: male, FEV1: forced expiratory volume in the first second, FVC: forced vital capacity, TLC: total lung capacity, DLCO: diffusing capacity of the lungs for carbon monoxide, L: liters.