Original Article

Radiographic Evidence of Sinonasal Inflammation in Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome: An Underrecognized Association

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What is already known about this topic? Sinonasal inflammation, which can be observed both clinically and radiographically, significantly impacts both asthma and chronic obstructive pulmonary disease (COPD).

What does this article add to our knowledge? In asthma-COPD overlap syndrome (ACOS) and COPD, mild radiographic evidence of sinonasal inflammation was a common comorbidity, whereas moderate-to-severe radiographic evidence of sinonasal inflammation and ethmoid sinus-dominant shadow were features in asthma.

How does this study impact current management guidelines? While managing patients with ACOS, we should be aware of sinonasal involvement. If sinonasal inflammation is present, we should treat these patients on the basis of "united airway."

BACKGROUND: Sinonasal inflammation on both clinical examinations and imaging significantly impacts both asthma and chronic obstructive pulmonary disease (COPD).
OBJECTIVE: The objective of this study was to examine the association between sinonasal inflammation and asthma-COPD overlap syndrome (ACOS).
METHODS: A total of 112 patients with a ratio of forced expiratory volume in 1 s to forced vital capacity of less than 70% were enrolled. COPD, asthma, and ACOS were clinically diagnosed according to the 2014 Global Initiative for Asthma and Global Initiative for Chronic Obstructive Lung Disease guidelines. Sinonasal inflammatory condition was evaluated using sinus computed tomography, and its severity was assessed according to the Lund-Mackay staging (LMS) system. Ethmoid sinus-dominant shadow was defined as the presence of greater LMS scores for the anterior and posterior ethmoid sinuses than for the maxillary sinus.
RESULTS: COPD, asthma, and ACOS were diagnosed in 55 (49.1%), 39 (34.8%), and 18 patients (16.1%), respectively. The frequency of radiographic evidence of sinonasal inflammation in patients with COPD, asthma, ACOS was 60.0%, 94.9%, and 72.2%, respectively. Patients with ACOS and COPD had only mild radiographic evidence of sinonasal inflammation (LMS score, 1-7), whereas moderate (LMS score, 8-11) and severe (LMS score, ≥12) radiographic evidence of sinonasal inflammation were detected only in patients with asthma. Furthermore, the frequency of ethmoid sinus-dominant shadow was significantly higher in patients with asthma than in those with COPD and ACOS.
CONCLUSIONS: Radiographic evidence of sinonasal inflammation was a common comorbidity in ACOS. Future studies are required to examine the role of sinonasal inflammation in ACOS. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Asthma-chronic obstructive pulmonary disease overlap syndrome; Sinonasal inflammation; Lund-Mackay staging score*

Asthma and chronic obstructive pulmonary disease (COPD) are common and chronic inflammatory lower airway conditions with significant public health impact.[1,2] Although the pathophysiological mechanisms underlying the 2 diseases may differ, in clinical practice, many patients, particularly older adults with a significant cigarette smoking history, exhibit overlapping clinical features.[3,4] A joint project of Global Initiative for Asthma (GINA)[1] and Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2014[2] described this clinical presentation as asthma-COPD overlap syndrome (ACOS), which is defined as persistent airflow limitation and the presence of several features

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Abbreviations used
ACOS- Asthma-chronic obstructive pulmonary disease overlap syndrome
COPD- Chronic obstructive pulmonary disease
CT- Computed tomography
FEF_{25-75}- Forced expiratory flow between 25% and 75% of vital capacity
FEV_1- Forced expiratory volume in 1 s
FVC- Forced vital capacity
GINA- Global Initiative for Asthma
GOLD- Global Initiative for Chronic Obstructive Lung Disease
HRCT- High-resolution computed tomography
ICS- Inhaled corticosteroid
LMS- Lund-Mackay staging

usually associated with asthma and several features usually associated with COPD. Patients with ACOS have a high health care burden because of frequent exacerbations and use of multiple respiratory medications.[5,6] Therefore, adequate phenotyping of ACOS is necessary to better understand the pathogenesis of the disease and for developing better treatment modalities.[3,4]

Sinonasal inflammation is a common inflammatory upper airway condition.[7] Sinonasal inflammation on clinical examinations often coexists with asthma and COPD and impacts lower airway inflammation and disease control, a concept commonly referred to as the "united airway."[7-13] Moreover, evidence of sinonasal inflammation on imaging, regardless of clinical symptoms, can impact on lower airway inflammation[14,15] and help distinguish between asthma and vocal cord dysfunction disease.[16] Therefore, it is important to investigate the presence of sinonasal inflammation in patients with lower airway diseases both clinically and radiographically. However, to date, no studies have evaluated the association between ACOS and sinonasal inflammation.

In clinical practice, we perform sinus computed tomography (CT) to evaluate the condition of upper airway for managing patients with asthma/COPD/ACOS on the basis of "united airway."[17,18] Therefore, in this study, we radiographically investigated the association between ACOS and sinonasal inflammation using sinus CT in patients with persistent airflow limitation, based on the 2014 GINA[1] and GOLD guidelines.[2]

METHODS

Study participants

In total, 112 consecutive non-current smokers with persistent airflow limitation underwent sinus CT at Mitsubishi Kyoto Hospital from February 2008 to February 2016. Persistent airflow limitation was defined as a ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) of less than 70% while on treatment with bronchodilators, including long-acting β_2-agonist and long-acting muscarinic antagonist, and/or inhaled corticosteroids (ICSs).[19] All data, including pulmonary function test, peripheral blood eosinophil counts, and total IgE levels, were collected no longer than 6 months before or after sinus CT was performed. These data, including sinus CT, were obtained from participants under treatment with bronchodilators, ICSs, intranasal steroids, leukotriene receptor antagonists, and omalizumab but without systemic corticosteroids. Medical information and clinical characteristics, including age, body mass index, pack-years, smoking status, pulmonary high-resolution CT (HRCT), current medication, and past history, were obtained from medical records. Pulmonary HRCT was performed at the end of inspiration during the study period, and all CT images were obtained using an Aquilion 64 scanner (Toshiba, Tokyo, Japan). According to pulmonary HRCT findings, radiographic evidence of emphysema was defined as intrapulmonary low attenuation area, pulmonary vascular pruning, pulmonary vascular distortion, and absence of a well-defined wall.[20]

Study design

This was a single-center, retrospective survey study. The local ethics committee of Mitsubishi Kyoto Hospital approved this study and waived off the requirement of obtaining written informed consent for all participants.

Diagnosis of COPD, asthma, and ACOS

COPD, asthma, and ACOS were clinically diagnosed based on the 2014 GINA[1] and GOLD guidelines.[2] These guidelines define 11 clinical features, which are related to (1) age at disease onset, (2) symptom pattern, (3) lung function, (4) lung function between symptoms, (5) past history and family history of asthma or allergy, (6) time course (seasonal symptoms, improvement after treatment with a bronchodilator or ICS, progressive worsening over time), and (7) chest x-ray.[1,2] The presence of 3 or more of the features listed for either COPD or asthma was needed for a diagnosis of COPD or asthma, respectively. The diagnosis of ACOS was made when a patient had a similar number of features for both COPD and asthma.[1,2]

Sinonasal inflammation assessed by sinus CT

All sinus CT scans were performed in patients without a respiratory infection in the last 4 weeks and out of season of seasonal allergic rhinitis. Sinus CT findings were graded according to the Lund-Mackay staging (LMS) system,[21] and the total LMS score was categorized as normal (LMS score, 0), mild (LMS score, 1-7), moderate (LMS score, 8-11), and severe (LMS score, $\geq$12) radiographic evidence of sinonasal inflammation.[12,22] Ethmoid sinus-dominant shadow was defined as the presence of greater LMS scores for the anterior and posterior ethmoid sinuses than for the maxillary sinus.[23] If more than 2 sinus CT scans were performed, CT scan data showing the lowest LMS score were selected.

Pulmonary function tests

Pulmonary function tests were performed in patients using the Minato System 21 spirometer (Minato Medical Science, Osaka, Japan). Parameters collected were FVC, FEV_1, percent predicted values of these parameters (%FVC and %FEV_1), FEV_1/FVC ratio, and the predicted value of forced expiratory flow between 25% and 75% of vital capacity (%FEF_{25-75}). Predicted values of pulmonary function tests were based on the guidelines of the Japanese Respiratory Society.[24]

Statistical analysis

Data were expressed as mean $\pm$ standard deviation or median with interquartile ranges when appropriate. For comparisons between the 3 groups, the Kruskal-Wallis test was used to determine the level of intergroup variability. When a significant difference was observed, the *post hoc* Steel-Dwass test was used to identify the statistical significance. Categorical and continuous variables were compared using the chi-square test and Pearson's correlation coefficients, respectively. All statistical analyses were performed using the JMP 10 statistical software package (SAS Institute, Cary, NC),