Clinical features of Japanese patients with chronic cough induced by gastroesophageal reflux

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ABSTRACT

Gastroesophageal reflux (GER) has been reported as a cause of chronic cough (CC) in the United States. It has been reported that 5–21% of CC cases are induced by GER. In Japan, however, detailed clinical features of CC induced by GER have not been described. The present study reports on six Japanese patients with GER-induced CC. The subjects were all females, with a mean age of 72 years. The average body mass index was 37 kg/m², indicating obesity. No abnormalities were found with regard to concentrations of C-reactive protein, peripheral eosinophil counts, serum IgE concentrations, serum titers of cold agglutinins or antibodies to Mycoplasma pneumoniae, chest radiograph findings, respiratory function tests or blood gas analyses. Bronchial biopsy was performed in three patients and showed chronic inflammation characterized by lymphocytic infiltration, squamous metaplasia and mucosal basement membrane thickening. In the study population (Japanese patients), GER-induced CC tended to occur in elderly obese women and may be attributable to airway inflammation.

Key words: bronchial biopsy, chronic inflammatory airway disease, cough, gastroesophageal reflux, Japanese.

INTRODUCTION

Chronic cough (CC) is defined as persistent cough of unknown etiology with a duration of at least 3 weeks.1,2

Postnasal drip syndrome, cough variant asthma3 and gastroesophageal reflux (GER) have been reported as major causes of this disorder in the United States.1,2 In Japan, however, few cases of CC induced by GER have been reported.4

Body mass index (BMI) and gastric acid pH, which are closely related to the risk of GER,5 differ among the human races.6,7 Thus, differences in factors associated with GER between patients in Japan and those in the United States may affect the incidence of GER-induced cough.

We report on the clinical features of Japanese patients with GER-induced CC. In addition, we discuss the etiology of CC, based on the results of bronchial biopsies performed using fiberoptic bronchoscopy.

METHODS

Patients

Of patients referred to the Medical Department at Niigata Prefectural Kakizaki Hospital and diagnosed with CC between April 1992 and March 1994, those that met the pre- and post-treatment diagnostic criteria of Irwin et al.1,2 were entered into the study.

The pretreatment criteria were: (i) symptoms of heartburn and a sour taste in the mouth; (ii) barium reflux during upper gastrointestinal contrast roentgenography; and (iii) esophagitis confirmed by esophagoscopy biopsy. The post-treatment criteria were recovery from cough after the following regimen: (i) an anti-reflux diet of high protein and low fat for three meals a day; (ii) avoiding eating and drinking 2–3 h prior to sleep except for taking medications, (iii) elevation of the upper body when lying down; and (iv) administration of metoclopramide and/or H₂ receptor antagonists.
Informed consent was obtained from each subject before the start of the study, which was approved by the institute’s committee on human research.

Clinical findings

The following clinical features were ascertained: age, sex, smoking history, past allergic history (bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis), sinus disease history, presence or absence of postnasal drip, BMI (kg/m²), time of cough (morning, afternoon, evening, bedtime, sleep or all day), duration of cough, time between treatment and recovery, levels of C-reactive protein (CRP), peripheral eosinophil counts, serum IgE concentration, serum titers of cold agglutinins and antibodies to Mycoplasma pneumoniae, vital capacity (%VC, %predicted values), forced expiratory volume in 1 s (FEV₁, %), blood gases (P<sub>0₂</sub> and A-aDO₂), chest roentgenogram, and esophagoscopic findings, classified according to Savary and Miller. Serum IgE concentration and titers of antibodies to M. pneumoniae were measured by enzyme immunoassay and complement fixation, respectively (Biomedical Laboratories Corp., Tokyo, Japan). Respiratory function was determined using a hot-wire flowmeter (Autospiro AS-7, Minato Corp., Tokyo, Japan). The %VC was predicted using the equation of Baldwin et al., and FEV₁₀₀% was calculated according to the method of Gaensler. Blood gases were analyzed as follows. After having the patient in a supine position for at least 15 min, blood was collected from the brachial artery into a heparinized container. P<sub>0₂</sub> and P<sub>CO₂</sub> were then measured with an automatic pH blood gas analyzer (Ciba Corning 278, Ciba-Corning-Diagnostic Corp., Tokyo, Japan). The ideal alveolar oxygen tension was calculated from P<sub>0₂</sub> according to the method of Comroe et al., and used to calculate the alveolar-arterial oxygen tension gradient (A-aDO₂). Esophagoscopic findings were evaluated by two or more gastroenterologists. In addition, patients underwent bronchial biopsy via flexible bronchoscopy with specimens taken from the segmental bronchi of the upper, middle and lower lobes.

Results are expressed as the mean ± standard deviation and range of values.

RESULTS

Forty-three patients were diagnosed with CC during the two years. The 43 cases included 22 cases of postinfectious cough, 7 of angiotensin-converting enzyme (ACE) inhibitor-induced cough, 7 of bronchodilator-resistant cough, and 1 of cough variant asthma. Six patients met the diagnostic criteria for GER-induced CC (Tables 1, 2). None of the patients had used ACE inhibitors. They were all female patients with a mean age of 72±6 years (range, 61–80), and did not have a history of smoking, allergies or sinus disease. No patient

Table 1. Clinical characteristics of the study groups

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Patient no.</th>
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<td>Age (years)</td>
<td></td>
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<td>61</td>
<td>69</td>
<td>72</td>
<td>73</td>
<td>76</td>
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<td>Smoking history</td>
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<td>Past allergic history</td>
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<td>Sinus disease history</td>
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<td></td>
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<tr>
<td>Postnasal drip</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<td>35</td>
<td>38</td>
<td>40</td>
<td>37</td>
<td>36</td>
<td>38</td>
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Table 2. Laboratory findings

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<th>C-reactive protein</th>
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<td>Peripheral eosinophil counts (/mm³)</td>
<td>180</td>
<td>34</td>
<td>55</td>
<td>150</td>
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<td>51</td>
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<tr>
<td>Serum IgE concentration (IU/mL)</td>
<td>22</td>
<td>49</td>
<td>11</td>
<td>121</td>
<td>246</td>
<td>14</td>
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<tr>
<td>Titer of cold agglutinins</td>
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<td>×16</td>
<td>×16</td>
<td>×8</td>
<td>×32</td>
<td>×4</td>
</tr>
<tr>
<td>Titer of antibodies to Mycoplasma pneumoniae (complement fixation method)</td>
<td>×4</td>
<td>×4</td>
<td>×4</td>
<td>×4</td>
<td>×4</td>
<td>×4</td>
</tr>
<tr>
<td>%VC</td>
<td>85.3</td>
<td>105.5</td>
<td>95.4</td>
<td>81.1</td>
<td>92.8</td>
<td>86.3</td>
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<tr>
<td>FEV₁₀₀%</td>
<td>68.4</td>
<td>79.7</td>
<td>86.4</td>
<td>86.4</td>
<td>78.7</td>
<td>73.0</td>
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<tr>
<td>P&lt;sub&gt;0₂&lt;/sub&gt; (torr)</td>
<td>81.0</td>
<td>86.5</td>
<td>73.7</td>
<td>79.1</td>
<td>79.8</td>
<td>77.2</td>
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<tr>
<td>A-aDO₂ (torr)</td>
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<td>12.6</td>
<td>22.1</td>
<td>19.9</td>
<td>11.5</td>
<td>23.2</td>
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<tr>
<td>Stage of reflux esophagitis&lt;sup&gt;5&lt;/sup&gt;</td>
<td>IV</td>
<td>II</td>
<td>I</td>
<td>I</td>
<td>I</td>
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A-aDO₂, alveolar-arterial oxygen tension gradient; FEV₁₀₀%, forced expiratory volume in 1 s; P<sub>0₂</sub>, arterial oxygen tension; VC, vital capacity.
had postnasal drip. The mean BMI was 37±2 kg/m² (range, 35–40). As regards the time of cough, all patients indicated that their cough occurred primarily during sleep. The mean duration of cough was 22±22 weeks (range, 5–64) and the mean period between treatment and recovery was 4.3±1.4 weeks (range, 3–6). CRP concentrations, peripheral eosinophil counts, serum IgE concentrations, and titers of cold agglutinins and antibodies to M. pneumoniae were all normal.

Mean values for %VC (91.1±8.8%), FEV₁₀₀% (78.8±7.2%), P_{O₂} (79.6±4.3 torr) and A–aDO₂ (18.6±5.2 torr) were all within normal range. Chest roentgenograms did not reveal any abnormalities.

Reflux esophagitis, as detected by esophagoscopy, was classified according to Savary and Miller’s criteria: eight patients had stage I esophagitis, 2 had stage II, and 1 had stage IV.

Bronchial biopsy was performed in 3 of the 6 cases before treatment. The results are shown in Figs 1, 2 and 3. All three had lymphocytic infiltration of the bronchial mucosal membranes, but no abnormal eosinophilic infiltration. Bronchial basement membrane thickening was

**Fig. 1** Histologic features of bronchial biopsy specimens (case 3) showing (a) chronic inflammation with lymphocytic infiltration in the submucosa (HE) and (b) mucosal basement membrane thickening and focal squamous metaplasia (HE).
observed in two cases. One case showed squamous metaplasia. Thus, these three patients were diagnosed with chronic airway inflammation accompanied by lymphocytic infiltration.

**DISCUSSION**

In the present study, all six cases of CC induced by GER occurred in elderly obese women who had neither an allergic history nor postnasal drip. They showed normal CRP concentrations, peripheral eosinophil counts, serum IgE concentrations, titers of cold agglutinins and antibodies to M. pneumoniae, chest roentgenograms, respiratory function tests and blood gases. In addition, three patients were diagnosed by bronchial biopsy as having chronic airway inflammation accompanied by lymphocytic infiltration. Irwin et al. reported that 10% of 49 CC cases were induced by GER, with a mean age of 67 years (range, 55-77). They also reported nine patients with GER having CC as the only symptom, consisting of four
male and five female patients with a mean age of 52 years. Our six patients were all female and older (mean age of 72 years) than those studied by Irwin et al. It is well known that ACE inhibitors induce cough more frequently in women than in men. Moreover, it has been reported that cough is induced more easily in women than in men. Therefore, a female predominance of GER-induced CC is compatible with these reports.

Bronchial asthma is considered to be a chronic inflammatory disease mainly induced by eosinophilic infiltration of the airways. In the present study, bronchial biopsy revealed that GER-induced CC may be due to chronic airway inflammation characterized by lymphocytic infiltration. Boulet et al. performed bronchial biopsies in seven patients with CC induced by GER (all females) as well as in five with CC induced by both GER and postnasal drip (one male and four females). They observed the presence of airway inflammation associated with a lymphocytic infiltration. Furthermore, in their study, 10 of the 11 cases were female with normal values for FVC and FEV,%. These results agree with the findings reported here.

With regard to the etiology of GER-induced CC, two hypotheses have been proposed. One is microaspiration of hydrochloric acid into the lung due to GER. The other is bronchoconstriction caused by vagal reflexes from the esophagus, trachea and bronchi, enhanced by stimulation of esophageal mucosa by hydrochloric acid. It is difficult to draw definitive conclusions regarding the mechanism underlying our results. However, based on the bronchial biopsy findings, we speculate that repeated tracheobronchial microaspiration of refluxed gastric acid or vagally mediated reflux may cause chronic inflammatory damage in bronchial mucosa, in most cases accompanied by lymphocytic infiltration, resulting in CC. In Japan, further study is needed to investigate the mechanism of reflux-induced cough and airway inflammation, to establish whether the mechanism is that of microaspiration or vagally mediated reflux.

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REFERENCES


