Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6682-20
Intern Med 60: 3463-3467, 2021
http://internmed.jp

【 CASE REPORT 】

Tracheobronchopathia Osteochondroplastica Associated with Fibrotic Interstitial Lung Disease

Jung Won Heo[1], Eung gu Lee[2], Bomi Gil[3], Hye Seon Kang[2] and Yong Hyun Kim[2]

Abstract:
Tracheobronchopathia osteochondroplastica (TPO) is a very rare, benign disorder involving the lumen of the trachea-bronchial tree. However, its etiology is unknown. In our first case, observation for several years showed that TPO worsened as interstitial lung disease was aggravated. In the second case, the lung parenchymal lesion on computed tomography (CT) was found to be compatible with interstitial lung abnormality (ILA). We believe that our cases suggest a common pathogenetic relationship between TPO and fibrotic interstitial lung disease. TGF-β is likely a common factor in the pathogenesis of TPO and fibrotic interstitial lung disease.

Key words: fibrotic interstitial lung disease, pathogenesis, tracheobronchopathia osteochondroplatica, transforming growth factor beta

(Intern Med 60: 3463-3467, 2021)
(DOI: 10.2169/internalmedicine.6682-20)

Introduction

Tracheobronchopathia osteochondroplastica (TPO) is a very rare, benign disorder involving the lumen of the trachea-bronchial tree and characterized by multiple submucosal osseous and cartilaginous nodules in the trachea and bronchus (1). There are many cases where it is incidentally diagnosed (2). Even though multiple theories of its pathogenesis and associations with other clinical conditions have been described, the exact cause of the disease remains unknown.

We herein report two patients with TPO combined with fibrotic interstitial lung disease (ILD).

Case Reports

Case 1

A 78-year-old man non-smoker presented with a 1-week history of cough and blood-tinged sputum. There was no history of tuberculosis. A physical examination was unremarkable. The arterial blood pressure was 100/70 mm Hg, pulse 86/min, respiratory rate 20/min, temperature 37.7℃, and SpO2 (arterial oxygen saturation) 95%. The laboratory data at admission: hemoglobin 13.8 g/dL, white blood cell 7.16×10^9/L, platelets 204×10^9/L, and high-sensitive C-reactive protein 0.8 mg/L (<3.0 mg/L).

Chest computed tomography (CT) showed nodularity, irregularity, and stenotic changes in the mucosa with areas of ossification throughout the tracheal lumen as well as in both main bronchi (Fig. 1). Emphysematous changes were observed throughout the lung. Faint ground-glass opacity (GGO), mild reticulation, and honeycombing cystic changes were observed in the subpleural area of both lower lobes (Fig. 2A). Two years later, follow-up CT showed interval increased extent of honeycombs, subpleural reticulation, and GGO in both lower lobes, indicating progression of ILD (Fig. 2B).

Flexible bronchoscopy was performed for a tracheal biopsy and to evaluate ILD. The biopsy findings for the trachea showed calcification in the mucosa and ossification in

[1]Department of Internal Medicine, Chung-Ang University H.C.S Hyundae Hospital, Republic of Korea, [2]Division of Pulmonary, Critical Care and Allergy, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Republic of Korea and [3]Department of Radiology, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Republic of Korea

Received for publication November 9, 2020; Accepted for publication March 21, 2021
Correspondence to Dr. Yong Kim, kyh30med@catholic.ac.kr

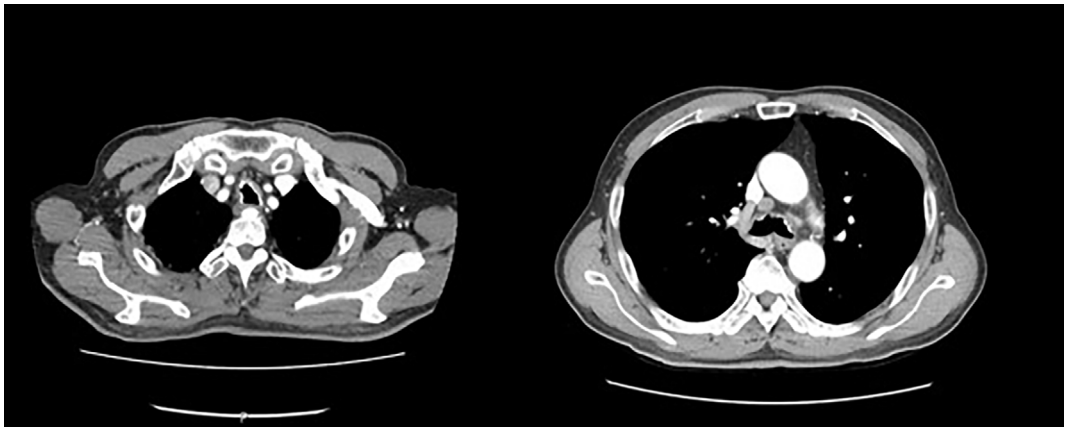

Figure 1. **Computed tomography (CT) shows multifocal irregular thickening and nodularity with calcified changes in the tracheobronchial tree, sparing the posterior tracheal wall.**

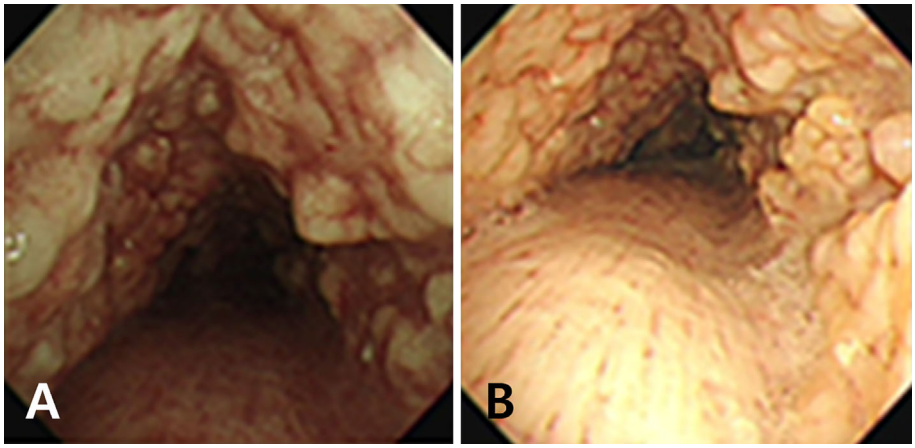

Figure 2. **At the time of the diagnosis, CT showed mild subpleural reticulation, ground-glass opacity and bronchiectasis in the left lower lobe medial basal segment (A). Two years later, follow-up CT showed an interval increased extent of subpleural fine reticulations, honeycomb and bronchiectasis in both lower lobe basal segments, suggesting the progression of underlying idiopathic pulmonary fibrosis (B).**

the submucosa (Fig. 3A). The histological examination was consistent with TPO. An analysis of the BAL fluid showed a total white blood cell area of 220 mm^3, including 13% neutrophils, 13% lymphocytes and 71% macrophages.

For the diagnosis, we performed a surgical lung biopsy, and the results showed diffuse interstitial fibrosis with focal fibroblastic proliferation and lymphocytic infiltration, suggesting possible usual interstitial pneumonia. Four years after the initial presentation, the patient was re-admitted with symptoms of cough. The previously noted multifocal honeycombs and subpleural reticulations were aggravated on chest CT. We performed flexible bronchoscopy again. There were no microorganisms identified. Compared with the previous findings, the lesions of TPO throughout the tracheal lumen had also progressed (Fig. 3B).

Case 2

A 64-year-old woman had been diagnosed with rheumatoid arthritis 10 years ago. She visited our hospital because of abnormal findings on CT performed for a regular check-up. On chest CT, very mild fine reticulations and coarse GGO in the left lower lobe were observed (Fig. 4C). There was also severe irregular nodular and calcified thickening of the mucosa throughout the entire trachea and in both main bronchi (Fig. 4A, B). Flexible bronchoscopy was performed. The nodules of the trachea were very hard, and tissue was difficult to obtain (Fig. 5). A histological examination revealed mild chronic inflammation with ossification and no evidence supporting other causes, so the patient was diagnosed with TPO.

Discussion

TPO is a rare, benign disease characterized by multiple submucosal osseous and cartilaginous nodules in the trachea and bronchus. The first description of TPO was made by Walk in 1857, and the term 'tracheo-bronchopathia osteochondroplastica' was proposed by Muckleston in 1909 and

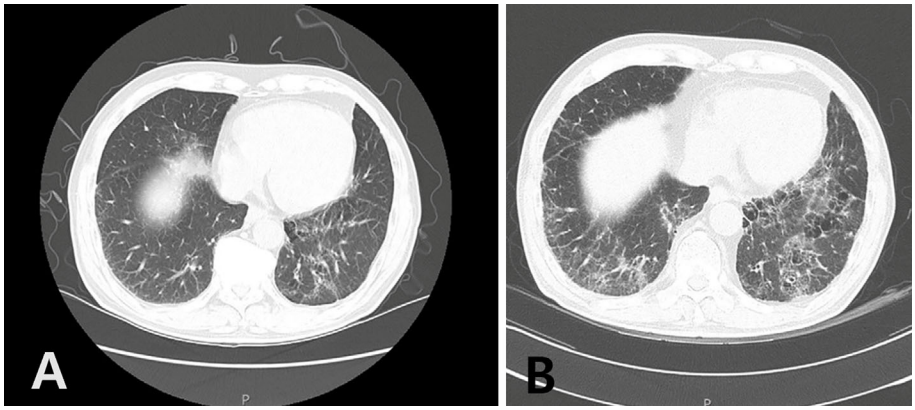

Figure 3. **An endoscopic view showing the involvement of the anterior and lateral aspects of the trachea (A) and the increased extent of calcified nodules (B).**

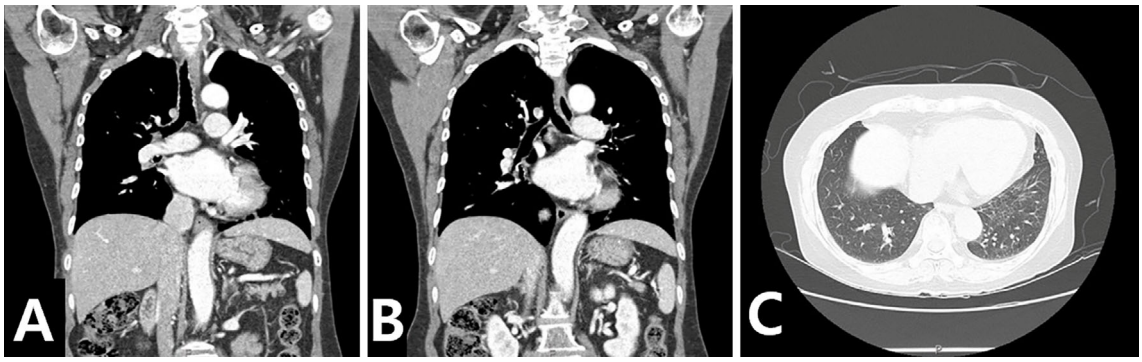

Figure 4. **(A, B) CT with coronal images shows diffuse small tracheobronchial nodules with/without calcification that produce luminal irregular narrowing of the tracheobronchial tree, sparing the posterior tracheal wall. (C) CT shows mild pure reticulation and faint ground-glass opacity in the left lower lobe medial basal segment, suggesting a possible interstitial lung abnormality.**

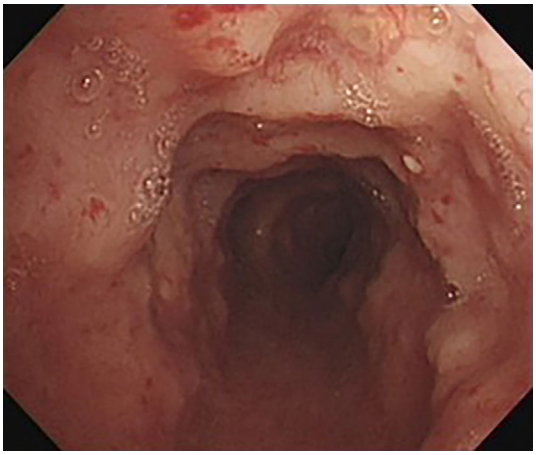

Figure 5. **Endoscopic view showing severe irregular nodules and calcification of the tracheobronchial tree, sparing the posterior tracheal wall.**

Aschoff in 1910 (3). The incidence of TPO is currently estimated to be approximately 0.11% (4). Most cases are diagnosed incidentally through bronchoscopy, and CT carried out for other reasons (5). TPO is often asymptomatic, but it can cause dry or productive cough, dyspnea, bronchial obstruction, hemoptysis and recurrent pneumonia (6). Decreased efficiency of clearing respiratory secretions may lead to lower respiratory infections (7). As there is no specific treatment, most patients are treated with antibiotics, and corticosteroids to relieve their symptoms (8), and in severe cases, intervention is performed with rigid bronchoscopy (9). The prognosis is generally favorable. Evidence derived from the literature has indicated minimal progression over time (10).

The etiology of TPO is unknown. TPO is usually combined with other disorders (10-13). According to published reports, chronic infections, inflammation, atrophic rhinitis, immunoglobulin A deficiency, metabolic abnormalities (e.g. amyloidosis), malignancy (e.g., lung cancer and non-Hodgkin lymphoma) and genetic predisposition are suggested as casual factors (6). Interestingly, some cases in the literature have indicated TPO to be associated with diseases causing fibrosis of the lung parenchyma, such as sarcoidosis and silicosis (12, 14).

Although its pathogenesis is unclear, Virchow first presented a hypothesis for the pathogenesis of TPO (14). Virchow considered this lesion to be a kind of ecchondrosis occuring in the trachea cartilage (15, 16). Dalgaard (17) showed that these nodules occur as a result of metaplastic processes in the submucosal and lamina propria. Some stud-

ies have shown that the transforming growth factor beta (TGF-β) / bone morphogenetic protein 2 (BMP-2) pathway is associated with TPO (13). BMP-2 is a member of the TGF-β superfamily and is believed to play a role in ectopic bone and cartilage formation by inducing differentiation of mesenchymal cells into osteoprogenitor cell (18). BMP-2 is localized in mesenchymal cells, osteoblastic cells and chondroblastic cells around the new nodules in the submucosa as well as in the nodules subjacent to the tracheal cartilage of patients with TPO. TGF-β1 was not detected in mesenchymal cells but did appear in mature chondrocytes and osteocytes in the nodules (19). According to Tajima et al. (19), TGF-β1 alone cannot induce cartilage and bone formation in an *in vivo* bioassay. TGF-β1 was detected in chondrocytes in newly formed nodules in the submucosa. Thus, BMP-2 may act synergistically with TGF-β1 to promote the nodules' inductive cascade in TPO (17).

TGF-β is one of the most well-studied profibrotic cytokines. In the lungs, TGF-β is produced by alveolar macrophages, neutrophils, alveolar epithelial cells, endothelial cells, fibroblasts, and myofibroblasts. In these cells, TGF-β also stimulates the expression of a number of proinflammatory and fibrogenic cytokines, thereby further enhancing and perpetuating the fibrotic response (20). Therefore, TGF-β is associated with the pathogenesis of idiopathic pulmonary fibrosis (IPF) and other fibrotic ILDs, and TGF-β antagonist agents have been used to treat IPF.

BMP/TGF-β pathway cross-talk is well recognized, and their relationships are very complex. Interacting with each other or in opposition to each other in several stages, it controls the overall fibrosis process such as the epithelial-mesenchymal transition (EMT) (21-23). As mentioned above, in the bronchial tree, BMP-2 is localized to mesenchymal cells, whereas TGF-β1 is not detected in mesenchymal cells but does appear in mature chondrocytes and osteocytes in nodules (19). This suggests that a signaling pathway involving BMP/TGF-β may be affected by the biological environment.

TGF-β1 can enhance chondrogenesis and osteogenesis mediated by BMP2 (21). One of the mechanisms involves TGF increasing the expression of bone morphogenetic protein receptor type IB (BMPR-IB), the BMP2 receptor in osteoblasts (21, 24). Through this route, BMP2- induced changes such as chondrogenesis, can develop only in specific cells or tissues with BMP2 receptors. If the expression of TGF-β1 is systematically increased, TGF-β1 in line with BMP might act differently depending on organs or tissues (25). However, the specific mechanism underlying the expression of BMP2 is unclear. In general, BMPs are believed to play a protective role against the fibrosis-promoting activity of TGF in lungs (21, 26). However, while the protective roles of BMP7 are clear, they are unclear for BMP2 (27). One study showed that BMP ligands are also able to bind and activate TGF receptors (28). In this way, BMP2, BMP11 and BMP16 can induce phosphorylation of SMAD2 and SMAD3 (21, 22). These SMADs are well known to be fibrotic effectors. BMP signaling can enhance the signaling of TGF by activating the protein arginine methyltransferase 1 (PRMT1), which methylates SMAD6/7, enabling SMAD1/3/5 activation and, ultimately promoting EMT during fibrosis (21, 23). These findings might explain the conflicting clinical presentations of the present two cases. Since chondrogenesis, osteogenesis, and lung fibrosis are complex processes involving various stages and are affected by various factors, we cannot be certain that our speculation is a valid assumption. Further studies with more cases and biologic samples are thus needed.

TGF-β seems to act as a common factor in the development and progression of TPO and lung fibrosis. The airway lesions and lung parenchymal fibrosis in our cases progressed simultaneously over time. In the first case, observation for four years showed that TPO advanced as ILD became aggravated. The degree of honeycomb, subpleural reticular and GGO observed in BLL was increased, while the extent and nodular thickening of the tracheobronchial mucosal lesion was aggravated on follow-up bronchoscopy, and abnormal breathing sounds, mimicking stridor, were newly audible on a follow-up physical examination. In the second case, the lung parenchymal lesion on CT was compatible with interstitial lung abnormality (ILA). ILA is defined as nondependent changes affecting more than 5% of any lung zone and includes ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing and traction bronchiectasis (17). ILA has been reported to progress to lung fibrotic disease, such as IPF. In addition, the progression of ILA is known to be associated with a reduction in the lung function and increase in the rate of mortality (29, 30). We therefore believe that our cases suggest a common pathogenetic relationship between TPO and fibrotic ILD.

Conclusion

We reported two cases of TPO coexisting with fibrotic ILD. To our knowledge, there have been no reported cases describing an association between these two conditions and follow-up observation with a long-term interval. Whether or not there is a common underlying pathogenesis between these two diseases remains unclear, but it seems likely that TGF-β is a common factor in the pathogenesis of both TPO and fibrotic ILD. More studies and observation for a longer term will be required to improve our understanding of the pathophysiology and potential link of both diseases.

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

The authors state that they have no Conflict of Interest (COI).

References

1. Luo S, Wu L, Zhou J, et al. Tracheobronchopathia osteochondroplastica: two cases and a review of the literature. Int J Clin Exp Pathol **8**: 9681-9686, 2015.
2. Agarwal A, Klair J, Joiner A, Meena NK. Nodular trachea: tracheobronchopathia osteochondroplastica. BMJ Case Rep **2015**: bcr 2015209860, 2015.
3. Coetmeur D, Bovyn G, Leroux P, Niel-Duriez M. Tracheobronchopathia osteochondroplastica presenting at the time of a difficult intubation. Respir Med **91**: 496-498, 1997.
4. Jabbardarjani HR, Radpey B, Kharabian S, Masjedi MR. Tracheobronchopathia osteochondroplastica: presentation of ten cases and review of the literature. Lung **186**: 293-297, 2008.
5. Abu-Hijeh M, Lee D, Braman SS. Tracheobronchopathia osteochondroplastica: a rare large airway disorder. Lung **186**: 353-359, 2008.
6. Baugnee PE, Delaunois LM. Mycobacterium avium-intracellulare associated with tracheobronchopathia osteochondroplastica. Eur Respir J **8**: 180-182, 1995.
7. Hussain K, Gilbert S. Tracheopathia osteochondroplastica. Clin Med Res **1**: 239-242, 2003.
8. Zhu Y, Wu N, Huang HD, et al. A clinical study of tracheobronchopathia osteochondroplastica: findings from a large Chinese cohort. PLoS One **9**: e102068, 2014.
9. Dutau H, Musani A. Treatment of severe tracheobronchopathia osteochondroplastica. J Bronchol **11**: 182-185, 2004.
10. Chrysikos S, Karampitsakos T, Tzouvelekis A, Dimakou K. Coexistence of tracheobronchopathia osteochondroplastica and sarcoidosis: accidental finding or something more? J Bronchology Interv Pulmonol **26**: e7-e8, 2019.
11. Baugnee PE, Delaunois LM. *Mycobacterium avium-intracellulare* associated with tracheobronchopathia osteochondroplastica. Eur Respir J **8**: 180-182, 1995.
12. Pinheiro G, Antao V, Muller N. Tracheobronchopathia osteochondroplastica in a patient with silicosis: CT, bronchoscopy, and pathology finding. J Compu Assist Tomogr **28**: 801-803, 2004.
13. Slabbynck H, de Beukelaar T, Surgeloose DD. Predominant dendriform pulmonary ossification in a usual interstitial pneumonia-like distribution: to be distinguished from idiopathic pulmonary fibrosis. Sarcoidosis Vasc and Diffuse Lung Dis **34**: 251-256, 2017.
14. Bergeron D, Cormier Y, Desmeules M. Tracheobronchopathia osteochondroplastica. Am Rev Respir Dis **114**: 803-806, 1976.
15. Pounder DJ, Pieterse AS. Tracheopathia osteoplastica: a study of the minimal lesion. J Pathol **138**: 235-239, 1982.
16. Paaske PB, Tang E. Tracheopathia osteoplastica in the larynx. J Laryngol Otol **99**: 305-310, 1985.
17. Dalgaard JB. Tracheopathia chondro-osteoplastica. A case elucidating the problems concerning development and ossification of elastic cartilage. Acta Pathol Microbiol Scand **24**: 118-134, 1947.
18. Kamegai A, Tanabe T, Nagahara K, Kumasa S, Mori M. Pathologic and enzyme histochemical studies on bone formation induced by bone morphogenetic protein in mouse muscle tissue. Acta Histochem **89**: 25-35, 1990.
19. Tajima K, Yamakawa M, Katagiri T, Sasaki H. Immunohistochemical detection of bone morphogenetic protein-2 and transforming growth factor beta-1 in tracheopathia osteochondroplastica. Virchows Arch **431**: 359-363, 1997.
20. Fernandez IE, Eickelberg O. The impact of TGF-b on lung fibrosis: from targeting to biomarkers. Proc Am Thorac Soc **9**: 111-116, 2012.
21. Dituri F, Cossu C, Mancarella S, Giannelli G. The interactivity between TGFβ and BMP signaling in organogenesis, fibrosis, and cancer. Cells **8**: 1130, 2019.
22. Herrera B, Addante A, Sánchez A. BMP signalling at the crossroad of liver fibrosis and regeneration. Int J Mol Sci **19**: 2017.
23. Katsuno Y, Qin J, Oses-Prieto J, et al. Arginine methylation of SMAD7 by PRMT1 in TGF-β-induced epithelial-mesenchymal transition and epithelial stem-cell generation. J Biol Chem **293**: 13059-13072, 2018.
24. Singhatanadgit W, Salih V, Olsen I. Up-regulation of bone morphogenetic protein receptor IB by growth factors enhances BMP-2-induced human bone cell functions. J Cell Physiol **209**: 912-922, 2006.
25. Walton KL, Johnson KE, Harrison CA. Targeting TGF-β mediated SMAD signaling for the prevention of fibrosis. Front Pharmacol **8**: 2017.
26. Shlyonsky V, Soussia IB, Naeije R, Mies F. Opposing effects of bone morphogenetic protein-2 and endothelin-1 on lung fibroblast chloride currents. Am J Respir Cell Mol Biol **45**: 1154-1160, 2011.
27. Pegorier S, Campbell GA, Kay AB, Lloyd CM. Bone morphogenetic protein (BMP)-4 and BMP-7 regulate differentially transforming growth factor (TGF)-beta1 in normal human lung fibroblasts (NHLF). Respir Res **11**: 85, 2010.
28. Katsuno Y, Lamouille S, Derynck R. TGF-β signaling and epithelial-mesenchymal transition in cancer progression. Curr Opin Oncol **25**: 76-84, 2013.
29. Araki T, Putman RK, Hatabu H, et al. Development and progression of interstitial lung abnormalities in the Framingham Heart Study. Am J Respir Crit Care Med **194**: 1514-1522, 2016.
30. Podolanczuk AJ, Oelsner EC, Barr RG, et al. High-attenuation areas on chest computed tomography and clinical respiratory outcomes in community-dwelling adults. Am J Respir Crit Care Med **196**: 1434-1442, 2017.