



Letters

Asthma and emphysema overlap in nonsmokers

Gold et al¹ reported the reversible loss of lung elastic recoil during an acute exacerbation among nonsmoking patients with asthma, followed by a return of normal spirometry. Subsequently, from 2000 to 2004, we documented long-term loss of lung elastic recoil in nonsmoking patients with asthma with persistent expiratory airflow limitation despite therapeutic intervention.² However, lung computed tomography (CT) did not reveal significant lung tissue breakdown, and diffusing capacity remained normal.² These observations created a radiographic-physiological dilemma that needed to be addressed pathologically to reach a meaningful understanding.

Mauad et al³ in 2004 and Dolhnikoff et al⁴ in 2009 noted abnormal alveolar attachments with decreased elastic fiber content in the distal lung in fatal asthma. However, there was no linkage to clinical, lung CT, or any physiological studies. From 2004 to present, we have reported 4 consecutive autopsied cases and 1 explanted left lung posttransplant obtained from 25 treated, never-smoked patients with chronic asthma with persistent expiratory airflow limitation, and all had a persistent measured loss of lung elastic recoil.^{5,6} Serum α 1-antitrypsin levels were normal.

Measured lung elastic recoil was significantly reduced, and it contributed almost equally to increased intrinsic airway resistance in limiting expiratory airflow at effort-independent lung volumes from 90% to 80% predicted total lung capacity (TLC) (78% to 70% observed TLC).^{5,6} All 5 patients with asthma had normal or mildly abnormal high-resolution thin-section (1 mm) lung CT, with normal voxel quantification and normal diffusing capacity.^{5,6} Immunologic and inflammatory studies were consistent with type 2 asthma in all cases. Formalin-inflated lungs obtained at autopsy and explanted left lung posttransplant exhibited mild to moderate centrilobular emphysema in bilateral upper and middle lung fields. Asthma-related remodeling was observed in the airways of these 5 nonsmoking patients with asthma. Furthermore, in addition to being nonsmokers, there was no known exposure to potentially toxic lung agents.^{5,6}

We now report our never-published, fifth consecutive asthma death with autopsy (sixth case) among our 25 nonsmoking patients with moderate to severe asthma followed up since 2004—all with a loss of lung elastic recoil. It occurred in a 65-year-old man with long-standing, treated type 2 asthma who had recurrent exacerbations over 15 years of coverage. With a stable disease at age 60 years (and 5 years before his death), he had mild to moderate expiratory airflow limitation with loss of lung elastic recoil, despite both normal diffusing capacity and normal lung CT. After nebulization with 270 μ g albuterol sulfate, the patient had a forced vital capacity (FVC) of 3.4 L (84% predicted), forced expiratory volume in

1 second (FEV₁) of 2.4 L (74%), FEV₁/FVC ratio of 71%, residual volume of 2.4 L (107%), TLC of 5.8 L (93%), specific airways conductance of 0.13 (57%), forced expiratory flow (FEF 25%-75%) of 2.4 L per second (90%), and forced expiratory flow (FEF 75%) of 0.9 L per second (35%). The measured lung elastic recoil at TLC was 12 cm H₂O (41% predicted); at 90% TLC was 7 cm H₂O (64%); at 80% TLC was 4.5 cm H₂O (45%); and at 70% TLC was 2.5 cm H₂O (33%). The loss of lung elastic recoil contributed equally to increased intrinsic airway resistance (upstream resistance) in limiting expiratory airflow at effort-independent lung volumes from 90% to 80% predicted TLC (78%-70% observed TLC), similar to previous studies.^{5,6} Serum α 1-antitrypsin level was also normal. The Thurlbeck emphysema score⁷ was normal in 1-mm high-resolution thin-section lung CT at full inspiration. Voxel quantification at less than or equal to 950 HU was 2.9% in the right and 2.6% in the left lung—all were normal (<10%). The inflammatory markers were all elevated and included the following: (1) total exhaled nitric oxide at 50 mL per second 63 parts per billion (210% predicted); (2) maximum airway wall nitric oxide flux at 2.8 nL per second (140%); and (3) nitric oxide alveolar concentration 8.5 parts per billion (160%). Blood immunoglobulin E level was 648 kU/L (648%), and the total blood eosinophil level was 402 cells/uL (133%)—all consistent with type 2 asthma. During the last 2 years of his life, he had frequent asthma exacerbations. His death was attributed to status asthmaticus; 6 days before his death, his FVC was 1.8 L (46% predicted), FEV₁ was 1.0 L (32%), FEV₁/FVC was 54%, and forced expiratory flow (FEF 25%-75%) was 0.5 L per second (15%). Autopsied lungs performed by one of the authors (Dr Grigorian) were formalin-inflated to 15 cm H₂O and had a Thurlbeck emphysema score of 30.⁷ Mild to moderate diffuse centrilobular emphysema was observed in bilateral upper and middle lung and measured intra-alveolar chord diameter (mean alveolar diameter) of 495 μ m (170% predicted) (Fig 1). In addition, there were typical asthma-related structural changes in central and peripheral airways.

Our nonsmoking patients with refractory asthma and reduced lung elastic recoil with centrilobular emphysema have been treated with long-term leukotriene antagonists, short-acting muscarinic antagonists, short-acting β -agonists, long-acting muscarinic antagonists, long-acting β -agonists, daily inhaled and intermittent oral corticosteroids, and antibiotics, as needed. Some have tried omalizumab (xolair), but none have been treated with the newer humanized monoclonal antibodies. Because this disease affects peripheral airways, inhalers that deliver small airway particles would be the preferred delivery devices.⁸ Furthermore, uncontrolled neutrophil elastase and eosinophils in the peripheral airways can release elastolytic enzymes, such as matrix metalloproteinase-9, all of which may destroy elastin fibers around small airways, resulting in centrilobular emphysema. This suggests that new biologic therapies that target type 2 inflammation, such as anti-interleukin 5 (IL-5) antibodies (mepolizumab or reslizumab),

Disclosures: The authors have no conflicts of interest to report.

Funding: The authors have no funding sources to report.

Trial Registration: ClinicalTrials.gov Identifier: NCT00576069.

<https://doi.org/10.1016/j.anai.2020.08.010>

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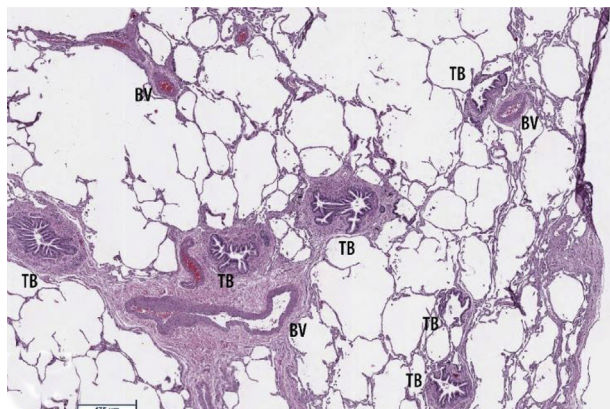


Figure 1. Low- and high-power views of H&E-stained microscopic fields. The bilateral upper/middle lung emphysema includes not only the disorganization and unevenly distributed enlarged airspaces but also the disrupted alveolar septa even visible at this magnification. There is also a breakdown of lung tissue surrounding TB. This is definitely emphysema with everything that is needed to meet the definition. There is permanent air space enlargement in the lower-left corner, next to the label TB. In that area, there is a partial loss of alveolated parenchyma, resulting in a pathologically large air space (not just simple overinflation). H&E, hematoxylin and eosin; TB, terminal bronchioles. (Available at: <https://goo.gl/b75UGR>.)

IL-5 receptor (benralizumab) or IL-4R α receptors (dupilumab), may be effective in improving asthma control and reducing exacerbations and possibly reducing progression in these patients.⁹ However, in glucocorticoid-dependent patients with severe asthma with an eosinophil count of greater than or equal to 300 cells/ μ L after dupilumab therapeutic intervention, the increase in pre-bronchodilator FEV₁ compared with placebo was only 0.220 L (95% confidence interval, 0.09–0.34).¹⁰

Review of the literature did not reveal similar publications from other authors that included measurements of lung elastic recoil, high-resolution thin-section 1-mm lung CT and voxel quantification, inflammatory and cytokine data, and pathologic studies involving autopsy or explanted lung in nonsmoking patients with asthma with recurrent or persistent expiratory airflow limitation. The epiphenomena of the asthma-emphysema overlap in non-smokers is sentinel and explained why these and similar nonsmoking patients with asthma have persistent expiratory airflow limitation despite aggressive therapeutic intervention. We suspect that an uncontrolled inflammatory response leads to a proteolytic cascade that results in lung tissue destruction, that is emphysema, which is responsible for the loss of lung elastic recoil. Ongoing additional collaborative clinical, physiological, immunologic, radiologic, and autopsy or surgically obtained pathologic studies will be needed to confirm our initial 6 sentinel observations.

Acknowledgments

The authors thank the following individuals for their assistance in the study: Roxanna Moridzadeh, PA-C, Diem Tran, PA, and Chris Fraser, RCP, CPFT, for performing pulmonary function studies;

Ouided Rouabhi and Susan Wood, PhD for performing lung CT voxel quantification; John Cupp, MD, J. Kollin, MD and Thais Mauad, MD, for performing pathology analysis; Eric Glassy, MD, for performing pathology analysis and Figure 1 URL imaging; Peter J. Barnes, FMedSci, FRS, for discussion concerning therapeutic intervention; Noe Zamel, MD, for performing physiological analysis; Mark J. Schein, MD, for performing radiology analysis; Marc Decramer, MD, for performing pulmonary analysis.

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