

Gastroesophageal Reflux Disease and Pulmonary Diseases Associated with Aspergillosis: Is There a Connection?

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Abstract

Introduction We studied the relationship between GORD and allergic bronchopulmonary aspergillosis (ABPA), chronic pulmonary aspergillosis (CPA), or *Aspergillus* bronchitis.

Background Gastroesophageal reflux disease (GORD) is well known to initiate or exacerbate pulmonary inflammatory conditions, inducing bronchial asthma and chronic obstructive lung disease.

Methods We reviewed four patients referred with elevated *Aspergillus* serology markers and marked pulmonary symptoms for ABPA, CPA, and *Aspergillus* bronchitis, and discussed the underlying pathophysiological relationship with GORD. Data were collected retrospectively from medical records included age, gender, predisposing factors for ABPA, chronic pulmonary aspergillosis, or *Aspergillus* bronchitis; presence of nocturnal reflux, nausea, epigastric pain, Medical Research Council dyspnea scale score, pH manometry data, endoscopic results (ulcers, Barrett's esophagus), treatment of GORD [proton-pump inhibitors (PPIs), surgical operation]; history of smoking, alcohol consumption; concomitant COPD; serological markers (anti-*Aspergillus* IgG, anti-*Aspergillus* IgE), and antifungal treatment.

Results Four patients with GORD were studied; following PPIs administration two achieved clinical improvement. One had ABPA, one CPA, and two had *Aspergillus* bronchitis; median age was 57 years [range 39–71]; males-to-females ratio was 1:3. Serological markers for aspergillosis were: median total IgE antibodies 573 KIU/L [range 13.1–850], median *Aspergillus* IgE-specific antibodies 1.2 kAU/L [range <0.4–24.7], and median *Aspergillus* IgG titers 71 mg/L [range 20–119]. *Aspergillus fumigatus* grew in one sputum sample.

Conclusion Clinicians caring for patients with gastroesophageal reflux disease presenting with elevated *Aspergillus* IgG or IgE antibodies should maintain a high index of suspicion for this association and proceed to appropriate evaluations, including laryngoscopy and endoscopy, initiating specific PPI-directed therapy when indicated.

Keywords Gastroesophageal reflux · *Aspergillus* lung disease

Introduction

Gastroesophageal reflux disease (GORD) is known to initiate or exacerbate pulmonary inflammatory conditions, inducing bronchial asthma and chronic obstructive lung disease [1–8]. Reflux of stomach contents may lead to aspiration of gastric acid into the lungs. Intrapulmonary gastric acid may damage respiratory

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epithelial cells, expose subepithelial membrane proteins, compromise innate host defenses, precipitate asthma, and cause aspiration pneumonia. Little is known, however, about the relationship between GORD and allergic bronchopulmonary aspergillosis (ABPA), chronic pulmonary aspergillosis (CPA), or *Aspergillus* bronchitis [9, 10]. All of these conditions are associated with elevated *Aspergillus* IgG or IgE antibodies or isolation of *Aspergillus* spp. in sputum or bronchoscopy samples. Our hypothesis is that GORD is a risk factor for chronic aspergillosis.

Here we review the clinical course of four patients who were referred with elevated *Aspergillus* serology markers and/or *Aspergillus* cultures and marked pulmonary symptoms that had not responded to first line therapies for asthma and COPD. We reviewed the diagnostic criteria for ABPA, CPA, and *Aspergillus* bronchitis and discuss the possible pathophysiological relationship between these conditions and GORD.

Materials and Methods

This was a retrospective chart study conducted in 2015–2016. We enrolled outpatients who were followed up at the National Aspergillosis Centre, at the University Hospital of South Manchester. We reviewed four cases of gastroesophageal reflux disease associated with severe asthma, bronchiectasis, and elevated *Aspergillus* serological markers. The following data were collected from each medical record: age, gender, predisposing factors for ABPA [11], CPA [12], or *Aspergillus* bronchitis [13]; parameters of severity of GORD (h/o of nocturnal reflux, nausea, epigastric pain, Medical Research Council (MRC) dyspnea scale (range 1–5; five is the worst score), pH manometry data, endoscopic results, ulcers, Barrett's esophagus); medical treatment of GORD [proton-pump inhibitors (PPIs)]; surgical therapy of GORD; factors contributing to GORD (obesity, alcohol, concomitant medicines [Ca++ channel blockers, nitrates, antihistamines, theophylline derivatives]); pulmonary comorbidities (number of lobes involved with bronchiectasis; asthma, concomitant COPD, history of smoking); WBC count with differential, CRP, serological markers (anti-*Aspergillus* IgG, anti-*Aspergillus* IgE), and sputum fungal cultures; corticosteroids (oral and inhalers, expressed in equivalents of beclometasone); antifungal therapy and response.

Results

Case 1 A 67-year-old male presented with hoarse voice being diagnosed with CPA in 2012. Thoracic CT scan demonstrated pleural plaques compatible with asbestosis and COPD with bullous emphysema. He was an ex-smoker of 20 cigarettes/day. His maximum WBC count was 12,100/ μ L (9.66 neutrophils, 1.10 lymphocytes, 1.19 monocytes), CRP 188 mg/L. His antifungal therapy consisted of itraconazole, 300 mg daily. His baseline MRC dyspnea score was between 3 and 4/5 and current is 4/5. His maximum *Aspergillus* IgG was 119 mg/L, total IgE 59.1 KUa/L, *Aspergillus* IgE < 0.4 KUa/L (Table 1). He reported heartburn episodes during sleep as well as chest tightness. He had a normal barium swallow, and laryngoscopy found erythema and gap between vocal cords. His GORD symptoms improved on a proton-pump inhibitor (PPI).

Case 2 A 71-year-old female presented with hoarse voice, recurrent respiratory infections, and asthma while living in a moldy house. She had been diagnosed with *Aspergillus* bronchitis within the past year, based on raised *Aspergillus* IgG antibodies, and compatible radiological picture; thoracic CT scan demonstrated mild bronchiectasis, bilateral opacification, mucous plugging, and atelectasis compatible with a chronic pattern of inflammation. Her maximum WBC count was 6500/ μ L (normal differential), CRP 4 mg/L. Her antifungal therapy consisted of itraconazole, up to 300 mg daily. Her current dyspnea score was 3–4/5. Maximum *Aspergillus* IgG was 40 mg/L, total IgE 13.1 KUa/L, Asp IgE < 0.4 KUa/L (Table 1). She also had a history of nocturnal reflux, chest tightness, dysphagia; pH manometry demonstrated moderate-to-severe GORD, and endoscopy revealed Barrett's esophagitis. Her GORD symptoms did not improve on PPI and ranitidine.

Case 3 A 39-year-old obese female presented with chronic cough, sore throat, and recurrent respiratory infections with a family history of maternal GORD and history of 3–4 cups of coffee per day. She was diagnosed with *Aspergillus* bronchitis in 2013 based on chronic productive cough, raised serological markers for *Aspergillus* and positive sputum culture for *Aspergillus fumigatus*. Thoracic CT scan was unremarkable. Her maximum WBC count was 17,800/ μ L (15.04 neutrophils, 1.92 lymphocytes), and CRP was 17 mg/L. Her antifungal treatment consisted of itraconazole 100 mg daily, which had to be stopped because of peripheral neuropathy, and nebulized

Table 1 Clinical and laboratory findings in the study population

Case	Symptoms/signs	Pulmonary aspergillosis	Total IgE (KIU/L)	<i>Aspergillus</i> IgE (kAU/L)	<i>Aspergillus</i> IgG (mg/L)	Sputum culture
1/M, 67	Hoarse voice, chest tightness, nocturnal reflux	Chronic pulmonary aspergillosis	59.1	<0.4	119	No growth
2/F, 71	Hoarse voice, chest tightness, nocturnal reflux, recurrent chest infections, asthma, dysphagia	<i>Aspergillus</i> bronchitis	13.1	<0.4	40	<i>Penicillium</i> spp.
3/F, 39	Nocturnal reflux, chronic cough, sore throat, recurrent chest infections	<i>Aspergillus</i> bronchitis	560	0.9	20	<i>Aspergillus fumigatus</i>
4/F, 46	Chest tightness, asthma, dysphagia, nausea	Allergic bronchopulmonary aspergillosis, nodular disease	850	24.7	31	No growth

amphotericin B. She was moderately dyspneic with an MRC dyspnea of 3. Her maximum *Aspergillus* IgG was 20 mg/L, total IgE 560 KUa/L, *Aspergillus* IgE 0.9 KUa/L (Table 1). She had a history of nocturnal reflux and a normal barium swallow. Laryngoscopy revealed vocal cord dysfunction, and laryngopharyngeal reflux. Her GORD symptoms improved on PPI.

Case 4 A 46-year-old female presented with asthma, atopy, and dysphagia and diagnosed with ABPA. Thoracic CT scan demonstrated proximal bronchiectasis in the right middle lobe, endobronchial plugging, and nodular disease. Her maximum WBC count was 19,800/ μ L (15.72 neutrophils, 2.45 lymphocytes 1.56 monocytes), CRP 55 mg/L. Her antifungal therapy was itraconazole, 200 mg BD. Her baseline MRC dyspnea score was 2 but had improved to 1. Her maximum *Aspergillus* IgG was 31 mg/L, total IgE 850 KUa/L, *Aspergillus* IgE 24.7 KUa/L (Table 1). She also had a history of chest tightness, nausea, vomiting, and pH manometry demonstrated severe GORD; gastroscopy revealed Barrett's esophagitis and gastritis. Due to lack of response to PPI, she underwent laparoscopic fundoplication. She was on chronic administration of corticosteroids (prednisolone 5 mg).

Underlying conditions, pulmonary manifestations, and laboratory parameters of ABPA, CPA, or *Aspergillus* bronchitis are delineated in Table 1.

Discussion

This report underscores the importance of concomitant GORD and pulmonary diseases associated with

aspergillosis. While the upper respiratory symptoms of sore throat and hoarse voice may be attributable to an infectious process, they may also reflect underlying GORD. Expanding the differential diagnosis, inquiring about symptoms specifically pertaining to GORD, and proceeding, when indicated, with laryngoscopy, endoscopy, and pH manometry are critical to being able to strategically intervene with PPIs for treatment. In the case of our patients, laryngoscopy revealed abnormalities, such as erythema, phonatory gap, vocal cord dysfunction, and laryngopharyngeal reflux. Endoscopy demonstrated esophagitis, Barrett's ulcer, and gastritis, while pH manometry identified severe GORD, which ultimately led to laparoscopic fundoplication in one patient.

Silent nocturnal aspiration is common in patients with GORD. Patients suffering from mild symptoms of reflux may develop mild to severe bronchiectasis, which may be further complicated by *Aspergillus* bronchitis. Following positive lung investigation tests for *Aspergillus*, a chest physician should consider ABPA diagnosis. As the clinical manifestations of GORD are heterogeneous [14, 15], a high index of suspicion is needed to distinguish the presence of this condition from other underlying conditions such as respiratory tract infections, in order to avoid unnecessary delayed diagnosis. Patients with progressive or refractory asthma may have clinically undetected or inadequately treated nocturnal reflux. Indeed, bronchial asthma, chronic cough, chronic bronchitis, bronchiectasis, aspiration pneumonia, and interstitial fibrosis may ensue as extra-esophageal manifestations in patients with GORD [1, 2, 7, 8].

GORD may precipitate bronchial inflammation and exacerbate asthma and/or chronic cough, particularly if it is nocturnal [6]. Gastric contents containing acid, food particles, and proteolytic enzymes during episodes of reflux damage airways and elicit bronchospasm. Acute episodes of aspiration-related inflammation may contribute to progression of bronchiectasis in patients with ABPA. Bacteria-laden food particles serve as foreign bodies that further contribute to abscess formation and progression of bronchiectasis.

There is a close epidemiological and pathophysiological relationship between GORD and asthma [5, 9]. Patients with asthma have a disproportionally higher frequency of GORD, whereas those with GORD have a higher frequency of asthma. Of note, all four patients were receiving systematic corticosteroid-based inhalers (fluticasone 125–500 mg BD and Beclometasone 500–1000 mg BD). This relationship provides a rationale for intervention of PPIs. The aggregate body of data supports treatment of asthmatic patients with GORD-related chronic cough and/or hoarse voice with PPIs. As chronic cough is a common manifestation of asthma in adults, one may infer that the use of PPI may be ameliorating bronchospasm by altering the process of GORD.

Despite these data, which correlate GORD in patients with asthma and chronic cough, there has been little consideration heretofore of the role of GORD in the pathogenesis of ABPA, chronic pulmonary aspergillosis, or *Aspergillus* bronchitis. Through PPI-mediated control of pH of refluxed gastric contents, chronic cough as a reflection of reactive airway diseases should diminish. Due to the retrospective nature of our study, we were not able to assess the effect of treatment of GORD on the course of pulmonary disease, in our patients. The presence of endobronchial gastric contents may damage respiratory epithelium and subepithelial tissue leading to bronchiectasis and persistent foci of *Aspergillus* spp. within the airways. Such persistence of organism in bronchiectatic segments allows constant antigenic exposure and potentially progressive ABPA, CPA and *Aspergillus* bronchitis. The ongoing inflammatory response to gastric contents may create local intrapulmonary immunodysregulation, ineffective antigen clearance, and insidious damage to airways.

Predominant GORD symptoms of which our patients complained of were chest tightness (75%),

heartburn episodes irritating sleep (75%), and hoarseness or sore throat (75%). One out of two had a history of asthma (50%) and recurrent chest infections (50%). Rest reported symptoms included dysphagia (50%) and nausea (25%). Notably, no one admitted excess consumption of caffeine or alcohol.

The patients in this report illustrate only the most severe clinically overt cases of GORD complicating ABPA, CPA, or *Aspergillus* bronchitis. As there is likely a larger population of patients who may also have concomitant clinically silent GORD, we recommend that all such patients who are suspected of having GORD-related symptoms be evaluated with a diagnostic trial of PPI therapy. For those patients who have persistent GORD-related symptoms, a more aggressive evaluation including endoscopy, esophageal manometry and pH monitoring off therapy should be considered. From a radiological point of view, as chronic pulmonary aspergillosis may manifest as single or multiple pulmonary nodular disease [16], as in case 4, physicians might consider initiating PPI therapy when patients complain of GORD-like symptoms, in parallel with investigating underlying etiology of the nodule (primarily excluding malignancy).

One specific therapeutic challenge in these patients is the interaction between PPIs and H₂ antagonists with antifungal agents. Itraconazole is frequently used for noninvasive aspergillosis, and therapeutic drug monitoring [17] is recommended, especially so in patients on treatment for GORD. Preferential use of itraconazole solution is recommended in this situation. Similarly, drug monitoring is highly recommended when voriconazole is co-administered with PPIs as this may result in unpredictably high antifungal drug levels [18]. In challenging cases where the antifungal therapeutic approach warrants reconsideration and posaconazole emerges as next step in our therapeutic armamentarium, tablets instead of liquid formulation should be administered. Isavuconazole is a new generation azole with potent activity against *Aspergillus* species. In a recent report, a patient with ABPA was successfully treated with isavuconazole, with minimal side effects [19]. Contrary to other azoles, there are no interactions between isavuconazole and PPIs (namely omeprazole and esomeprazole), and therefore, no dose adjustments are needed [20].

Limitations of this study are its retrospective nature and the limited number of patients. Despite the small sample size, we believe that our novel findings will

help physicians in the proper management of patients with this rare but serious disease. Based on our case series, prospective studies should explore the possible association between GORD and chronic fungal pulmonary diseases. An additional limitation is that only two patients underwent pH manometry, which established the presence of GORD. Yet, the diagnosis of GORD has been well established in all four cases based on the typical clinical presentation and endoscopic findings. Also, in half cases, GORD symptomatology improved after successful treatment with PPIs.

In summary, we describe the association between GORD and conditions of ABPA, chronic pulmonary aspergillosis, and *Aspergillus* bronchitis with the conclusion that clinicians caring for these respiratory patients should maintain a high index of suspicion for this association and proceed to appropriate management, including laryngoscopy, endoscopy, and specific PPI-directed therapy when indicated. Thus, we suggest that GORD should be treated promptly, particularly in patients who are at high risk for aspergillosis.

Author's Contribution MNG reviewed the patient charts, collected, and analyzed the clinical and laboratory data, and drafted the manuscript. DWD conceived the idea, wrote the protocol, revised the manuscript, and has had the supervision of the project.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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